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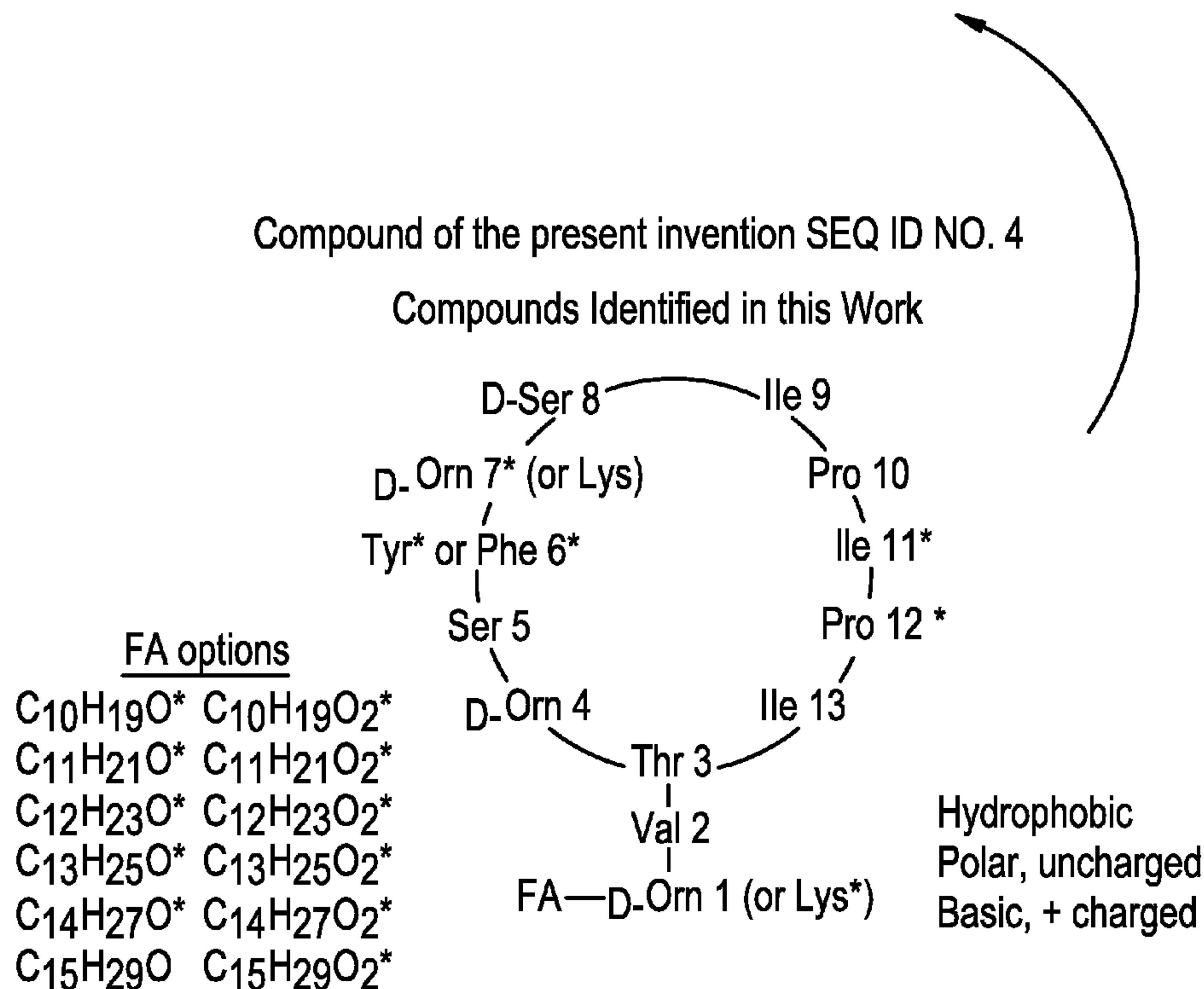
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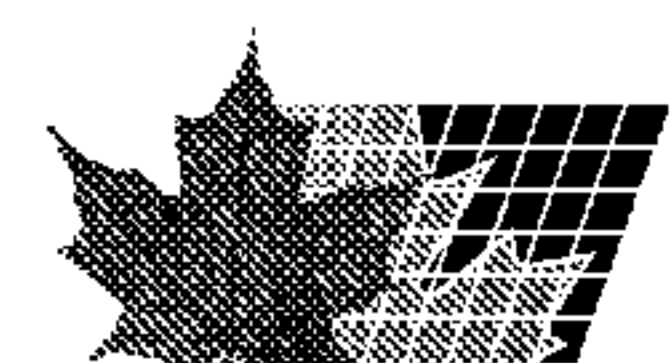
(54) **Title: ANTIMICROBIAL PEPTIDES, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USE THEREOF**

## FIG. 8B



(57) **Abrégé/Abstract:**

Disclosed herein are novel antimicrobial peptides, pharmaceutical compositions containing the peptides, and methods of use of the peptides to inhibit the growth or proliferation of microbes. The antimicrobial peptides are particularly useful to treat infections of dangerous gram positive organisms such as MRSA and VRSA.



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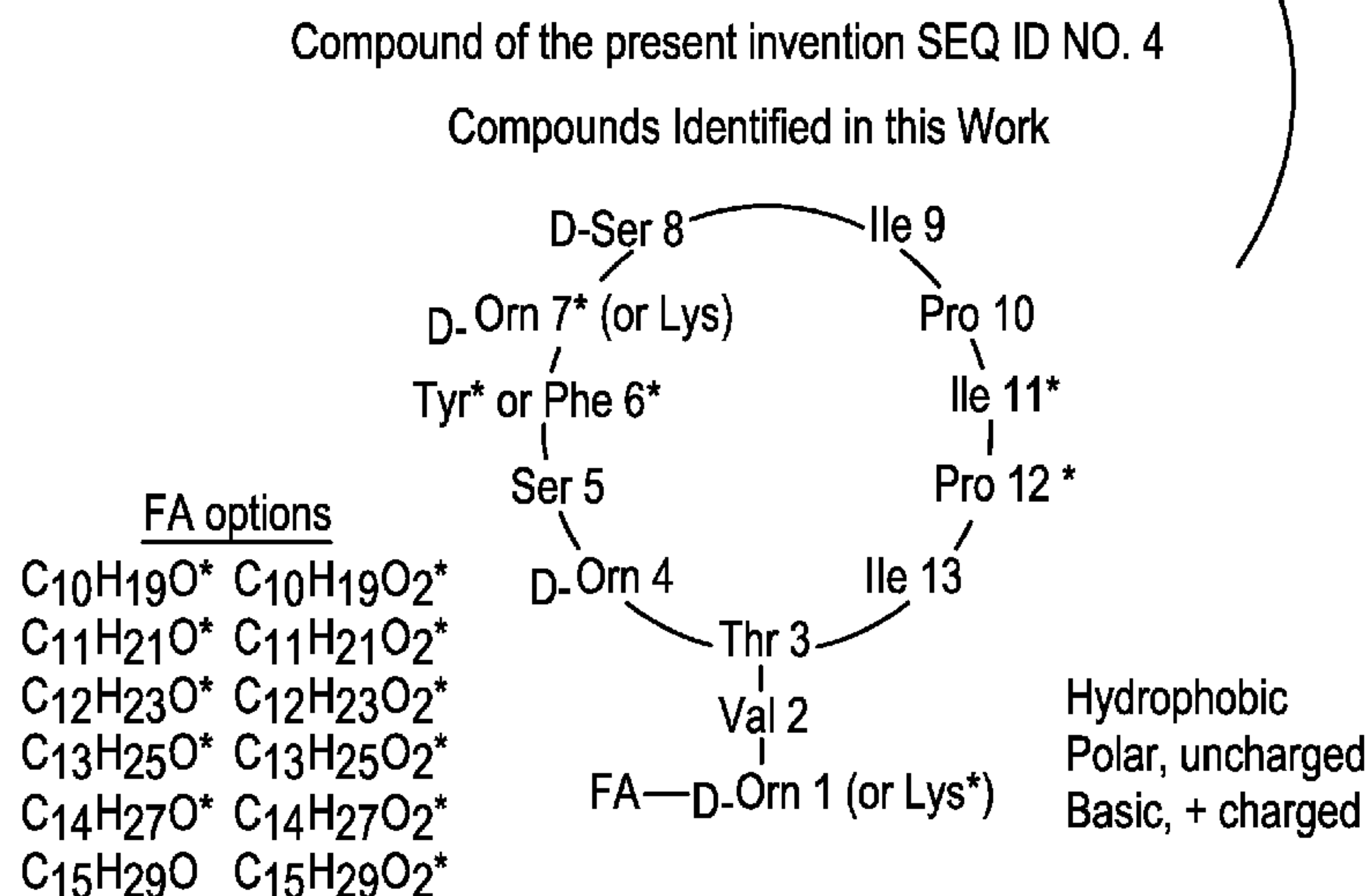
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(54) Title: ANTIMICROBIAL PEPTIDES, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USE THEREOF

## FIG. 8B



(57) Abstract: Disclosed herein are novel antimicrobial peptides, pharmaceutical compositions containing the peptides, and methods of use of the peptides to inhibit the growth or proliferation of microbes. The antimicrobial peptides are particularly useful to treat infections of dangerous gram positive organisms such as MRSA and VRSA.

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## ANTIMICROBIAL PEPTIDES, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USE THEREOF

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 62/009467 filed on June 9, 2014, which is incorporated herein by reference in its entirety.

### FIELD OF THE DISCLOSURE

[0001] The present disclosure is related to antimicrobial peptides, pharmaceutical compositions containing the antimicrobial peptides, and methods of treating microbial infections with the antimicrobial peptides.

### BACKGROUND

[0002] Antibiotic-resistant pathogenic bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA), fluoroquinolone resistant *Pseudomonas aeruginosa* and *Clostridium difficile*, and multi-drug resistant *Salmonella* spp. are an emerging problem in modern medicine. The loss of efficacy of current antibiotics makes the identification and development of new antibiotics more critical. The environment, for example, is an important source of microbial strains capable of producing potent antimicrobials which can be isolated and purified from their natural sources.

[0003] *Paenibacillus*, spore-forming species widely distributed in the environment, are a potential source of new antimicrobials. Strains of *Paenibacillus* can produce diverse antimicrobial agents including lantibiotics, lipopeptides, and macrolides. Lipopeptides, for example, are compounds that are generally not synthesized by ribosomes, and that are active against a wide range of bacteria, fungi, and oomycetes. Lipopeptides can act as antiviral and antitumor agents, immunomodulators or specific toxins and enzyme inhibitors.

[0004] There is thus a need to identify and develop antimicrobial agents that are effective against a broad spectrum of microbial pathogens such as Gram-positive and Gram-negative bacteria.

### BRIEF SUMMARY

[0005] In an aspect, included herein is a peptide of the sequence  
Xaa<sub>1</sub>-Xaa<sub>2</sub>-Xaa<sub>3</sub>-Xaa<sub>4</sub>-Xaa<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Xaa<sub>8</sub>-Xaa<sub>9</sub>-Pro<sub>10</sub>-Xaa<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 2),

wherein Xaa<sub>6</sub> is Tyr, Phe, or Trp; Xaa<sub>1</sub>, Xaa<sub>4</sub> and Xaa<sub>7</sub> are each independently Lys or Orn; Xaa<sub>2</sub>, Xaa<sub>9</sub> and Xaa<sub>11</sub> are each independently Leu, Ile, Val, or Ala; Xaa<sub>3</sub>, Xaa<sub>5</sub>, and Xaa<sub>8</sub> are each independently Cys, Tyr, Thr, or Ser; wherein the peptide optionally includes a saturated or unsaturated, substituted or unsubstituted, linear or branched C<sub>4</sub>-C<sub>20</sub> fatty acid group, or a saturated or unsaturated, linear or branched C<sub>4</sub>-C<sub>20</sub> ester covalently linked to Xaa<sub>1</sub>.

[0006] In another aspect, included herein is a peptide of the sequence Xaa<sub>1</sub>-Val<sub>2</sub>-Thr<sub>3</sub>-Xaa<sub>4</sub>-Ser<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Ser<sub>8</sub>-Ile<sub>9</sub>-Pro<sub>10</sub>-Xaa<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 3), wherein Xaa<sub>6</sub> is Tyr, Phe, or Trp; Xaa<sub>11</sub> is Leu, Ile, Val, or Ala; and Xaa<sub>1</sub>, Xaa<sub>4</sub> and Xaa<sub>7</sub> are independently Lys or Orn, wherein the peptide optionally includes a saturated or unsaturated, substituted or unsubstituted, linear or branched C<sub>4</sub>-C<sub>20</sub> fatty acid group, or a saturated or unsaturated, linear or branched C<sub>4</sub>-C<sub>20</sub> ester covalently linked to Xaa<sub>1</sub>.

[0007] In certain aspects, the peptides are cyclized through a bond between Thr<sub>3</sub> and Ile<sub>13</sub>.

[0008] Further included herein is a composition comprising the peptides described above and a carrier, vehicle, excipient, or diluent.

[0009] In yet another aspect, a process for preparing the peptides described above comprises (a) cultivating a host cell under conditions that allow for production of the peptide; and (b) purifying and isolating the peptide.

[0010] In a further aspect, a process for preparing a composition comprising the peptides described above comprises (a) cultivating a host cell under conditions that allow for production of the peptide; (b) purifying and isolating the peptide, and (c) producing a composition comprising the isolated peptide and a carrier, vehicle, excipient, or diluent.

[0011] In a still further aspect, a method of inhibiting growth or proliferation of a microbe comprises contacting the microbe or a surface or product which may contain a microbe with the peptide described above.

[0012] In a still further aspect, a method of inhibiting growth or proliferation of a microbe in a subject comprises administering to the subject a composition comprising one or more of the peptides described above, wherein the peptide is administered in an amount effective to inhibit growth or proliferation of the microbe.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 shows *in vitro* inhibition of foodborne pathogens and tomato bacterial phytopathogens by *Paenibacillus alvei* TS-15 (Figure 1A; ATCC PTA-121756) and A6-6i (Figure 1B; ATCC PTA-121885) on tryptic soy agar (TSA). The inhibition zones (mm) were measured against strains from *Salmonella* spp., *Escherichia coli* (*E. coli*), *Cronobacter sakazakii* (CS), *Listeria monocytogenes* (LM), *Shigella dysenteriae* (SD), Methicillin sensitive *Staphylococcus aureus* (MSSA), Methicillin resistant *Staphylococcus aureus* (MRSA), *Ralstonia solanacearum* race 5 (*R. solanacearum*), *Pseudomonas syringae* pv. tomato strain dc3000 (*P. syringae*), and *Erwinia carotovora* subsp. *carotovora* (*E. carotovora*). The plots represents the lowest, highest, and average measurements in each of the species listed above. The experiment was repeated twice.

[0014] Figure 2 shows growth inhibition of major foodborne pathogens in *P. alvei* A6-6i cell free culture supernatant (CFCS). Brain Heart Infusion (BHI) broth was used as a control. Bacterial growth of A) *L. monocytogenes* (LM), *S. dysenteriae* (SD), *E. coli* O157, *C. sakazakii* (CS), and *S. Newport* strains; and B) Methicillin resistant *S. aureus* (MRSA) strains in *P. alvei* A6-6i CFCS and BHI was determined in five replicates by measuring O.D.<sub>600</sub> at 20-minute intervals for 24 hours. The experiment was repeated twice.

[0015] Figure 3 shows a polymyxin B standard on a *Salmonella* lawn. A 10  $\mu$ L volume of 2-fold serial polymyxin B dilutions starting from 1 mg/mL to 1  $\mu$ g/mL was spotted on a lawn of  $10^6$  cells of *Salmonella enterica* serovar Montevideo strain 29N. The zone of inhibition (ZI) was observed after 24 hour incubation at  $35 \pm 2^\circ\text{C}$ .

[0016] Figure 4 shows TS-15 1-minute active fractions against pathogens. A 10  $\mu$ L volume from the 1-minute fractions of *P. alvei* strains TS-15 was spotted on a lawn of  $10^6$  cells of A) *Escherichia coli* O157:H7 strain EDL933; B) Methicillin-resistant *Staphylococcus aureus* strain #12. After incubation at  $35 \pm 2^\circ\text{C}$  for 24 hours, the antimicrobial activity exhibited by the 1-minute fractions was observed as a clear zone of inhibition (ZI). These experiments were also done for *P. alvei* strain A6-6i (data not shown).

[0017] Figure 5 shows MALDI-TOF MS results for fractions 20-26 from TS-15. The unlabeled arrows indicate a mass difference of 14 Da, which indicates a difference in  $\text{CH}_2$ ; an asterisk indicates MW 1623, which is designated as the primary sequence; two examples of a mass difference of 2 and 16 Da are labeled, which correspond to the other molecular variants.

[0018] Figure 6 shows MS/MS similarity. MALDI-TOF MS/MS comparison of two compounds that differ by 14 Da in molecular weight. Mass-to-charge ratios with an asterisk indicate an observed mass difference of 14 Da in the comparison between the two spectra.

[0019] Figure 7 shows partial sequence information from MALDI-TOF MS/MS spectrum of MW 1623 elucidated by manual *de novo* sequencing.

[0020] Figure 8 shows schematics of a previously published identified lipopeptide and the peptides discovered in current work. A. Molecule described in U.S. Publication No. US2013/0164317 and referred to as paenibacterin. B. Molecule(s) discovered in current work. The “R” group corresponds to an attached acyl chain in structure A and B; however, the “R” group for the structure in B. can also be an ester, for example, when Tyr is at position 6.

[0021] Figure 9 shows a representative example of different product ion series in an MS<sup>n</sup> spectrum (MS<sup>3</sup> 642<sup>2+</sup>). The corresponding sequences are coded to the amino acids in the inset schematic of the cyclic peptide structure.

[0022] Figures 10A and 10B show product ion assignments as a result of combined interpretation of multiple MS<sup>n</sup> analyses. Representative examples of MS<sup>2</sup> spectra are shown for two of the most abundant compounds, containing a Phe (MW 1607) or Tyr (MW 1623) at position 6, respectively. These product ion assignments led to the chemical structure shown in Figure 8. .

[0023] Figure 11 shows MS<sup>2</sup> spectra. Three series of compounds within the class of antibiotics differ by an amino acid or a difference in their attached fatty acid. Compounds that contain a Tyr at position 6 have  $m/z$  657<sup>2+</sup> as a consistent product ion in their resulting MS/MS spectra, while Phe at position 6 results in  $m/z$  649<sup>2+</sup>. The  $m/z$  values with an asterisk indicate a mass difference of 16 Da between the MS<sup>3</sup> spectra, which is the mass difference between Phe and Tyr. The mass difference between MW 1623 and MW 1625 corresponds to one less CH<sub>2</sub> group and an additional oxygen in the attached fatty acid (-CH<sub>2</sub>+O)..

[0024] Figure 12 shows three representative MS<sup>3</sup> spectra that demonstrate sequence similarity between compounds of molecular weights that differ by 14 Da and their corresponding complementary ion pair MS<sup>3</sup> spectra. MS<sup>2</sup> spectra are outlined and MS<sup>3</sup> spectra are outlined, with product ions selected for MS<sup>3</sup> highlighted .

[0025] Figure 13 shows MS/MS comparison of MW 1637 (top) and MW 1639 (bottom). The  $m/z$  values with an asterisk indicate a 1.979 Da mass difference between product ions in the two spectra, corresponding to one less CH<sub>2</sub> and an additional oxygen in the attached fatty acid compared to the dominant molecular species.

[0026] Figure 14 shows different MS/MS spectra for three compounds of the same molecular weight indicate Lys or Orn at Position 7 in Figure 8 and potential diversity in the

structure of the attached fatty acid due to distinct chromatographic peaks shown in the extracted ion chromatogram (EIC).

[0027] Figure 15 shows a schematic of a chemically synthesized, fatty acid modified peptide.

[0028] Figure 16 is a ptbA alignment for strains A6-6i, TS-15 and OSY SE.

[0029] Figure 17 is a ptbB alignment for strains A6-6i, TS-15 and OSY SE.

[0030] Figure 18 is a ptbC alignment for strains A6-6i, TS-15 and OSY SE.

[0031] The above-described and other features will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

## DETAILED DESCRIPTION

[0032] Described herein are novel peptides, specifically cyclic peptides, that have antimicrobial and broad-spectrum antibacterial activity. Specifically, the peptides are active against dangerous Gram-positive organisms such as MRSA and VRSA.

[0033] Recently, tomatoes have been implicated as a primary vehicle in foodborne outbreaks of *Salmonella Newport* and other *Salmonella* serovars. Long-term intervention measures to reduce *Salmonella* prevalence on tomatoes remain elusive for growing and post-harvest environments. A naturally-occurring bacterium identified by 16S rDNA sequencing as *Paenibacillus alvei* was isolated epiphytically from plants native to the Virginia Eastern Shore tomato growing region. After initial antimicrobial activity screening against *Salmonella* and 10 other bacterial pathogens associated with the human food supply, strain TS-15 was further used to challenge an attenuated strain of *S. Newport* on inoculated tomatoes, leaves, and blossoms of tomato plants in an insect-screened high tunnel with a split-plot design. Survival of *Salmonella* after inoculation was measured for groups with and without the antagonist at days 0, 1, 2, 3, and 5 for blossoms and day 6 for tomatoes and leaves, respectively. TS-15 exhibited broad range antimicrobial activity against both major foodborne pathogens and major tomato plant-associated bacterial pathogens. After *P. alvei* strain TS-15 was applied onto the tomatoes, leaves, and blossoms of tomato plants, the concentration of *S. Newport* was significantly lower ( $p \leq 0.05$ ) compared with controls. Surprisingly, more than 90% of the plants had no detectable levels of *Salmonella* by day 5 for blossoms. The naturally occurring antagonist strain TS-15 is highly effective in reducing carriage of *Salmonella Newport* on whole tomato plants. The application of *P. alvei* strain

TS-15 is a promising approach for reducing the risk of *Salmonella* contamination during tomato production. In addition, *Paenibacillus* strain A6-6i was found to retain comparable properties. Given to the fact that this activity can be attributed to the bactericidal compounds within, the present inventors have chemically isolated, purified, and identified certain compounds responsible for anti-*Salmonella* and other antibiotic effects including effects on dangerous gram positive organisms such as MRSA and VRSA.

[0034] More specifically, antimicrobial compounds were isolated from these *Paenibacillus* strains and a combination of low and high resolution mass spectrometry with multiple-stage tandem mass spectrometry was used for identification. A group of closely related cyclic lipopeptides was identified, differing primarily by fatty acid chain length and one of two possible amino acid substitutions. Variation in the fatty acid length resulted in mass differences of 14 Da and yields groups of related MS<sup>n</sup> spectra. Despite the inherent complexity of MS/MS spectra of cyclic compounds, straightforward analysis of these spectra was accomplished by determining differences in complementary product ion series between compounds that differ in molecular weight by 14 Da.

[0035] An “antimicrobial compound” is a compound that exhibits antimicrobial activity or a compound that affects microbial activity, meaning a compound that slows or stops growth and/or proliferation, slows or stops the rate of growth and/or proliferation, or stuns, inactivates, or kills a microbe. Antimicrobial compounds include antibiotics, antibacterials (e.g., bactericidal or bacteriostatic agents), antivirals (e.g., virucidal agents), antifungals (e.g., fungicidal or fungistatic agents), mold-inhibiting agents, anthelmintics (e.g., vermifuge or vermucidal agents), antiparasitics, and the like. Antimicrobial activity can be determined using methods described herein as well as methods known in the art.

[0036] As used herein, amino acids include alpha-amino acids of the general formula  $\text{H}_2\text{NCH(R)COOH}$  when free and  $\text{HNCH(R)CO}$  when in a polypeptide, wherein R is an amino acid side chain comprising an organic substituent, as well as uniquely structured amino acids such as, for example, proline. Amino acids include, for example, isoleucine, leucine, alanine, asparagine, glutamine, lysine, aspartic acid, glutamic acid, methionine, cysteine, phenylalanine, threonine, tryptophan, glycine, valine, proline, serine, tyrosine, arginine, histidine, norleucine, ornithine, taurine, selenocysteine, selenomethionine, lanthionine, 2-aminoisobutyric acid, dehydroalanine, hypusine, citrulline, 3-aminopropanoic acid, aminobutyric acid (alpha, beta, and gamma) diaminobutyric acid, and the like. The term

“amino acid side chain” refers to the various organic substituent groups (e.g., “R” in H<sub>2</sub>NCHR<sub>1</sub>COOH) that differentiate one amino acid from another.

[0037] In one aspect, an antimicrobial peptide has the sequence:

Xaa<sub>1</sub>-Val<sub>2</sub>-Thr<sub>3</sub>-Xaa<sub>4</sub>-Ser<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Ser<sub>8</sub>-Ile<sub>9</sub>-Pro<sub>10</sub>-Ile<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 1),

wherein Xaa<sub>6</sub> is Tyr, Phe, or Trp, specifically Tyr or Phe; Xaa<sub>1</sub>, Xaa<sub>4</sub>, and Xaa<sub>7</sub> are each independently Lys or Orn; or,

Xaa<sub>1</sub>-Xaa<sub>2</sub>-Xaa<sub>3</sub>-Xaa<sub>4</sub>-Xaa<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Xaa<sub>8</sub>-Xaa<sub>9</sub>-Pro<sub>10</sub>-Xaa<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 2)

wherein Xaa<sub>6</sub> is Tyr, Phe, or Trp, specifically Tyr or Phe; Xaa<sub>1</sub>, Xaa<sub>4</sub>, and Xaa<sub>7</sub> are each independently Lys or Orn; Xaa<sub>2</sub>, Xaa<sub>9</sub> and Xaa<sub>11</sub> are each independently a hydrophobic amino acid selected from Leu, Ile, Val, and Ala; Xaa<sub>3</sub>, Xaa<sub>5</sub>, and Xaa<sub>8</sub> are each independently an amino acid selected from amino acids that can form a hydrogen bond, a disulfide bond, a thioether bond, or an ester bond, such as Cys, Tyr, Thr, and Ser.

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[0038] In a more specific aspect, an antimicrobial peptide has the sequence:

Xaa<sub>1</sub>-Val<sub>2</sub>-Thr<sub>3</sub>-Xaa<sub>4</sub>-Ser<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Ser<sub>8</sub>-Ile<sub>9</sub>-Pro<sub>10</sub>-Xaa<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 3),

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wherein Xaa<sub>6</sub> is Tyr, Phe, or Trp, specifically Tyr or Phe; Xaa<sub>1</sub>, Xaa<sub>4</sub>, and Xaa<sub>7</sub> are each independently Lys or Orn; Xaa<sub>11</sub> is a hydrophobic amino acid selected from Leu, Ile, Val, and Ala. In a specific embodiment, Xaa<sub>1</sub> and Xaa<sub>4</sub> are Orn and Xaa<sub>11</sub> is Ile; more specifically,

Orn<sub>1</sub>-Val<sub>2</sub>-Thr<sub>3</sub>-Orn<sub>4</sub>-Ser<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Ser<sub>8</sub>-Ile<sub>9</sub>-Pro<sub>10</sub>-Ile<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 4),

wherein Xaa<sub>6</sub> is Tyr or Phe; and Xaa<sub>7</sub> is Lys or Orn.

[0039] In a specific embodiment, the peptide is

Orn<sub>1</sub>-Val<sub>2</sub>-Thr<sub>3</sub>-Orn<sub>4</sub>-Ser<sub>5</sub>-Tyr<sub>6</sub>-Lys<sub>7</sub>-Ser<sub>8</sub>-Ile<sub>9</sub>-Pro<sub>10</sub>-Ile<sub>11</sub>-Pro<sub>12</sub>-Ile<sub>13</sub>, (SEQ ID NO. 77).

[0040] In certain embodiments, the peptides of SEQ ID NOs. 1-4 include a fatty acid group, particularly a saturated or unsaturated, substituted or unsubstituted, linear or branched C<sub>4</sub>-C<sub>20</sub> fatty acid group, or a saturated or unsaturated, linear or branched C<sub>4</sub>-C<sub>20</sub> ester covalently linked to the amino acid at the 1 position, e.g., Xaa<sub>1</sub>. The fatty acid chain is

diverse in the number of  $-\text{CH}_2$ . For example, the molecular formula of the acyl chain can be  $\text{C}_{10}\text{H}_{19}\text{O}$ ,  $\text{C}_{11}\text{H}_{21}\text{O}$ ,  $\text{C}_{12}\text{H}_{23}\text{O}$ ,  $\text{C}_{13}\text{H}_{25}\text{O}$ ,  $\text{C}_{14}\text{H}_{27}\text{O}$ , or  $\text{C}_{15}\text{H}_{29}\text{O}$ . The ester group differs similarly ( $\text{C}_{10}\text{H}_{19}\text{O}_2$ ,  $\text{C}_{11}\text{H}_{21}\text{O}_2$ ,  $\text{C}_{12}\text{H}_{23}\text{O}_2$ ,  $\text{C}_{13}\text{H}_{25}\text{O}_2$ ,  $\text{C}_{14}\text{H}_{27}\text{O}_2$ , or  $\text{C}_{15}\text{H}_{29}\text{O}_2$ ).

[0041] Depending on the functional groups, peptides can be cyclized C-terminus to N-terminus, C-terminus to side-chain, side-chain to N-terminus, or side-chain to side-chain. In one aspect, the peptide is cyclized through a bond between Thr<sub>3/4</sub> and Ile<sub>13/14</sub>.

[0042] In a specific embodiment, when Xaa<sub>6</sub> is Tyr, the amino acid at the 1 position is covalently linked to a fatty acid group or an ester group, and when Xaa<sub>6</sub> is Phe, the amino acid at the 1 position is covalently linked to a fatty acid group.

[0043] It is noted that the presently disclosed compounds are distinct from the cyclic peptides disclosed in US2013/0164317, which requires that X<sub>12</sub> is an amino acid with a charged side chain. In the present compounds, X<sub>12</sub> is a Proline, which is expected to impart a unique structure and also antimicrobial properties to the disclosed peptides.

[0044] Also included herein are methods of producing an antimicrobial compound, specifically an antimicrobial peptide, by (a) cultivating a host cell under conditions that allow for production of the antimicrobial peptide; and optionally (b) purifying/isolating the antimicrobial peptide.

[0045] Host cells are cultivated in a nutrient medium suitable for production of the antimicrobial peptide using techniques known in the art. For example, the cell is cultivated by shake flask cultivation, small-scale or large-scale fermentation (including continuous, batch, fed-batch, or solid state fermentations) in laboratory or industrial fermentors performed in a suitable medium and under conditions allowing the polypeptide to be expressed and/or isolated. A suitable nutrient medium (e.g., a medium comprising carbon and nitrogen sources, inorganic salts, etc.) is used to cultivate the cells. In embodiments wherein the antimicrobial peptide is secreted from the cell into the nutrient medium, the antimicrobial peptide can be recovered directly from the medium. If the antimicrobial peptide is not secreted, it can be recovered from cell lysates or as inclusion bodies. The antimicrobial peptide may be recovered from the nutrient medium or cell lysates by procedures including, but not limited to, centrifugation, filtration, extraction, spray-drying, evaporation, and precipitation.

[0046] The antimicrobial peptides disclosed herein may be purified by a variety of procedures including, but not limited to, chromatography (e.g., ion exchange, affinity, hydrophobic, chromatofocusing, and size exclusion), electrophoretic procedures (e.g.,

preparative isoelectric focusing), differential solubility (e.g., ammonium sulfate precipitation), SDS-PAGE, and extraction.

[0047] Bacterial cultures for the production of the antimicrobial peptides can be grown using suitable methods and media useful for bacterial cell growth, maintenance, and/or protein production.

[0048] In some embodiments of this process, the antimicrobial peptide is isolated and/or purified using a suitable technique known in the art, including liquid chromatography, phase separation, using organic solvents and/or aqueous solvent or buffer systems. In some embodiments the antimicrobial peptide is purified to about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more. Analysis of purity can be made using an analytical method or technique such as, for example, mass spectrometry, gel electrophoresis, fluorescence, colorimetric assays, NMR, UV-Vis, total amino acid hydrolysis, chromatographic separation methods that utilize, for example, liquid chromatographic methods such as HPLC, FPLC, size exclusion, affinity binding, hydrophobic interaction, ionic charge, where purity can be assessed based on peak area.

[0049] In other embodiments, the antimicrobial peptides can be generated by standard chemical and/or protein and peptide synthetic techniques as are known in the art. Some embodiments relate to a synthetic strategy that incorporates a combination of chemical, peptide, and enzymatic (e.g., cyclase) synthetic steps. Chemical techniques for cyclizing peptides are well-known in the art.

[0050] Aspects of the disclosure relate to compositions and formulations, including pharmaceutical compositions and formulations that comprise an effective amount of at least one antimicrobial peptide. Such compositions and formulations comprise an effective amount of an antimicrobial peptide in combination with a carrier, vehicle, excipient, or diluent, including pharmaceutically and/or agriculturally acceptable carriers, vehicles, excipients, and diluents. An “effective amount” relates to a quantity of an antimicrobial peptide that is high enough to provide a significant positive result (e.g., slow or stop microbial activity) or positive modification of the subject's condition to be treated, and is suitably low enough to avoid serious side effects (at a reasonable benefit/risk ratio). Carriers, vehicles, excipients, and diluents are one or more compatible substances that are suitable for administration to a mammal such as, for example, solid or liquid fillers, diluents, hydrotopes, surface-active agents, and encapsulating substances. “Compatible” means that the components of the composition are capable of being mixed with the active agent, and with

each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers, vehicles, excipients, and diluents are suitably of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated, such as a human subject. The carrier, vehicle, excipient, or diluent can be inert, or it can possess pharmaceutical benefits and/or aesthetic benefits, or both. Suitable carriers, vehicles, excipients, and diluents are known in the art.

[0051] The antimicrobial compositions are applicable in a variety of products and applications, ranging from, for example, products of low and high pH-values, highly concentrated and diluted products, products usable in the technical field (e.g., in detergents for industrial or house-hold use), in the pharmaceutical field (e.g., for cleaning/disinfection of equipment or in the preparation of pharmaceutical compositions or their packaging, and in surgical supplies and sterilization of tools/hospital operating rooms), in personal care (e.g., in manufacture of cosmetics, shampoos, creams and lotions), in the feed industry (e.g., for cleaning of equipment, in the manufacture, storage, handling and preparation of animal feed and drink products) and in the food and drink industry (post-harvest foods, food processing surfaces and packaging). The antimicrobial peptides are also useful in post-surgical bandage and wound dressing prep, external wound healing and cleansing. In addition, the antimicrobial peptides are useful in post-harvest and food preservation applications against spoilage organisms. In embodiments relating to use of the compositions in a product, the antimicrobial composition can be provided as an ingredient in the final product (e.g., cosmetic, detergent, pharmaceutical, food, or drink product). Accordingly, in some embodiments, the compositions are effective against certain yeasts, fungi, and bacteria commonly associated with food-spoilage. Standard methods can be used in the manufacture of such products that comprise one or more of the antimicrobial peptide described herein.

[0052] In some embodiments, the antimicrobial composition is present on the surface of the products or inside the products. In some embodiments, the disclosure includes a method for reducing or preventing the presence, growth or activity of a microbe (e.g., gram-positive or gram-negative bacteria) in a product, such as a food or drink product, wherein the method comprises contacting the food or drink product during one or more of the various stages in the food processing process including the stages of the manufacture, the handling, the storage and/or the preparation of the food or drink product with the antibacterial compositions that are disclosed herein. The antimicrobial composition may be applied or

introduced by a suitable route or method such as, for example, as a spray, a rinse or a wash solution or as solution wherein the various food products are dipped. Further, the antimicrobial composition may be used to treat containers or packaging film prior to, simultaneously with, or subsequently after packaging the products.

[0053] In one aspect, a method of inhibiting growth or proliferation of a microbe comprises contact of the microbe with an antimicrobial peptide as described herein. “Contacting,” as used herein as in “contacting a cell,” refers to contacting a cell directly or indirectly in vitro, ex vivo, or in vivo (i.e., within a subject, such as a mammal, including humans, mice, rats, rabbits, cats, and dogs). Contacting a cell, which also includes “reacting” a cell, can occur as a result of administration to a subject. Contacting encompasses administration to a cell, tissue, mammal, subject, patient, or human. Further, contacting a cell includes adding an agent to a cell culture. Other suitable methods may include introducing or administering an agent to a cell, tissue, mammal, subject, or patient using appropriate procedures and routes of administration as defined herein.

[0054] The antimicrobial compositions described herein may be provided in solid or liquid form. When in liquid form, the composition is typically an aqueous composition, which may be a solution, emulsion, or dispersion.

[0055] Accordingly, the methods described herein include administration of one or more pharmaceutical compositions, in which an antimicrobial peptide is admixed together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

[0056] “Pharmaceutically acceptable,” as used herein, pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g., a human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

[0057] The formulations may conveniently be presented in unit dosage form and may be prepared by methods known in the art of pharmacy. Such methods include the step of bringing into association the active compound(s) with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

[0058] Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

[0059] Formulations suitable for oral administration (e.g., by ingestion) are typically presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

[0060] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); and preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Molded tablets are made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets are optionally coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets are optionally provided with an enteric coating, to provide release in parts of the gut other than the stomach.

[0061] Formulations suitable for parenteral administration (e.g., by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal injection), include aqueous and nonaqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilizers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's

Injection. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

[0062] Formulations suitable for topical administration (e.g., transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents. Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

[0063] Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide.

[0064] It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from subject to subject. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments described herein. The selected dosage level will depend on a variety of factors including, but not limited to, the species of the particular subject, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, whether other drugs, compounds, and/or materials are used in combination, and the age, sex, weight, condition, general health, and prior medical history of the subject. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local

concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

[0065] Administration in vivo can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

[0066] In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 mg per kilogram body weight of the subject per day, administered in a single or multiple doses per day.

[0067] A method of inhibiting growth or proliferation of a microbe in a subject comprises administering to the subject a composition comprising an antimicrobial peptide, wherein the antimicrobial peptide is administered in an amount effective to inhibit growth or proliferation of the microbe.

[0068] In an embodiment, a method of treating a condition or disease associated with the presence of a microbe comprises administering to a subject in need thereof a composition comprising an antimicrobial peptide, wherein the antimicrobial peptide is administered in an amount effective to treat the condition or disease.

[0069] In an embodiment, a method of treating a microbial infection comprises administering to a subject in need thereof a composition comprising an antimicrobial peptide, wherein the antimicrobial peptide is administered in an amount effective to treat the microbial infection. Exemplary infections include MRSA, VRSA, and CRE infections.

[0070] “Administration” or “administering,” as used herein, refers to providing, contacting, and/or delivery of a compound or compounds by an appropriate route to achieve the desired effect. Administration may include, but is not limited to, oral, sublingual, parenteral (e.g., intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection), transdermal, topical, buccal, rectal, vaginal, nasal, ophthalmic, via inhalation, and implants.

[0071] As used herein, the terms “treatment,” “treating,” or “treat” refer to both therapeutic treatment and prophylactic or preventative measures. Those subjects in need of treatment include those already showing clinical signs of the particular disease, disorder, or

condition as well as those prone to having or developing the disease, disorder, or condition, or those in which the disease, disorder, or condition is to be prevented. Many diseases, disorders, and conditions relate to the presence of microbes and are known to those of skill in the art, including secondary conditions resulting from opportunistic infections arising from other primary diseases and disorders (e.g., immune-suppressing conditions). Thus, a variety of patient classes can benefit from the methods of treatment described herein.

[0072] As used herein, the term “subject” is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, e.g., a disorder described herein, or a normal subject. The term “non-human animals” includes all vertebrates, e.g., non-mammals (such as fowl (e.g., ducks, chickens, etc.), amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals (such as horses, goats, sheep, dogs, cats, cows, pigs, etc.), and rodents (such as mice, rats, hamsters, guinea pigs, etc.).

[0073] In some embodiments the “effective amount” is an amount sufficient to stop or slow the progression of the disease, disorder, or condition. In some embodiments the effective amount is an amount sufficient to reverse disease, disorder, or condition, or repair the clinical signs of a disease, disorder, or condition. In embodiments the amount is sufficient to stop or slow the progression of an infection that is directly or indirectly related to a microbe. In some embodiments the effective amount is sufficient to stop or slow the proliferation and/or growth of a microbe. In further embodiments, the effective amount is sufficient to kill a microbe.

[0074] “Co-administered,” as used herein, refers to simultaneous or sequential administration of multiple compounds or agents. A first compound or agent may be administered before, concurrently with, or after administration of a second compound or agent. The first compound or agent and the second compound or agent may be simultaneously or sequentially administered on the same day, or may be sequentially administered within 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks or one month of each other. Suitably, compounds or agents are co-administered during the period in which each of the compounds or agents are exerting at least some physiological effect and/or has remaining efficacy. In some embodiments, the methods described herein can comprise co-administering two or more active agents disclosed herein. In some embodiments, the methods comprising co-administering two or more active agents include at least one antimicrobial agent disclosed herein in combination with a known active agent

against a particular indication. In some further embodiments, the known active agent also exhibits antimicrobial activity.

[0075] Additional antimicrobial agents can be selected based on the particular method and indication, such that it can provide an additive or a synergistic antimicrobial effect when compared to administration of the antimicrobial agent alone. For example, other antibiotics such as polymyxin B can be concurrently applied to increase its effect against gram-negative bacteria. Furthermore, fungicides can be co-administered for broader protection.

[0076] The invention is further illustrated by the following non-limiting examples.

## Examples

### Methods

[0077] Bacterial Cell Culture: *Paenibacillus alvei* strains A6-6i and TS-15, naturally-occurring bacterium previously isolated from plant and soil native to the Virginia Eastern Shore tomato growing region, were propagated on tryptic soy agar (TSA) at 35°C. The indicator strains (Table 1) included were also propagated on TSA at 35°C. Stock cultures grown overnight at 35°C on TSA were resuspended in brain heart infusion broth (BHI) with 25% glycerol and stored at -80°C. Three tomato plant-associated bacterial pathogens including *Erwinia carotovora* subsp. *carotovora*, *Pseudomonas syringae* pv. tomato strain dc3000, and *Ralstonia solanacearum* race 5 were grown on TSA at 25°C (Table 1).

Table 1

| Strain                                                                 | Reference or source                  |
|------------------------------------------------------------------------|--------------------------------------|
| <i>Salmonella enterica</i> subsp. <i>enterica</i> serovar Newport #17  | CFSAN laboratory collection          |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Saintpaul            | CFSAN laboratory collection          |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Montevideo 42N       | CFSAN laboratory collection          |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Javiana              | CFSAN laboratory collection          |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Typhimurium 368477   | CFSAN laboratory collection          |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Typhimurium SAR C #1 | SGSC <sup>a</sup>                    |
| <i>Salmonella enterica</i> subsp. <i>enterica</i> Typhi SAR C #3       | SGSC                                 |
| <i>Salmonella enterica</i> subsp. <i>arizonae</i> SAR C #5             | SGSC                                 |
| <i>Salmonella enterica</i> subsp. <i>arizonae</i> SAR C #7             | SGSC                                 |
| <i>Salmonella enterica</i> subsp. <i>arizonae</i> SAR C #9             | SGSC                                 |
| <i>Salmonella bongori</i> SAR C #11                                    | SGSC                                 |
| <i>Salmonella bongori</i> SAR C #13                                    | SGSC                                 |
| <i>Salmonella bongori</i> SAR C #15                                    | SGSC                                 |
| <i>Escherichia coli</i> O157:H7 IS O57                                 | CFSAN laboratory collection          |
| <i>Escherichia coli</i> O157:H7 EDL933                                 | CFSAN laboratory collection          |
| <i>Escherichia coli</i> ATCC 51434                                     | ATCC <sup>b</sup>                    |
| <i>Escherichia coli</i> ATCC BAA-179                                   | ATCC                                 |
| <i>Shigella dysenteriae</i> 2457T                                      | CFSAN laboratory collection          |
| <i>Shigella dysenteriae</i> BS103                                      | CFSAN laboratory collection          |
| <i>Cronobacter sakazakii</i> E932                                      | CFSAN laboratory collection          |
| <i>Cronobacter sakazakii</i> E784                                      | CFSAN laboratory collection          |
| <i>Listeria monocytogenes</i> N1-225                                   | CFSAN laboratory collection          |
| <i>Listeria monocytogenes</i> R2-583                                   | CFSAN laboratory collection          |
| Methicillin-resistant <i>Staphylococcus aureus</i> #9                  | CFSAN laboratory collection          |
| Methicillin-resistant <i>Staphylococcus aureus</i> #12                 | CFSAN laboratory collection          |
| Methicillin-resistant <i>Staphylococcus aureus</i> #28                 | CFSAN laboratory collection          |
| Methicillin-resistant <i>Staphylococcus aureus</i> #29                 | CFSAN laboratory collection          |
| Methicillin-resistant <i>Staphylococcus aureus</i> #30                 | CFSAN laboratory collection          |
| <i>Staphylococcus aureus</i> NRS70                                     | NARSA <sup>c</sup>                   |
| <i>Staphylococcus aureus</i> NRS106                                    | NARSA                                |
| <i>Staphylococcus aureus</i> NRS107                                    | NARSA                                |
| <i>Staphylococcus aureus</i> NRS271                                    | NARSA                                |
| <i>Salmonella enterica</i> Newport #17 $\Delta tolC::aph$              | CFSAN laboratory collection          |
| <i>Erwinia carotovora</i> subsp. <i>carotovora</i>                     | Dr. Dilip Lakshman, ARS <sup>d</sup> |
| <i>Pseudomonas syringae</i> pv. <i>tomato</i> strain dc3000            | Dr. Dilip Lakshman, ARS              |
| <i>Ralstonia solanacearum</i> race 5                                   | Dr. Dilip Lakshman, ARS              |

<sup>a</sup> SGSC, Salmonella Genetic Stock Centre, University of Calgary, Canada

<sup>b</sup> ATCC, American Type Culture Collection, Manassas, VA, USA

<sup>c</sup> NARSA, Network on Antimicrobial Resistance in *Staphylococcus aureus*, Chantilly, VA, USA

<sup>d</sup> ARS, Agricultural Research Service, Department of Agriculture, Beltsville, MD, USA

#### [0078] Determination of Mode of Action and Spectrum of Antimicrobial Activities

To determine mode of action and antimicrobial spectrum of the bacterial antagonists, both agar plug assay (using bacterial culture) and bioscreen assay (using culture supernatant) were performed against a broad spectrum of major foodborne pathogens and bacterial phytopathogens (Table 1). In the agar plug assay, bactericidal effects against pathogenic bacterial strains in the zone of inhibition were confirmed when no viable cells were recovered on TSA plates. In the bioscreen assay, the antagonist supernatant from overnight culture was filter sterilized with a 0.22  $\mu$ m pore-size cellulose acetate (CA) membrane filter. Each 3 ml

TS-15 cell-free culture supernatant (CFCS) was inoculated with 3  $\mu$ l of  $10^8$  cfu/mL bacterial culture (Table 1). Aliquots (200  $\mu$ l) were then dispensed into sterile Bioscreen C microwell plates (Growth Curves USA, Piscataway, NJ) and incubated as described for the respective bacterial strains. Bacterial growth was determined in five replicates by measuring O.D.<sub>600</sub> at 20-min intervals for 24 hours.

[0079] Fraction Collection: The modified method was based on methods known in the art. Cells were removed from Petri dishes using cell scrapers and were deposited into Eppendorf tubes. A final volume of 100  $\mu$ L of acetonitrile was added for every dish of scraped cells. The samples were shaken for 30 minutes and centrifuged at 7710 g for 15 minutes. The supernatant was removed and evaporated. The sample was reconstituted in water and was filtered with a 0.22  $\mu$ m Nylon filter. Fraction collection by liquid chromatography (LC) was achieved using a Shimadzu Nexera with a Kinetex C18 column (1.7 $\mu$ , 100 $\text{\AA}$ , 150 $\times$ 2.10 mm). The separation was performed with a column temperature of 60°C and a flow rate of 400  $\mu$ L/min using water with 0.1% formic acid (v/v) and acetonitrile with 0.1% formic acid (v/v) with the following gradient: 5 min hold at 95% water, 50 min linear gradient from 95% to 5% water, 5 min equilibration at 95% water. Fractions were concentrated and biological activity was tested against MRSA and *E. coli*. Fractions with activity were further examined by multiple mass spectrometry (MS) platforms.

[0080] Bioactivity Assay: Ten microliters of the 1-minute fractions from *Paenibacillus alvei* strain A6-6i or TS-15 were spotted directly on plates containing a lawn of  $10^6$  cells of *Escherichia coli* O157:H7 strain EDL933 and Methicillin-resistant *Staphylococcus aureus* strain #12, respectively. After incubation at  $35 \pm 2^\circ\text{C}$  for 24 hours, the antimicrobial activity exhibited by 1-minute fractions was observed as a clear zone of inhibition (ZI). The fraction that exhibited the ZI was focused henceforth. As a control experiment, 10  $\mu$ L of serial two-fold polymyxin B (Sigma-Aldrich, St. Louis, MO) dilutions starting from 1 mg/mL stock were spotted on a lawn of  $10^6$  cells of *Salmonella enterica* serovar Montevideo strain 29N.

[0081] Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF/MS) Analysis: Fractions that were found to be active were diluted 1:30 in water and 1  $\mu$ L was placed onto the MALDI target with 1  $\mu$ L of prepared CHCA matrix (20 mg/mL in 70% acetonitrile with 0.1% formic acid). The MALDI instrument used to analyze the samples was an Applied Biosystems/MDS Sciex 4800 MALDI TOF/TOF Analyzer. The laser power was optimized for each analysis to use the

minimum level required for sufficient ionization. Tandem mass spectrometry (MS/MS) was also performed on ions of interest using post-source decay (PSD).

[0082] LC/MS Analysis with High-Resolution Mass Spectrometry: The sample extract (prior to fraction collection) and resulting fractions were analyzed using the same LC conditions listed previously coupled to a high-resolution mass spectrometer (Q-Exactive™, Thermo Scientific). The Q-Exactive™ settings used were: 140,000 resolution, 1e6 AGC target, Maximum IT 60 ms, and a mass range of 300-4000 Da was monitored; the settings for the heated electrospray ionization probe (HESI-II) were: 4 kV spray voltage, 50 psi sheath gas, 15 (arbitrary units) auxiliary gas, 380 °C capillary temperature, and 300°C heater temperature. Active fractions were further analyzed with LC-MS/MS with the following modified conditions: 1 µL injection of the 1:30 diluted fraction, 35,000 resolution for full scan mode, and Maximum IT of 120 ms.

[0083] MS<sup>n</sup> Analysis: Multiple-stage mass spectrometry experiments (MS<sup>n</sup>) were performed using an Orbitrap Elite™ (Thermo Scientific). Fractions were diluted 1:30 in 70% methanol with 0.1% formic acid. Infusion for nanospray was accomplished using the Triversa Nanomate (Advion) with 1.5 kV voltage and 0.3 psi gas pressure. A mass range of 225 to 2000 was monitored in full MS mode with 120,000 resolution. Both collision-induced dissociation (CID) and electron-transfer dissociation (ETD) were used for MS/MS and MS<sup>n</sup> experiments.

[0084] 16S rRNA Gene Amplification and Sequencing: Genomic DNA of potential bacterial antagonists was extracted using the Wizard® genomic DNA purification kit (Promega, Madison, WI). A pair of universal primers specific for bacterial 16S rRNA, Eubac27 and R1492, were used to amplify the corresponding gene. PCR amplification of the 16S rRNA was performed with a Hotstart Taq® plus DNA polymerase kit (QIAGEN, Valencia, CA) under the following conditions: after an initial 5-minute incubation at 95°C, the mixture was subjected to 30 cycles, each including 1 minute at 95°C, 1 minute at 58°C, and 1 minute at 72°C. A final extension was performed at 72°C for 10 minutes. Both strands of purified PCR products were directly Sanger sequenced using the following primers: 27F (5'-AGAGTTTGATCCTGGCTCAG-3'; SEQ ID NO. 72), 1492R (5'-GGTTACCTTGTTACGACTT-3'; SEQ ID NO. 73), 357F (5'-CTCCTACGGGAGGCAGCA-3'; SEQ ID NO. 74), 518R (5'-CGTATTACCGCGGCTGCTGG-3'; SEQ ID NO. 75), and 1100R (5'-AGGGTTGCGCTCGTTG-3'; SEQ ID NO. 76). Sequence fragments were edited and

assembled into contigs using Molecular Evolutionary Genetics Analysis software v.5.0(MEGA 5.0). The BLAST algorithm was used for a homology search against Genbank. Only results from the highest-score queries were considered for phylotype identification, with 99% minimum similarity.

[0085] Whole Genome Sequencing: Genomic DNA was isolated from an overnight culture of each strain using a QIAGEN DNeasy® blood and tissue kit (QIAGEN Inc., Valencia, CA). Genome sequencing was performed using 454 Titanium sequencing technology (Roche, Branford, CT), achieving > 25X average genome coverage. *De novo* assembly was created for each genome using the 454 Life Sciences Newbler software package, v.2.5.3 (Roche). The genomic DNA of *P. alvei* strains TS-15 and A6-6i was also sequenced using the Pacific Biosciences (PacBio) RS sequencing platform. A single 10-kb library was sequenced using C<sub>2</sub> chemistry on 8 single-molecule real-time (SMRT) cells with a 90-min collection protocol on the PacBio RS. The 10-kb continuous-long-read (CLR) data were *de novo* assembled using the PacBio hierarchical genome assembly process (HGAP)/Quiver software package, followed by Minimus 2, and they were polished with Quiver. The assembled contigs from both approaches were annotated with the NCBI Prokaryotic Genomes Automatic Annotation Pipeline.

[0086] Identification and Characterization of the pbt Gene Cluster: Genomic comparison of pbt gene cluster (NRPS genes involved in the biosynthesis of a non-ribosomal lipopeptide antibiotic) between these two strains and *P. thiaminolyticus* strain OSY-SE (accession #ALKF000000000) as described in U.S. Publication No. US2013/0164317 was performed. The nonribosomal peptide synthetase (NRPS) machinery is composed of modular multi-domain enzymes which act as an assembly line to incorporate each amino acid monomer by one module. A typical module (C-A-T) in an NRPS contains a carrier Thiolation (T) domain and two catalytic domains, an adenylation (A) domain for amino acid activation and selectivity and a condensation (C) domain catalyzing peptide bond formation. In the termination module (C-A-T-Te), the Te-domain is responsible for releasing the assembled peptide. Additionally, optional epimerase (E) domain may also be present for L- to D-epimerization of amino acids. The NRPS in *P. alvei* strains A6-6i and TS-15 genomes was analyzed by NRPSpredictor2, a webserver for predicting NRPS adenylation domain. The A domain possesses a conserved binding pocket for amino acid recognition and activation. The substrate specificity of A-domain for amino acid was identified using NRPSpredictor2, based

on the fingerprint residues at the substrate-binding site. In addition, epimerization (E) domains and the Te domain were identified (PKS/NRPS analysis webserver).

#### Example 1: Broad Antimicrobial Spectrum of *P. alvei* Strains A6-6i and TS-15

[0087] *In vitro* agar plug assays showed inhibition zones against all the indicator strains including six major foodborne pathogens and three major tomato bacterial phytopathogens when challenged with both *P. alvei* isolates (Figures 1A and 1B). Notably, the antagonist migrated outward from the plug after forming the inhibition zone with SD (*S. dysenteriae*) or LM (*L. monocytogenes*), and the antagonistic growth ring expanded with time, especially in the case of *Listeria*. Both A6-6i and TS-15 had a wide range of inhibition against MRSA strains with zone diameters from 15 to 35 mm, and 15 to 20 mm, respectively. It is also interesting to note that strain A6-6i showed strong inhibitory effects on various MRSA strains tested despite the fact that some strains were resistant to up to 14 different antimicrobial drugs.

[0088] When supernatants were tested against the panel of gram-negative and gram-positive bacteria using the Bioscreen assay, both A6-6i (Figure 2) and TS-15 (not shown) CFCS exhibited a broad spectrum of antimicrobial activity, in which the lag phase was significantly extended in all the pathogens tested and the cell density was largely reduced at the end of incubation. Furthermore, the lag phase in CS (*C. sakazakii*), SD (*S. dysenteriae*), LM (*L. monocytogenes*), and some MRSA strains were extended to almost 24 hours in both A6-6i and TS-15 CFCS. Compared to A6-6i, CFCS from TS-15 had a much stronger inhibitory effect when tested against SN (*S. Newport*) (not shown).

#### Example 2: Bioactivity Results

[0089] Polymyxin B showed clear antimicrobial dose response against *S. Montevideo* (control experiment). The minimum inhibitory concentration for polymyxin B to show clear ZI was 4 µg/mL on the lawn of *S. Montevideo* strain 29N (Figure 3). Seven of the 1-minute fractions showed antimicrobial activity against both *E. coli* O157:H7 strain EDL933 and Methicillin-resistant *S. aureus* strain #12 (Figure 4). Similarly, multiple 1-minute fractions from *P. alvei* strain A6-6i exhibited antimicrobial activities against both strains as well (results not shown).

#### Example 3: Identification of the Primary Peptide Sequence

[0090] MALDI-TOF MS analysis revealed a number of compounds that were present in each of the seven bioactive fractions, as shown in Figure 5. The MALDI spectra provided a view of the full complement of compounds from each bioactive fraction within a single spectrum where clusters of these compounds differed by 14 Da, indicated by unlabelled arrows. The compound with a molecular weight of 1623 will be referred to as the primary compound (ion indicated with an asterisk in Figure 5), although multiple variants of similar abundances are present (Figure 5).

[0091] The MALDI-TOF MS/MS analyses of these molecular species revealed similar fragmentation patterns, which confirmed that the compounds that differ by 14 Da were related. As illustrated in Figure 6, comparison of MS/MS spectra of the primary compound, MW 1623, and the compound of MW 1637, which differ in molecular weight by 14 Da, revealed a series of product ions that shared the same mass and a second product ion series that differed by 14 Da, suggesting that the mass discrepancy between compounds was localized to one region of the molecule. This enabled identification of complementary product ion pairs, with one direction corresponding to the product ion series retaining the region of the molecule that contained the 14 Da mass-shift and the other direction corresponding to product ions that were identical between the two peptides (Figure 7). Manual *de novo* sequencing resulted in a partial amino acid sequence, yielding a putative sequence assignment.

[0092] A compound of the present invention is shown in Figure 8 B.

[0093] Analysis of MALDI-TOF MS/MS spectra only revealed partial sequence tags. To improve sequence coverage, individual fractions were infused and analyzed with the Orbitrap Elite, allowing for the collection of MS<sup>n</sup> data. Again, pairs of MS<sup>n</sup> spectra were analyzed and complementary ion pairs were identified based on the presence of 14 Da mass differences. The combined MS<sup>n</sup> data allowed a complete amino acid sequence to be determined (Figure 8B). This amino acid sequence was similar to a previously identified cyclic compound isolated from a different *Paenibacillus* strain which also showed broad-spectrum activity against MRSA and *E. coli*; the structure of that compound, designated as paenibacterin, is shown in Figure 8 A.

[0094] By determining which series of product ions did or did not contain the molecular component that results in the 14 Da difference, *de novo* sequencing by MS<sup>n</sup> analysis was more straightforward. This was particularly critical because the compounds were cyclic and resulting MS<sup>n</sup> spectra can be difficult to interpret due to multiple ring

opening events occurring at a distribution of sites. An example is shown in the MS<sup>3</sup> spectrum in Figure 9 where the ring opens at different amino acid positions, yielding a number of different sequence series within the same spectrum; thus, *de novo* sequencing of the primary sequence of cyclic peptides can be challenging. However, by using the described approach, the assignment of product ions and the identification of the primary sequence and sequence variants were accomplished without linearizing the molecule. The cumulative ion assignments for the primary amino acid sequence can be found in in Figure 10A, B.

[0095] Subsequent analysis with UPLC coupled to high resolution MS provided accurate mass data which confirmed that there were actually three predominant compound series, with each series containing groups of compounds that differ by 14.02 Da. The most pronounced differences between the three observed series were either a decrease of 15.99 Da or an increase of 1.98 Da in mass compared to the primary compound series; examples are designated with arrows in Figure 5. A comprehensive list of these compounds and their accurate mass molecular weights can be found in Table 2. These are designated as F, Y, and Y, -CH<sub>2</sub>+O in the table and throughout the figures; F and Y correspond to phenylalanine or tyrosine at position 6 in Figure 8 B and -CH<sub>2</sub>+O corresponds to a molecular difference in the fatty acid chain.

Table 2

| F                              |                           | Y                              |                           | Y<br>-CH <sub>2</sub> +O       |                           |
|--------------------------------|---------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|
| 649.390 <sup>2+</sup>          |                           | 657.394 <sup>2+</sup>          |                           | 657.394 <sup>2+</sup>          |                           |
| Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair | Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair | Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair |
|                                |                           | 1581                           | 269.222 <sup>1+</sup>     |                                |                           |
| 1579                           | 283.238 <sup>1+</sup>     | 1595                           | 283.238 <sup>1+</sup>     |                                |                           |
| 1593                           | 297.255 <sup>1+</sup>     | 1609                           | 297.253 <sup>1+</sup>     |                                |                           |
| 1607                           | 311.269 <sup>1+</sup>     | 1623                           | 311.269 <sup>1+</sup>     | 1625                           | 313.248 <sup>1+</sup>     |
|                                |                           | 1637                           | 325.285 <sup>1+</sup>     | 1639                           | 327.264 <sup>1+</sup>     |
|                                |                           | 1651                           | 339.301 <sup>1+</sup>     | 1653                           | 341.279 <sup>1+</sup>     |

[0096] Two compound series in the bioactive fractions differed from each other by 15.99 Da and exhibited MS<sup>2</sup> spectra with all the compounds in one series yielding a product ion at  $m/z$  657<sup>2+</sup> while the other series generates a product at  $m/z$  649<sup>2+</sup> (Figure 11). Figure 12 illustrates the MS<sup>n</sup> spectra of three precursor ions that differed by 14 Da, all of which generated an MS<sup>2</sup> product ion at  $m/z$  657<sup>2+</sup>. Because these were conserved product ions

within a precursor series that included compounds that differed in molecular weight by 14 Da, we were able to conclude that the region of the compound that yields product ions  $657^{2+}$  or  $649^{2+}$  does not contain the fatty acid. The  $MS^3$  spectra of  $657^{2+}$  were consistent with one another confirming that the region of the peptide that generated this sequence was conserved between these compounds (Figure 12). The  $MS^3$  spectra from the ion series that generated an  $MS^2$  product ion at  $649^{2+}$  were similar to the  $657^{2+}$   $MS^3$  spectra, except for a series of product ions that differed by 16 Da (masses with asterisks in Figure 12). This enabled the distinction between tyrosine and phenylalanine at position 6 (Figure 8), designated as Y and F in the tables and figures, respectively; these amino acids differ in molecular weight by 16 Da. Assignments for the MS/MS spectrum for a peptide containing Phe are illustrated in Figure 10A-B, where a direct comparison can be observed between the peptides containing Phe and Tyr at position 6.

#### Example 4: Identification of the Attached Fatty Acid

[0097] The  $MS^2$  spectra of the series of compounds that contain a Tyr at position 6 were dominated by product ion  $657^{2+}$  and its complementary ion pair (Figure 11). While  $657^{2+}$  was conserved within the Tyr compound series, its complementary ion contained the same 14 Da mass shift as its precursor (*i.e.*,  $m/z$  311, 325, and 339 in Figure 12). The same trend was also present for the Phe ion series. A list of the multiple complementary ions for  $657^{2+}$  and  $649^{2+}$  are listed in Table 3. When these complementary ions were dissociated (examples shown in Figure 12), a loss of ornithine was observed. Subtracting the cyclized peptide sequence mass from the mass of the entire compound yields the mass attributed to an attached fatty acid; molecular formula generation of these masses yield the molecular formulae of the different fatty acid variants (Table 4 and Figure 8). These fatty acids are similar to what was observed in Guo, *et al.*, although the lengths of the carbon chains differ and both the TS-15 and A6-6i strains presented in the current work exhibit a greater variability in chain length and composition.

[0098] As mentioned previously, three major series of compounds were determined: two series containing a tyrosine at position 6 and one containing phenylalanine. The two compound series containing Tyr differed by a molecular weight of 1.979 Da. Similar to the MS spectral analysis methodology shown in Figure 2, these compound series also had similar  $MS^2$  fragmentation patterns, where some product ion masses are conserved and others differ by 1.979 Da (Figure 13). This mass difference corresponded to one less  $CH_2$  and an

additional oxygen (labeled as -CH<sub>2</sub>+O) in the attached fatty acid compared to the tyrosine molecular series.

Table 3

| F                              |                           | Y                              |                           | Y<br>-CH <sub>2</sub> +O       |                           |
|--------------------------------|---------------------------|--------------------------------|---------------------------|--------------------------------|---------------------------|
| 649.390 <sup>2+</sup>          |                           | 657.394 <sup>2+</sup>          |                           | 657.394 <sup>2+</sup>          |                           |
| Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair | Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair | Nominal<br>Molecular<br>Weight | Complementary<br>Ion Pair |
|                                |                           | 1581                           | 269.222 <sup>1+</sup>     |                                |                           |
| 1579                           | 283.238 <sup>1+</sup>     | 1595                           | 283.238 <sup>1+</sup>     |                                |                           |
| 1593                           | 297.255 <sup>1+</sup>     | 1609                           | 297.253 <sup>1+</sup>     |                                |                           |
| 1607                           | 311.269 <sup>1+</sup>     | 1623                           | 311.269 <sup>1+</sup>     | 1625                           | 313.248 <sup>1+</sup>     |
|                                |                           | 1637                           | 325.285 <sup>1+</sup>     | 1639                           | 327.264 <sup>1+</sup>     |
|                                |                           | 1651                           | 339.301 <sup>1+</sup>     | 1653                           | 341.279 <sup>1+</sup>     |

Table 4

| Y<br>657.394 <sup>2+</sup>                    |                                   |                                   |                                   |                                   |                                   |                                   |                         |
|-----------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------------|
| MS <sup>2</sup><br>Product Ions <sup>1+</sup> | 269.222                           | 283.238                           | 297.253*                          | 311.269                           | 325.285*                          | 339.301*                          |                         |
| MS <sup>3</sup><br>Product Ions <sup>1+</sup> | 251.212<br>115.086                | 265.227<br>115.086                | 279.243<br>115.086                | 293.258<br>115.086                | 307.274<br>115.086                | 321.290<br>115.086                | Water loss<br>Ornithine |
| Molecular<br>Formula of the<br>Fatty Acid     | C <sub>10</sub> H <sub>19</sub> O | C <sub>11</sub> H <sub>21</sub> O | C <sub>12</sub> H <sub>23</sub> O | C <sub>13</sub> H <sub>25</sub> O | C <sub>14</sub> H <sub>27</sub> O | C <sub>15</sub> H <sub>29</sub> O |                         |

#### Example 5: Multiple Compounds with the Same Molecular Weight

[0099] It was also observed that more than one of the complementary ion pairs were occasionally present within the same MS<sup>2</sup> spectrum in the infusion experiment data. This corresponded to two compounds of the same precursor mass being fragmented within the same isolation window. There were multiple examples in the UPLC and NanoLC/MS data that showed several eluting peaks for entities with the same mass (example shown in Figure 14). The MS<sup>2</sup> spectra of the ions in each of these chromatographic peaks showed small differences in the fragmentation pattern and thus, the primary sequences of these respective peptides. Nearly identical amino acid sequences were confirmed for compounds with an identical molecular weight (1579): a compound with Lys at position 7 and a compound with

ornithine at position 7 with an additional CH<sub>2</sub> in the attached fatty acid (Lys and ornithine differ by a CH<sub>2</sub> in their side chains). Specifically, the product ion at  $m/z$  649<sup>2+</sup> corresponds to Lys at position 7 and  $m/z$  642<sup>2+</sup> corresponds to ornithine at position 7. The two chromatographic peaks with Lys at position 7 may indicate a structural difference in the attached fatty acid resulting in the observed difference in retention time (Figure 14). A similar substitution was also found at position 1. Some of the subsequent MS<sup>3</sup> analyses of the fatty acid containing fragment ions ( $m/z$  325<sup>1+</sup> and 339<sup>1+</sup> in Figure 5B) indicated that Lys can also be present at position 1 rather than ornithine ( $m/z$  129<sup>1+</sup> in MS<sup>3</sup> spectra in Figure 12). A Lys at position 1 and a decrease of CH<sub>2</sub> in the attached fatty acid resulted in identical molecular weights for each compound.

#### Example 6: Identification and Characterization of the pbt Gene Cluster

[0100] The sequence shown in Figure 8B was confirmed by genome mining for non-ribosomal peptide synthesis. Many pharmacologically important peptides in bacteria are synthesized by nonribosomal peptide synthetases (NRPS). NRPS machinery is composed of modular multi-domain enzymes which act as an assembly line to incorporate each amino acid monomer by one module. A typical module in an NRPS contains an adenylation (A) domain which possesses a conserved binding pocket for the recruitment of amino acid monomers that are to be incorporated into the final peptide product. A single contig of 6536324 bp (G+C content, 46.63%) and a single contig of 6784766 bp (G+C content, 46.69%) representing the complete chromosome for *P. alvei* strains A6-6i and TS-15 was generated, respectively. The draft genome sequences of strain A6-6i and TS-15 are available in DDBJ/EMBL/GenBank under GenBank accession # ATMS000000000 and ATMT000000000, respectively. The DNA sequences of A6-6i ptbA, ptbB, and ptbC are SEQ ID NOs. 5, 6, and 7, respectively. The DNA sequences of TS-15 ptbA, ptbB, and ptbC are SEQ ID NOs. 8, 9, and 10, respectively. The protein sequences for A6-6i ptbA, ptbB, and ptbC are SEQ ID NOs. 11, 12, and 13, respectively. The protein sequences for TS-15 ptbA, ptbB, and ptbC are SEQ ID NOs. 14, 15, and 16, respectively. A local BLASTX analysis against pbt gene cluster in *P. thiaminolyticus* strain OSY-SE (accession #ALKF000000000; U.S. Publication No. US2013/0164317) identified a 49-kb DNA region responsible for the compounds biosynthesis (Table 5). The protein sequences for OSY-SE ptbA, ptbB, and ptbC are SEQ ID NOs. 17, 18, and 19, respectively. Comparative genomic analysis showed 64% to 70% similarities in DNA sequences of the pbt gene cluster between the two *P. alvei* strains and *P.*

*thiaminolyticus* strain OSY-SE; and only 60% to 67% similarities in amino acid sequences (Figures 16-18). This DNA region encodes three peptide synthetase units which consist of thirteen modules (Table 5) responsible for incorporating the thirteen amino acids in the compounds. The predicted peptide sequence agreed with the chemical structure of the compounds determined by MS/MS (Table 4). In addition, epimerization (E) domains were found in modules for Orn<sub>1</sub>, Orn<sub>4</sub>, Orn<sub>7</sub>, and Ser<sub>8</sub>, which indicated that those amino acids might be in the D-form.

[0101] The bacterially-produced cyclic peptides are synthesized by a class of enzymes known as the nonribosomal peptide synthetases (NRPSs). NRPSs are found in many organisms and synthesize a number of medically-important peptides such as antibiotics and immunosuppressants. By sequence analysis, 14 NRPS genes have been identified in the *P. alvei* A6-6i and TS-15 genomes. Three NRPS genes which covered 49 kb were found to control the production of the compounds in the current application. NRPSs are large enzymes that are organized into modules made up of functional domains. The entire length of the amino acid sequence showed homology to the Pbt encoded by the *pbt* gene cluster of *P. thiaminolyticus* strain OSY-SE in the prior art patent (66% similarity to *pbtA* gene, 66% similarity to *pbtB* gene, and 59% similarity to *pbtC* gene). Detailed analysis of the *pbtABC* gene cluster showed that each gene had domain and module organization as in Table 5B. To predict the substrate specificity-conferring amino acids in the adenylation (A) domain of each module, the structural regions, A3 and A6 motifs in the A domain, were blasted against the NCBI protein database and showed only 36% identity to the ptbB1 module, 38% identity to the ptbC1 module, and 35% identity to the ptbC2 module, indicating structurally unique antibiotics from paenibacterin in the prior art patent.

Table 5

## A. Amino acid similarities between A6-6i, TS-15, and OSY-SE

|      | A6-6i  | TS-15  |
|------|--------|--------|
| pbtA | 66.95% | 66.73% |
| pbtB | 66.66% | 66.79% |
| pbtC | 59.72% | 59.31% |

## B. Modules and domains predicted in the gene cluster

|      |                                                                                                         |
|------|---------------------------------------------------------------------------------------------------------|
| pbtA | CA <sub>Orn1</sub> TECA <sub>Val2</sub> TCA <sub>Thr3</sub> TCA <sub>Orn4</sub> TECA <sub>Ser5</sub> T  |
| pbtB | CA <sub>Tyr6</sub> TCA <sub>Orn7</sub> TECA <sub>Ser8</sub> TECA <sub>Ile9</sub> TCA <sub>Pro10</sub> T |
| pbtC | CA <sub>Ile11</sub> TCA <sub>Pro12</sub> TCA <sub>Ile13</sub> TTe                                       |

[0102] Table 5 shows the predicted amino acids of the antimicrobial peptides generated by the PKS/NRPS web server. For example, the pbtA gene (encoding a non-ribosomal peptide synthetase) contains 5 modules, each comprised of a C (condensation) domain, an A (adenylation) domain, and a T (thiolation) domain. The A domain is responsible for amino acid activation and selectivity. Because the binding pocket of each A domain is a conserved sequence, the amino acid substrate can be predicted. Additionally, epimerization (E) domains were found in modules for Orn<sub>1</sub>, Orn<sub>4</sub>, Orn<sub>7</sub>, and Ser<sub>8</sub>, which indicate that those amino acids may be in the D-form. Likewise, pbtB gene contains 5 modules and pbtC gene contains 3 modules.

## C. Predicted amino acid substrates in the adenylation (A) domain in each module.

## A6-6i

| Module | Active site residue with 8 A of the amino acid substrate | Binding pocket               | Predicted substrate |
|--------|----------------------------------------------------------|------------------------------|---------------------|
| PbtA1  | LAWAFDVFTGDRESVVGSDLNSYGVTEACVDACY<br>SEQ ID NO. 20      | DVGEVGSVDK<br>SEQ ID NO. 21  | D-Orn               |
| PbtA2  | LGASFDAATFEGWMLVGGDINGYGPTENTTFTCC<br>SEQ ID NO. 22      | DAFWLGGTFK<br>SEQ ID NO. 23  | Val                 |
| PbtA3  | LNSHFDFSVWEGNQIFGGEINMYGITETTVHVTY<br>SEQ ID NO. 24      | DFWNIGMVHK<br>SEQ ID NO. 25  | Thr                 |
| PbtA4  | MAWAFDVFSGDRESIIIGSDINSYGVTEACVDSSY<br>SEQ ID NO. 26     | DVGEIGSVDK<br>SEQ ID NO. 27  | D-Orn               |
| PbtA5  | RWMTFDVSVWEWHFFTSGEINLYGPTTEATVDVTY<br>SEQ ID NO. 28     | DVWHFSLVDK<br>SEQ ID NO. 29  | Ser                 |
| PbtB1  | AWRFFDGFVMSICTLAGEFNEYGPTENS SVVATC<br>SEQ ID NO. 30     | DGMITAEVVK<br>SEQ ID NO. 31  | Tyr                 |
| PbtB2  | MAWAFDVFSGDRDCAVGSDINSYGVTECTCIDASY<br>SEQ ID NO. 32     | DVG DAGSIDK<br>SEQ ID NO. 33 | D-Orn               |
| PbtB3  | RWMTFDVSVWEWHFFTSGEINLYGPTTEATVDVTY<br>SEQ ID NO. 34     | DVWHFSLVDK<br>SEQ ID NO. 35  | D-Ser               |
| PbtB4  | VETSF DGSTFDGFI LFGGEKHVYGPTTESTVFATC<br>SEQ ID NO. 36   | DGFFLG VVFK<br>SEQ ID NO. 37 | Ile                 |
| PbtB5  | LYQAFDVCYQESFIITAGEHNHYGPSETHVVTY                        | DVQFIAHVVK                   | Pro                 |

|       |                                                      |                             |     |
|-------|------------------------------------------------------|-----------------------------|-----|
|       | SEQ ID NO. 38                                        | SEQ ID NO. 39               |     |
| PbtC1 | INTSFDGSAFDGLILFGGEKHAYGPSESTVYATW<br>SEQ ID NO. 40  | DGFLLGAVYK<br>SEQ ID NO. 41 | Ile |
| PbtC2 | LYQAFDVCYQESYIITAGEHNHYGPSETHVVTY<br>SEQ ID NO. 42   | DVQYIAHVVK<br>SEQ ID NO. 43 | Pro |
| PbtC3 | VDASFDGSTFDGFILFGGEKHVYGPTTESTVFATS<br>SEQ ID NO. 44 | DGFFLGVVFK<br>SEQ ID NO. 45 | Ile |

## TS-15

| Module | Active site residue with 8 A of the amino acid substrate | Binding pocket              | Predicted substrate |
|--------|----------------------------------------------------------|-----------------------------|---------------------|
| PbtA1  | LAWAFDVFTGDRESVVGSDLNSYGVTEACVDACY<br>SEQ ID NO. 46      | DVGEVGSVDK<br>SEQ ID NO. 47 | D-Orn               |
| PbtA2  | LAASFDAATFEGWMLVGGDINGYGPTENTTFTCC<br>SEQ ID NO. 48      | DAFWLGGTFK<br>SEQ ID NO. 49 | Val                 |
| PbtA3  | LNSHFDFSWEQNGIFGGEINMYGITETTVHVTY<br>SEQ ID NO. 50       | DFWNIGMVHK<br>SEQ ID NO. 51 | Thr                 |
| PbtA4  | MAWAFDVFSGDRESIIGSDINSYGVTEACVDSSY<br>SEQ ID NO. 52      | DVGEIGSVDK<br>SEQ ID NO. 53 | D-Orn               |
| PbtA5  | RWMTFDVSVWEWHFFTSGEINLYGPTTEATVDVTY<br>SEQ ID NO. 54     | DVWHFSLVDK<br>SEQ ID NO. 55 | Ser                 |
| PbtB1  | AWRFFDGFVMSCICTLAGEFNEYGPTENSVVATC<br>SEQ ID NO. 56      | DGMITAEVVK<br>SEQ ID NO. 57 | Tyr                 |
| PbtB2  | MAWAFDVFSGDRDCAVGSDINSYGVTECIDASY<br>SEQ ID NO. 58       | DVGDAJSIDK<br>SEQ ID NO. 59 | D-Orn               |
| PbtB3  | RWMTFDVSVWEWHFFTSGEINLYGPTTEATVDVTY<br>SEQ ID NO. 60     | DVWHFSLVDK<br>SEQ ID NO. 61 | D-Ser               |
| PbtB4  | VETSFDGSTFDGFILFGGEKHVYGPTTESTVFATC<br>SEQ ID NO. 62     | DGFFLGVVFK<br>SEQ ID NO. 63 | Ile                 |
| PbtB5  | LYQAFDVCYQESFIITAGEHNHYGPSETHVVTY<br>SEQ ID NO. 64       | DVQFIAHVVK<br>SEQ ID NO. 65 | Pro                 |
| PbtC1  | INTSFDGSAFDGLILFGGEKHAYGPSESTVYATW<br>SEQ ID NO. 66      | DGFLLGAVYK<br>SEQ ID NO. 67 | Ile                 |
| PbtC2  | LYQAFDVCYQESYIITAGEHNHYGPSETHVVTY<br>SEQ ID NO. 68       | DVQYIAHVVK<br>SEQ ID NO. 69 | Pro                 |
| PbtC3  | VDASFDGSTFDGFILFGGEKHVYGPTTESTVFATS<br>SEQ ID NO. 70     | DGFFLGVVFK<br>SEQ ID NO. 71 | Ile                 |

[0103] Table 5 shows the identification and characterization of the pbt gene cluster. A. DNA sequence similarities and amino acid sequence similarities of the pbt gene cluster between *P. alvei* strains A6-6i and TS-15 and *P. thiaminolyticus* strain OSY-SE. B. Modules and domains identified in the NRPS subunits: C, A, T, E, and Te representing condensation domain, adenylation domain, thiolation domain, epimerization domain, and thioesterase domain, respectively. C. Substrate prediction for each of the 13 modules in the peptide.

[0104] It is worth noting that genome mining did not predict the presence of abundant sequence variants. As Lys and ornithine differ by CH<sub>2</sub>, their binding affinities are likely similar which may be contributing to the observed molecular diversity. Likewise, Tyr and Phe differ by a hydroxyl group. Furthermore, NRPSpredictor 2 has lower single amino acid

substrate prediction scores for Phe and Lys, which may indicate why these were not additionally predicted in the primary sequence. NRPSpredictor2 also predicted that the epimerization (E) domain was in modules 1, 4, 7, and 8, which indicated that these resulting amino acid substrates may be in the D-form. As expected, NRPS analysis does not offer information about the presence or length of the alkyl chain.

[0105] The NRPS analysis confirmed both the presence and order of the amino acids of the peptide assignments made through the combination of MALDI-MS, high-resolution mass spectrometry, and MS<sup>n</sup> analysis. NRPS can be used as a screening technique to identify potential nonribosomal peptides which may act as antibiotics; however, it does not yield information regarding any molecular variants that may be produced. Moving forward, NRPS analysis and mass spectrometry can be used to combine rapid prediction of candidate peptides with the molecular specificity of mass spectrometry to enable identification of cyclic antibiotics and their sequence and fatty acid variants despite the presence of molecular diversity and complicated spectra.

#### Example 6: Design and characterization of a synthetic peptide

[0106] Based on the identified sequence in Figure 8B, a peptide was chemically synthesized in accordance with Figure 15, referred to herein as synthetic depsipeptide A.

[0107] Minimum inhibitory concentrations (MICs) of synthetic depsipeptide A against selected bacteria, including antibiotic-resistant strains (Table 6), were determined by the broth microdilution method following the procedure of the Clinical and Laboratory Standards Institute (CLSI) as is known in the art. Briefly, synthesized depsipeptide was dissolved in Optima grade water to reach 25.6mg/ml as the stock concentration. After 100 times dilution in cation-adjusted Mueller-Hinton II broth (CAMHBII) (Becton, Dickinson & Co., Sparks, MD), the depsipeptide was then further two-fold serially diluted in CAMHBII in clear, sterile, non-treated round bottom 96-well plates (Nunc, Roskilde, Denmark). Bacterial cultures were suspended in demineralized water to achieve a turbidity equivalent to a 0.5 McFarland turbidity standard (Remel, Lenexa, KA). An equal volume of culture suspension was added to the diluted depsipeptide to give a final volume of 100µl/well in the assay plates. Polymyxin B (Sigma, St Louis, MO) and vancomycin (Sigma) were used as positive controls in the AST assays. Strains *Escherichia coli* ATCC 25853, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, and *Staphylococcus aureus* ATCC 29213 were used as quality control strains in the assays. The MIC end point refers to the lowest

concentration of an antimicrobial agent that completely inhibits growth of bacterial cells after incubation at 35C for 20-24 h.

Table 6

Table 6. Minimum inhibitory concentrations (MICs) of synthesized depsipeptide and other antibiotics

| Bacterial strain                                                | MIC( $\mu$ g/ml)            |            |            |
|-----------------------------------------------------------------|-----------------------------|------------|------------|
|                                                                 | Synthesized<br>depsipeptide | PolymyxinB | Vancomycin |
| <i>E.coli</i> ATCC 25853                                        | 4                           | 0.5        | -          |
| <i>Salmonella</i> Newport #17                                   | 16                          | 1          | -          |
| <i>Enterobacter sakazakii</i> E784                              | 8                           | 0.5        | -          |
| <i>E. coli</i> O157:H7 EDL933                                   | 4                           | 0.5        | -          |
| <i>Serratia marcescens</i> SBJ-9047 (CRE,<br>clinical isolate)  | 32                          | >128       | -          |
| <i>Klebsiella pneumoniae</i> SBJ-9149 (clinical<br>isolate)     | 4                           | 0.5        | -          |
| <i>Serratia marcescens</i> SBJ-8283 (CRE,<br>clinical isolate)  | 32                          | >128       | -          |
| <i>Enterobacter cloacae</i> SBJ-9395 (CRE,<br>clinical isolate) | 4                           | >128       | -          |
| <i>Enterobacter cloacae</i> SBJ-7612 (clinical<br>isolate)      | 4                           | 1          | -          |
| <i>Klebsiella pneumoniae</i> SBJ-9483 (clinical<br>isolate)     | 4                           | 0.5        | -          |
| <i>Klebsiella pneumoniae</i> SBJ-9388 (clinical<br>isolate)     | 4                           | 0.5        | -          |
| <i>Enterobacter cloacae</i> SBJ-9222 (clinical<br>isolate)      | 8                           | 1          | -          |
| <i>P. aeruginosa</i> ATCC-27853                                 | 8                           | 1          | -          |
| <i>P. aeruginosa</i> SBJ-10884 (PMB-R, clinical<br>isolate)     | 4                           |            |            |
| <i>P. aeruginosa</i> -03 (PMB-R, clinical isolate)              | 8                           |            |            |
| <i>P. aeruginosa</i> -02 (PMB-R, clinical isolate)              | 8                           |            |            |
| <i>P. aeruginosa</i> -01 (PMB-R, clinical isolate)              | 8                           |            |            |
| <i>P. aeruginosa</i> SBJ-10886 (PMB-R, clinical<br>isolate)     | 4                           |            |            |
| <i>E. faecalis</i> ATCC 29212                                   | 4                           | -          | 2          |
| <i>Listeria monocytogenes</i> R2-583                            | 2                           | -          | 1          |
| <i>S. aureus</i> ATCC25923                                      | 2                           | -          | 1          |
| <i>S. aureus</i> 19 (MRSA, MDR clinical isolate)                | 4                           | -          | 1          |
| <i>S. aureus</i> 14 (MRSA, MDR clinical isolate)                | 4                           | -          | 1          |
| <i>S. aureus</i> 12 (MRSA, MDR clinical isolate)                | 4                           | -          | 1          |
| <i>S. aureus</i> ATCC 29213                                     | 4                           | -          | 1          |
| <i>S. aureus</i> 10 (MRSA, MDR clinical isolate)                | 4                           | -          | 1          |
| <i>S. aureus</i> 8 (MRSA, MDR clinical isolate)                 | 4                           | -          | 1          |

|                                                 |   |   |   |
|-------------------------------------------------|---|---|---|
| <i>S. aureus</i> 6 (MRSA, MDR clinical isolate) | 4 | - | 1 |
| <i>S. aureus</i> 4 (MRSA, MDR clinical isolate) | 4 | - | 1 |
| <i>S. aureus</i> 2 (MRSA, MDR clinical isolate) | 4 | - | 1 |

PMB-R, polymyxin B-resistant; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; CRE, carbapenem-resistant.

[0108] The synthetic depsipeptide showed a broad antimicrobial spectrum against both Gram-negative and Gram-positive bacteria, including against significant antibiotic-resistant clinical isolates (Table 1). Specifically, the synthesized depsipeptide showed very potent activity against those carbapenem-resistant (CRE) strains and MRSA strains. Additionally, bacteria showed much greater sensitivity to this peptide than to paenibacterin in U.S. Publication No. US2013/0164317.

[0109] It is striking that the peptides found in this study are amphiphilic with distinct hydrophilic and hydrophobic regions: hydrophobicity on one side, the other side being predominantly polar and charged amino acids, and a hydrophobic fatty acid chain (Figure 8B). Major differences between paenibacterin and the compounds discovered in this work are the length of the attached fatty acid, the different combinations of lysine and ornithine at positions 1 and 7, and the amino acids at position 6 and 12. This is particularly interesting because the amino acids at position 6 and 12 have different properties (e.g., hydrophobic, hydrophilic, or positively charged). Furthermore, the presence of D-amino acids influences the structure and properties of the peptide and will also make the compound more resistant to enzymatic degradation and thus inherently more stable.

[0110] Aspects of paenibacterin's mode of action have been previously studied. The results suggest that the compound has a high affinity to the negatively-charged outer membrane of gram-negative bacteria. This is likely due to the presence of positively charged amino acids in the molecule, which is similar to the mode of action of polymyxin. Three positively charged amino acids were found in the molecules discovered here compared to four in paenibacterin (Figure 8), which may result in varying degrees of effectiveness. However, the Lys to Pro substitution at position 12 also increases the hydrophobicity of that portion of the molecule which may result in a better affinity to the hydrophobic core of cellular membranes, a characteristic that may aid in its disruption. Similarly, the presence of Tyr at position 6 contributes to a more polar region of the molecule. The mode of action may also be due to the amphiphilic nature of the compound, acting as a surfactant to disrupt cell membranes. It is notable that polymyxin also has distinct hydrophilic and hydrophobic domains.

[0111] It was also determined that paenibacterin resulted in the permeabilization of both gram-positive and -negative cell membranes, which was probably disrupted by the attached fatty acid. The chain length will likely affect observed antimicrobial activity, although it is uncertain if it will be less or more effective with a longer/shorter chain. For polymyxin, it is hypothesized that the fatty acyl chain disrupts the cellular membrane. Studies on the fatty acid chain of polymyxin indicate that antimicrobial activity correlates with the length and bulkiness of this moiety. However, reports are varied and subsequent experiments to design fatty acid analogues for the compounds in this study will yield insight into how this affects antimicrobial activity. It is also interesting that a single strain of bacteria can produce such a large number of molecular variants. This may enable the strain to exert a more concerted antimicrobial effect and may have resulted from extensive selection pressure in the community from which it was isolated.

[0112] The major significance of the antimicrobial peptides described herein relates to overcoming the worldwide public health crisis of drug resistance by several major classes of bacterial human pathogens. Several of the most dangerous bacterial pathogens such as MRSA, VRSA, and CRE are resistant to nearly every antibiotic currently in the arsenal of human antimicrobial prophylaxis. CRE, for instance, has no known antibiotic weakness. What is most important is that these antimicrobial peptides may represent entirely new classes of antibiotics, each with the ability to control these deadly bacteria and cure associated pathology. Safety studies in rat with the host organism that produces the antimicrobial peptides was most encouraging, with rats showing no overt pathology from this strain.

[0113] The use of the terms “a” and “an” and “the” and similar referents (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms first, second etc. as used herein are not meant to denote any particular ordering, but simply for convenience to denote a plurality of, for example, layers. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”) unless otherwise noted. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods

described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein.

[0114] While the invention has been described with reference to an exemplary embodiment, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the appended claims. Any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

## Claims

1. A peptide of the sequence  
 $\text{Xaa}_1\text{-Xaa}_2\text{-Xaa}_3\text{-Xaa}_4\text{-Xaa}_5\text{-Xaa}_6\text{-Xaa}_7\text{-Xaa}_8\text{-Xaa}_9\text{-Pro}_{10}\text{-Xaa}_{11}\text{-Pro}_{12}\text{-Ile}_{13}$ , (SEQ ID NO. 2),  
 wherein  $\text{Xaa}_6$  is Tyr, Phe, or Trp;  $\text{Xaa}_1$ ,  $\text{Xaa}_4$  and  $\text{Xaa}_7$  are each independently Lys or Orn;  $\text{Xaa}_2$ ,  $\text{Xaa}_9$  and  $\text{Xaa}_{11}$  are each independently Leu, Ile, Val, or Ala;  $\text{Xaa}_3$ ,  $\text{Xaa}_5$ , and  $\text{Xaa}_8$  are each independently Cys, Tyr, Thr, or Ser; wherein the peptide optionally includes a saturated or unsaturated, substituted or unsubstituted, linear or branched,  $\text{C}_4\text{-C}_{20}$  fatty acid group, or a saturated or unsaturated, linear or branched  $\text{C}_4\text{-C}_{20}$  ester covalently linked to  $\text{Xaa}_1$ .
2. The peptide of claim 1 having the sequence  
 $\text{Xaa}_1\text{-Val}_2\text{-Thr}_3\text{-Xaa}_4\text{-Ser}_5\text{-Xaa}_6\text{-Xaa}_7\text{-Ser}_8\text{-Ile}_9\text{-Pro}_{10}\text{-Xaa}_{11}\text{-Pro}_{12}\text{-Ile}_{13}$ , (SEQ ID NO. 3),  
 wherein  $\text{Xaa}_6$  is Tyr, Phe, or Trp;  $\text{Xaa}_{11}$  is Leu, Ile, Val, or Ala; and  $\text{Xaa}_1$ ,  $\text{Xaa}_4$ , and  $\text{Xaa}_7$  are independently Lys or Orn, wherein the peptide optionally includes a saturated or unsaturated, substituted or unsubstituted, linear or branched  $\text{C}_4\text{-C}_{20}$  fatty acid group, or a saturated or unsaturated, linear or branched  $\text{C}_4\text{-C}_{20}$  ester covalently linked to  $\text{Xaa}_1$ .
3. The peptide of claim 2, wherein  $\text{Xaa}_6$  is Tyr or Phe;  $\text{Xaa}_{11}$  is Ile;  $\text{Xaa}_1$  and  $\text{Xaa}_4$  are Orn; and  $\text{Xaa}_7$  is Lys or Orn.
4. The peptide of any one of claims 1-3, wherein the peptide comprises a saturated or unsaturated, substituted or unsubstituted, linear or branched  $\text{C}_4\text{-C}_{20}$  fatty acid group covalently linked to  $\text{Xaa}_1$ .
5. The peptide of claim 4, wherein the fatty acid group has the formula  $\text{C}_{10}\text{H}_{19}\text{O}$ ,  $\text{C}_{11}\text{H}_{21}\text{O}$ ,  $\text{C}_{12}\text{H}_{23}\text{O}$ ,  $\text{C}_{13}\text{H}_{25}\text{O}$ ,  $\text{C}_{14}\text{H}_{27}\text{O}$ , or  $\text{C}_{15}\text{H}_{29}\text{O}$ .
6. The peptide of claim 5, wherein  $\text{Xaa}_6$  is Phe.
7. The peptide of any one of claims 1-3, wherein  $\text{Xaa}_6$  is Tyr and the peptide comprises a saturated or unsaturated, linear or branched  $\text{C}_4\text{-C}_{20}$  ester covalently linked to  $\text{Xaa}_1$ .

8. The peptide of claim 7, wherein the ester has the formula  $C_{10}H_{19}O_2$ ,  $C_{11}H_{21}O_2$ ,  $C_{12}H_{23}O_2$ ,  $C_{13}H_{25}O_2$ ,  $C_{14}H_{27}O_2$ , or  $C_{15}H_{29}O_2$ .

9. The peptide of any one of claims 1-8, wherein the peptide is cyclized through a bond between Xaa<sub>3</sub> or Thr<sub>3</sub> and Ile<sub>13</sub>.

10. A composition comprising the peptide of any one of claims 1-9 and a carrier, vehicle, excipient, or diluent.

11. The composition of claim 10, wherein the composition is a cleaning product, a disinfecting product, a personal care product, an animal feed product, or a food product.

12. The composition of claim 10, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

13. A process for preparing the peptide of any one of claims 1-9, comprising  
(a) cultivating a host cell under conditions that allow for production of the peptide;  
and  
(b) purifying and isolating the peptide.

14. A process for preparing a composition comprising the peptide of any one of claims 1-9, comprising  
(a) cultivating a host cell under conditions that allow for production of the peptide;  
(b) purifying and isolating the peptide, and  
(c) producing a composition comprising the isolated peptide and a carrier, vehicle, excipient, or diluent.

15. The process of claim 14, wherein the composition is a cleaning product, a disinfecting product, a personal care product, an animal feed product, or a food product.

16. The process of claim 14, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

17. A method of inhibiting growth or proliferation of a microbe, comprising contacting the microbe or a surface or product which may contain a microbe with the peptide of any one of claims 1-9.

18. The method of claim 17, wherein the surface or product which may contain a microbe is a surface associated with post-harvest foods, a food process surface, a food package, a household surface, a food preparatory tool, a surface in a hospital, a surgical supply, a surgical tool, a post-surgical bandage, a wound dressing, or an external wound.

19. A method of inhibiting growth or proliferation of a microbe in a subject comprises administering to the subject a composition comprising the peptide of any one of claims 1-9, wherein the peptide is administered in an amount effective to inhibit growth or proliferation of the microbe.

20. The method of claim 19, wherein the subject has a disease or condition associated with the presence of a microbe.

21. The method of claim 20, wherein the individual has a microbial infection.

22. The method of claim 21, wherein the infection is a MRSA, VRSA, or CRE infection.

23. The method of claim 19, wherein the subject is a mammal.

24. The method of claim 23, wherein the subject is a human subject.

FIG. 1A

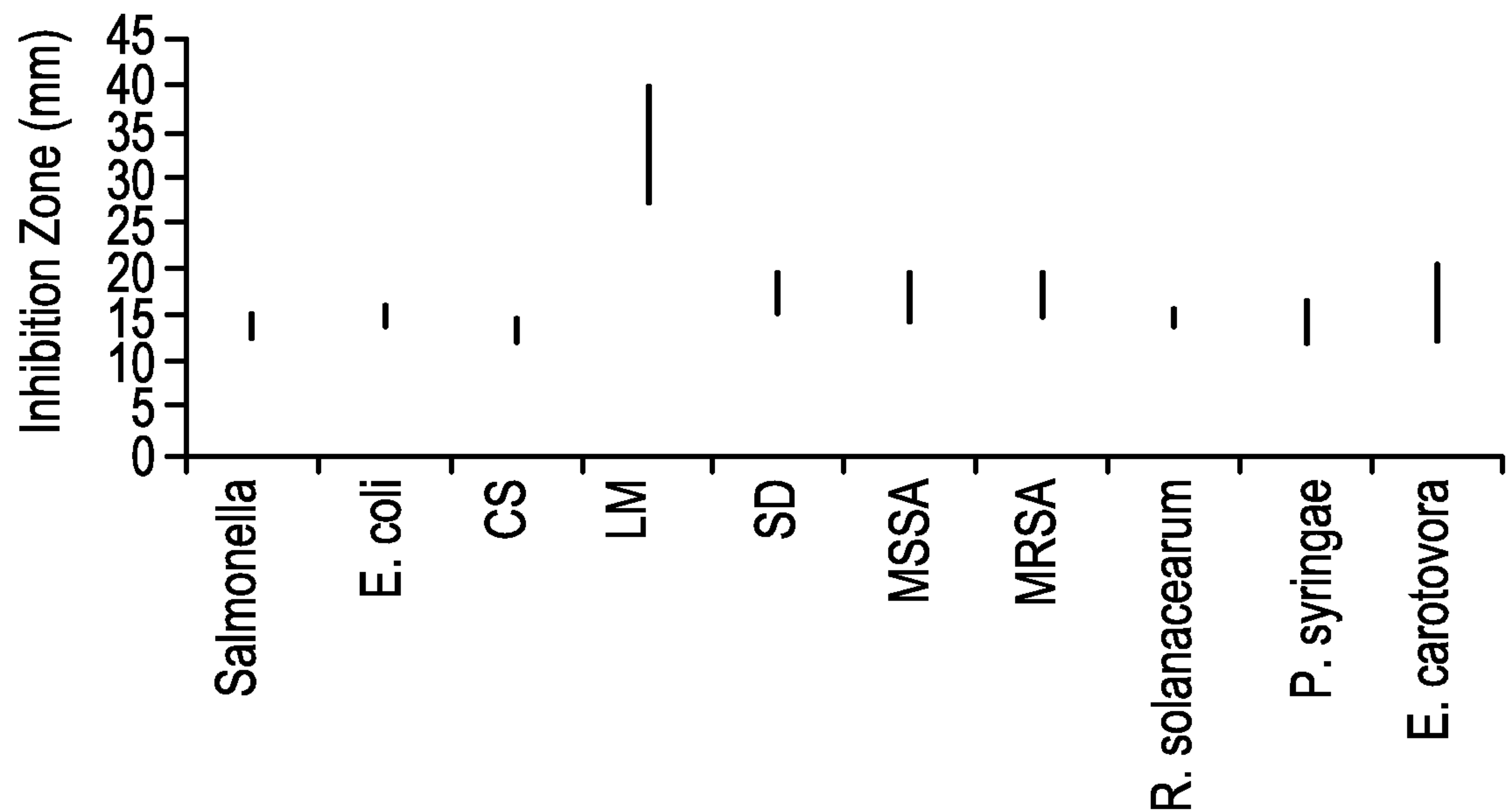
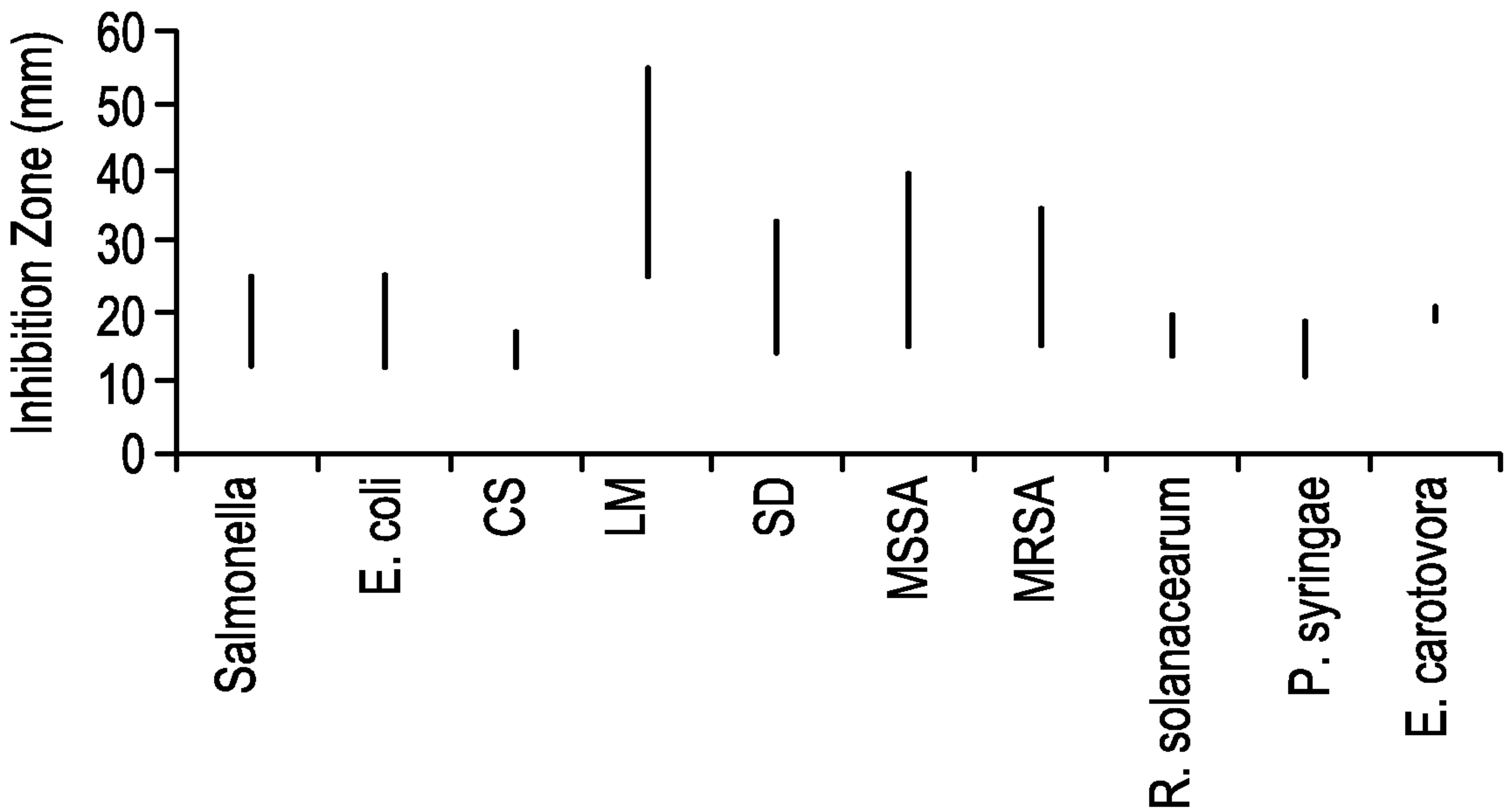


FIG. 1B



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FIG. 2A

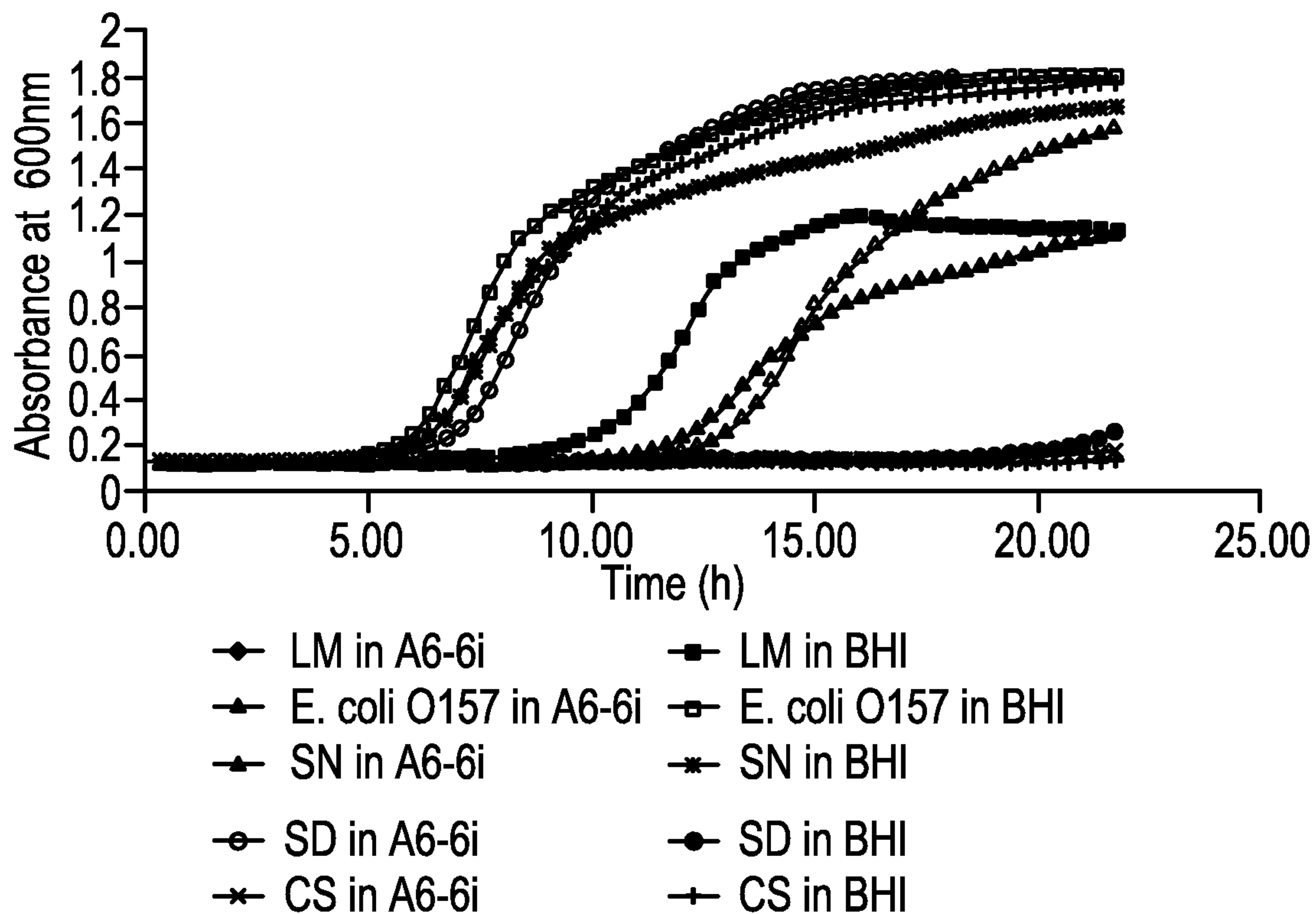
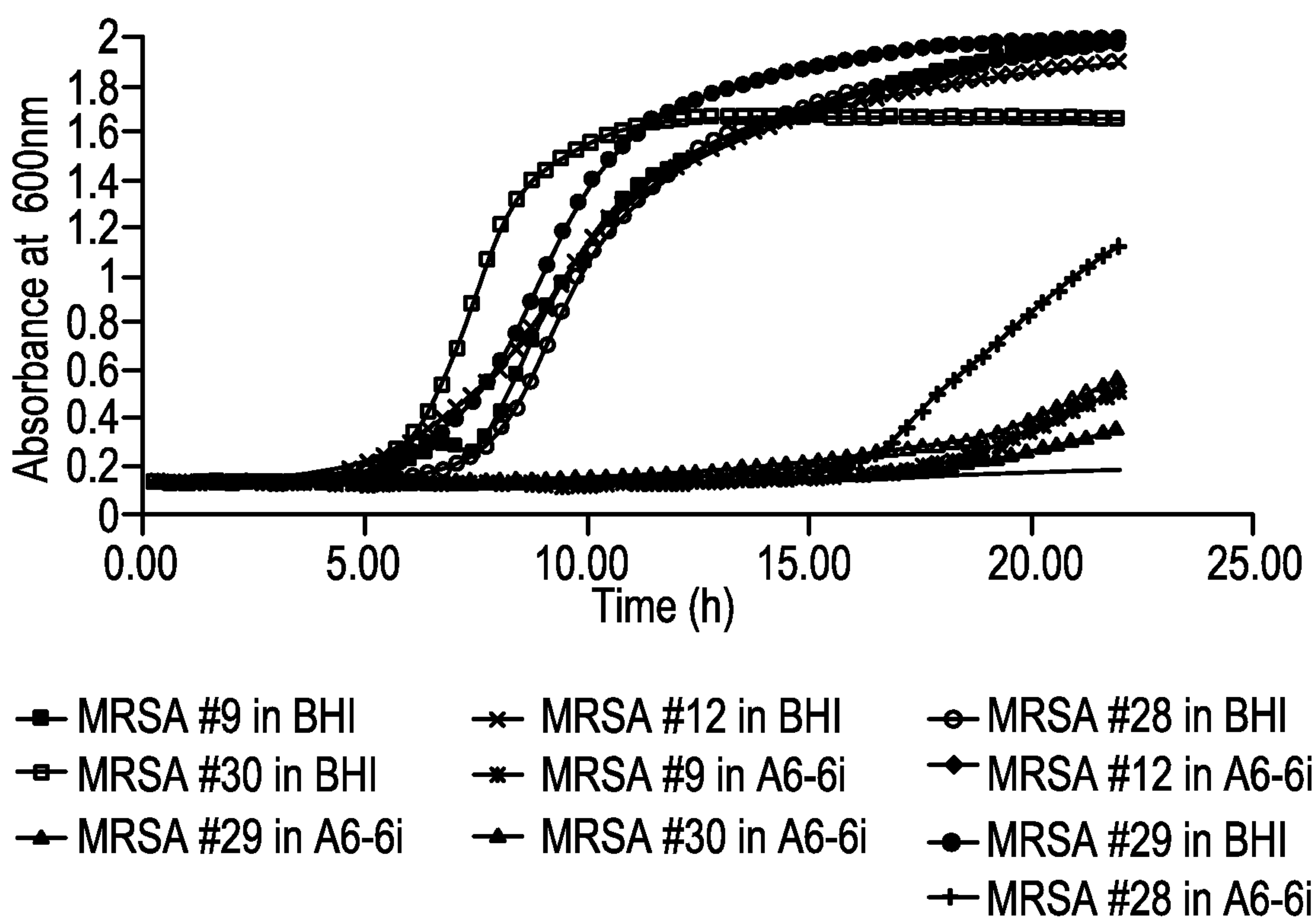
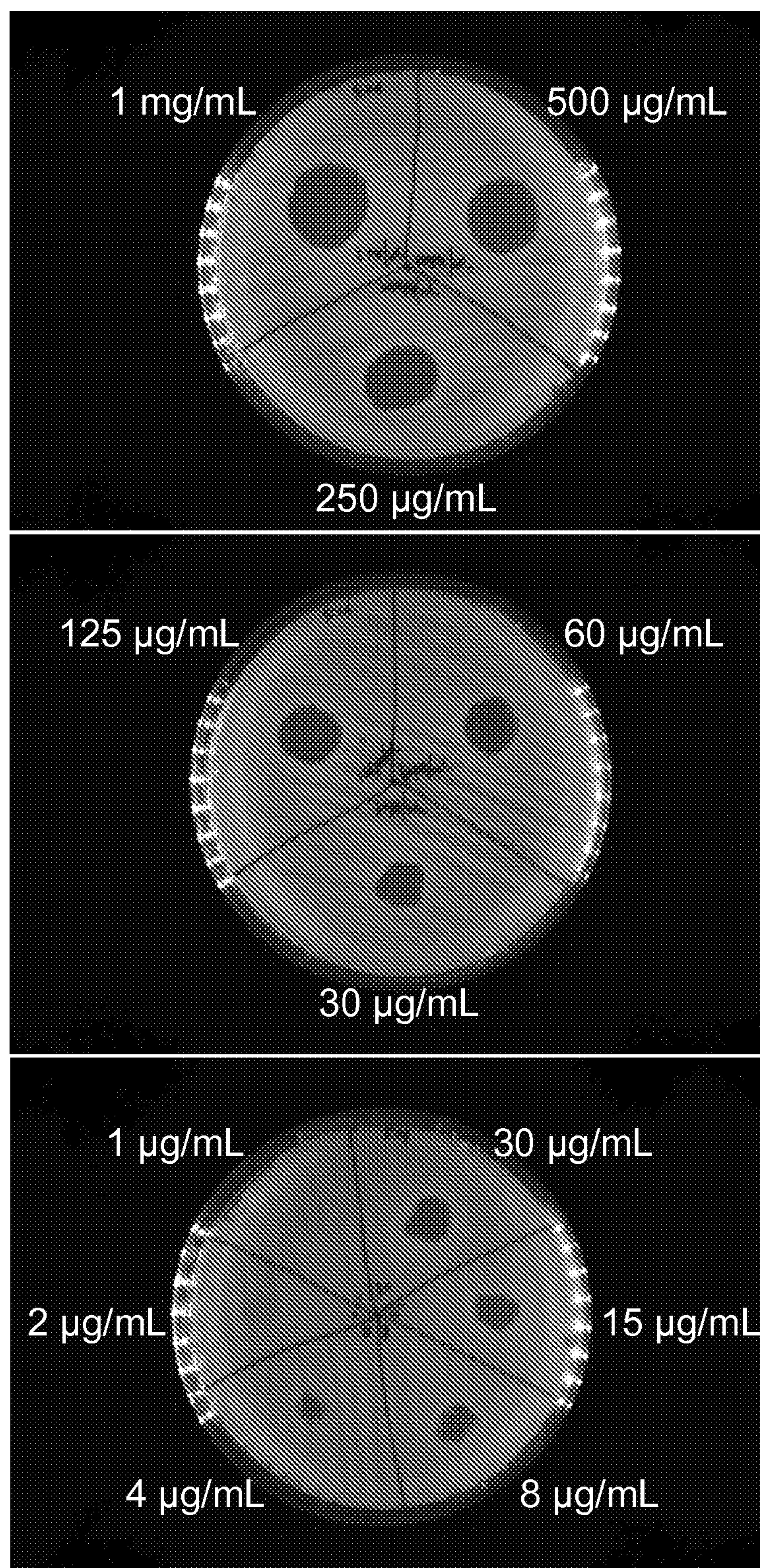


FIG. 2B



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FIG. 3



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FIG. 4

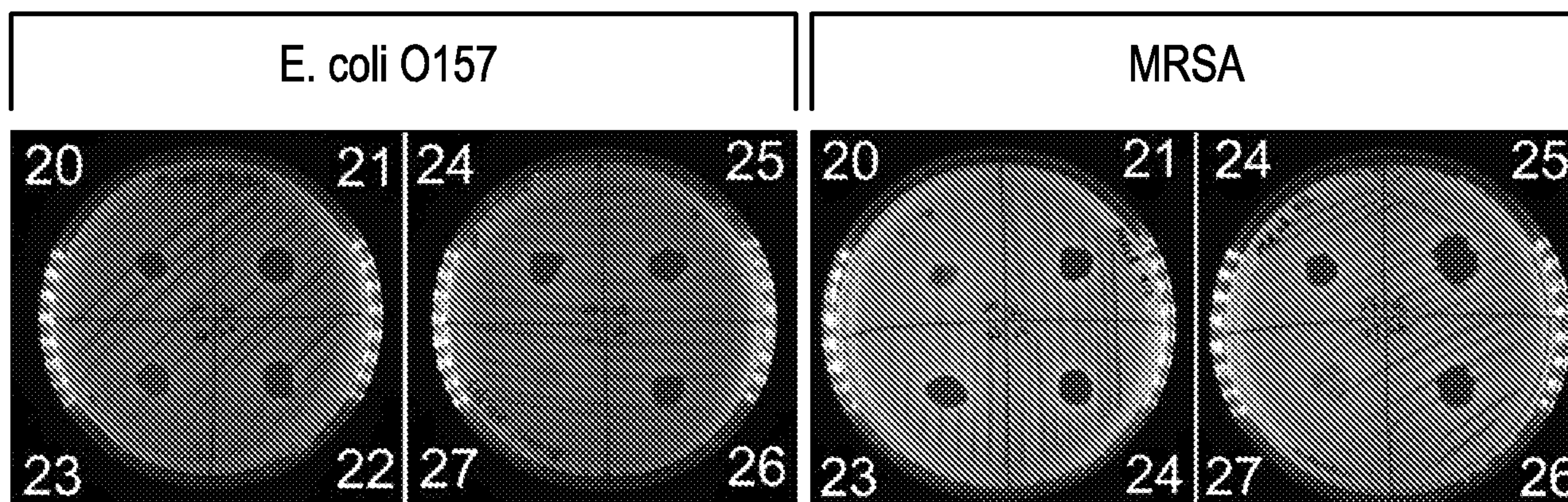


FIG. 5

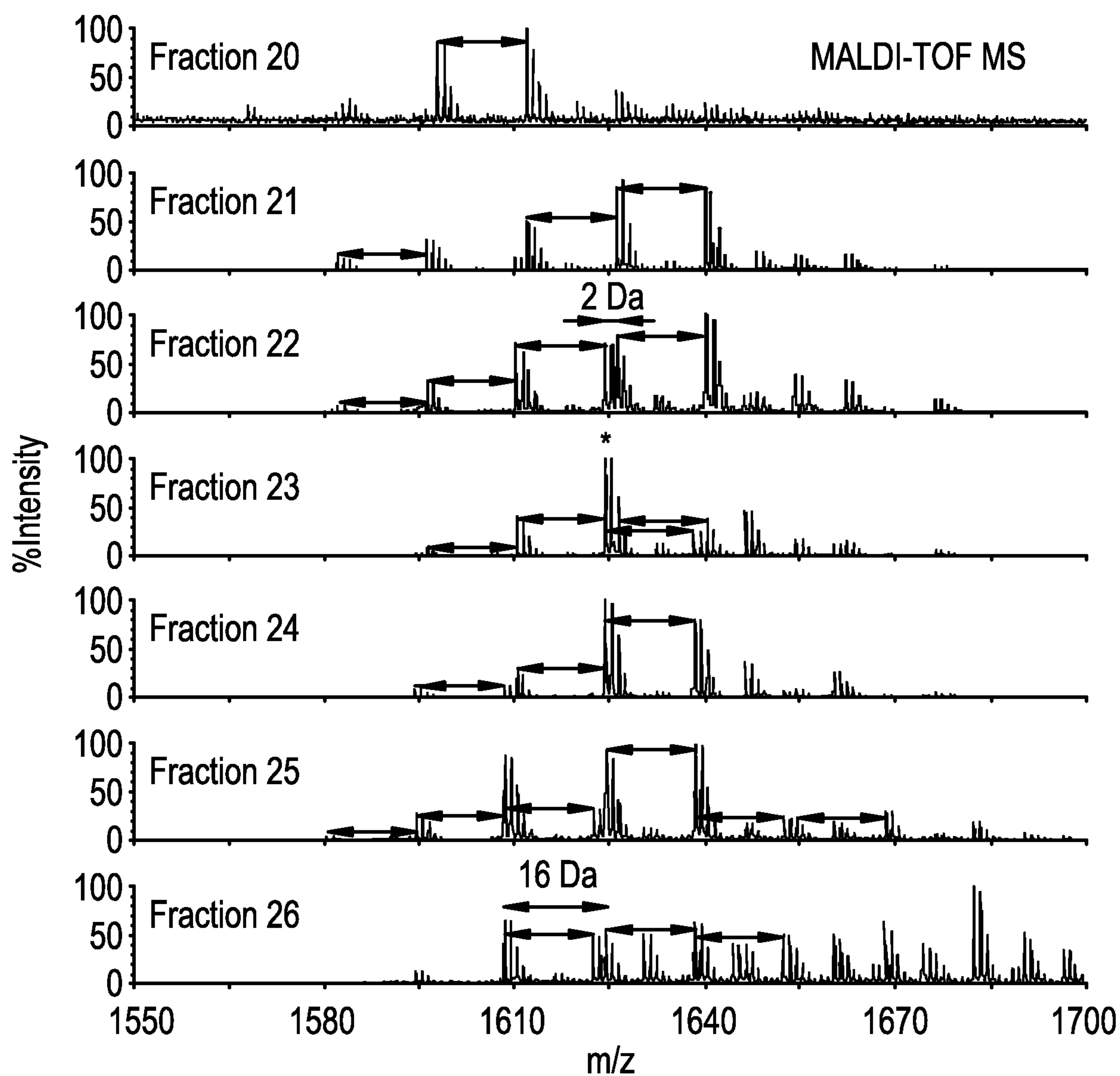


FIG. 6

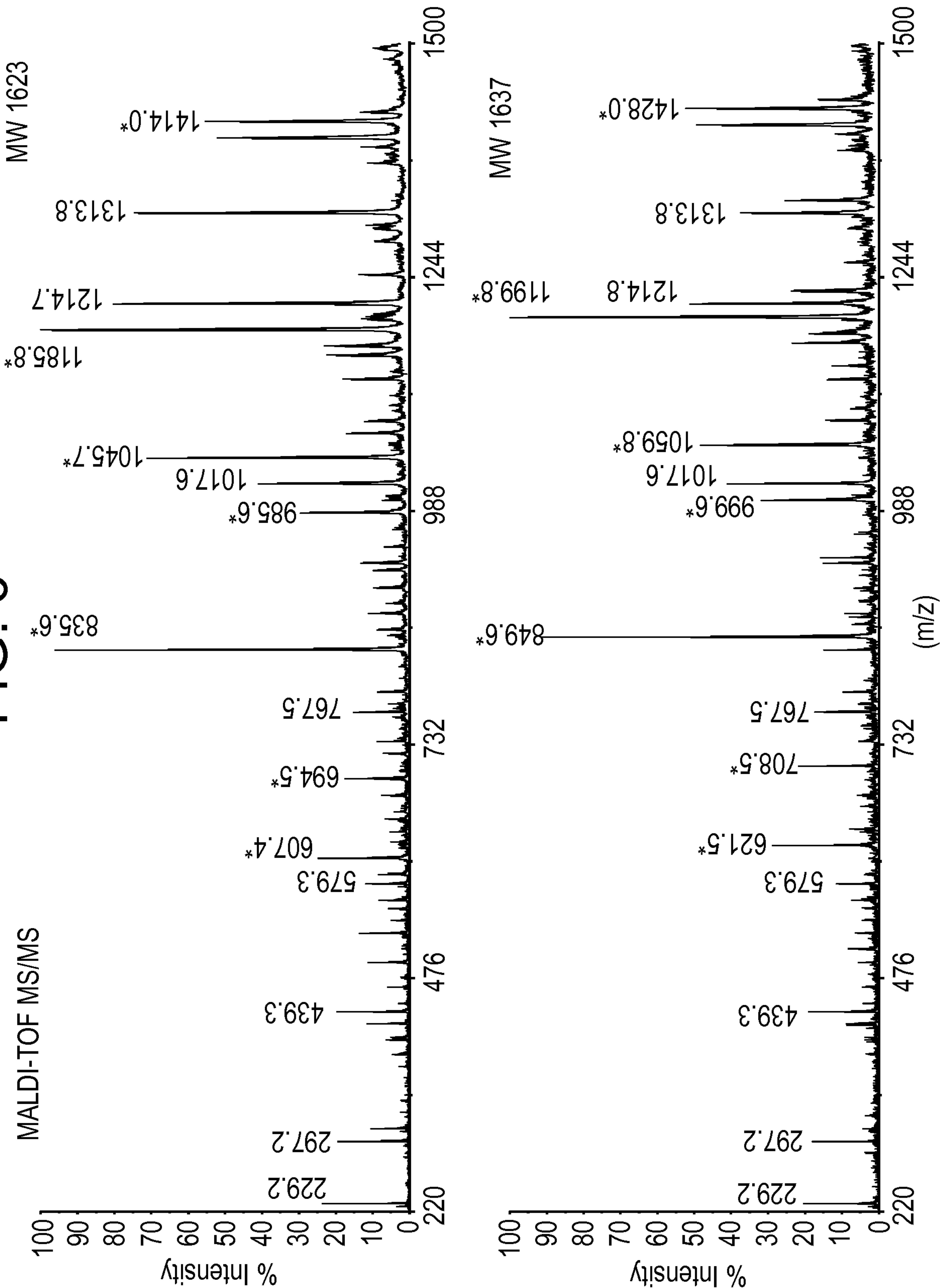


FIG. 7

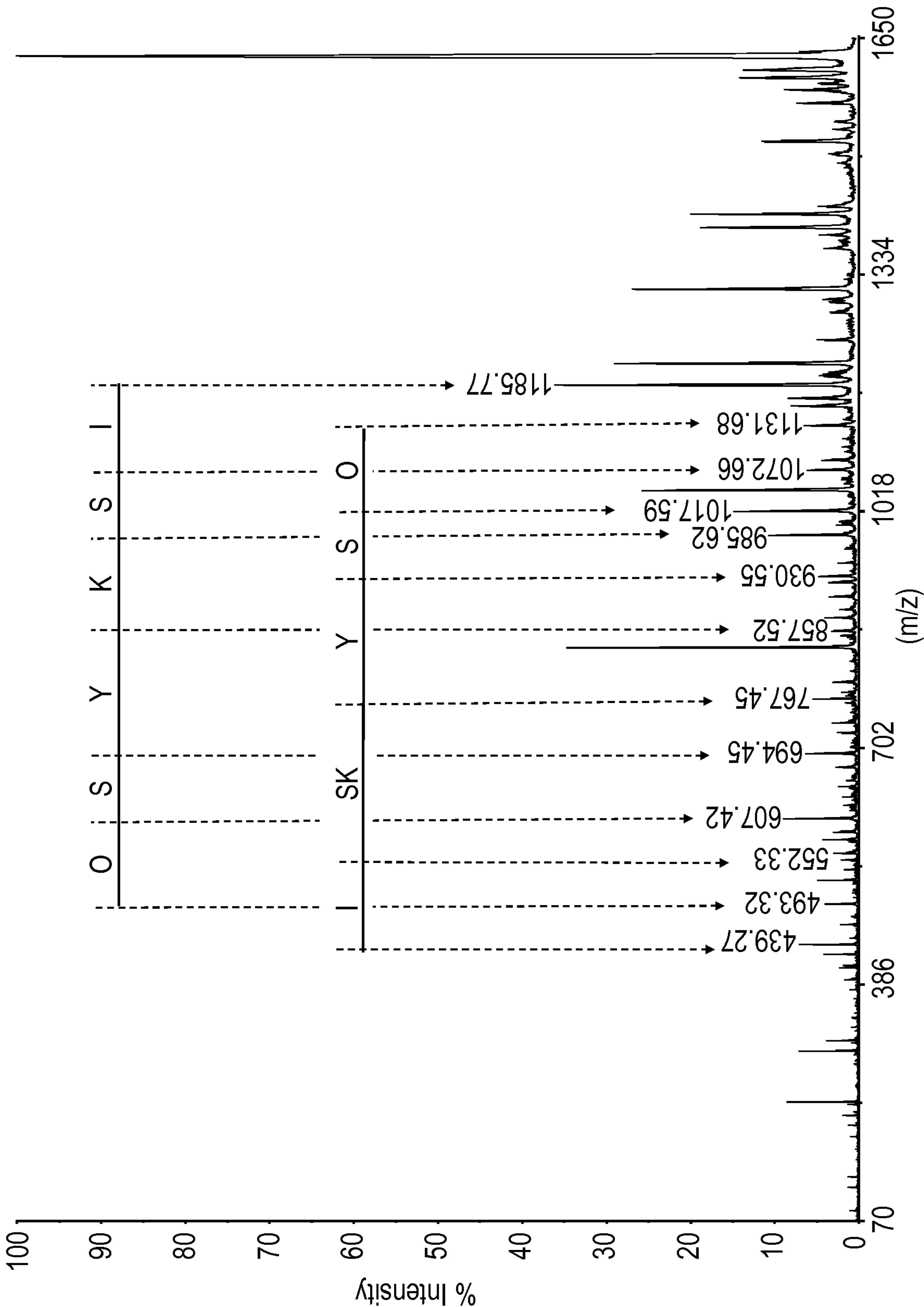


FIG. 8A  
Prior Art

SEQ ID NO. 78

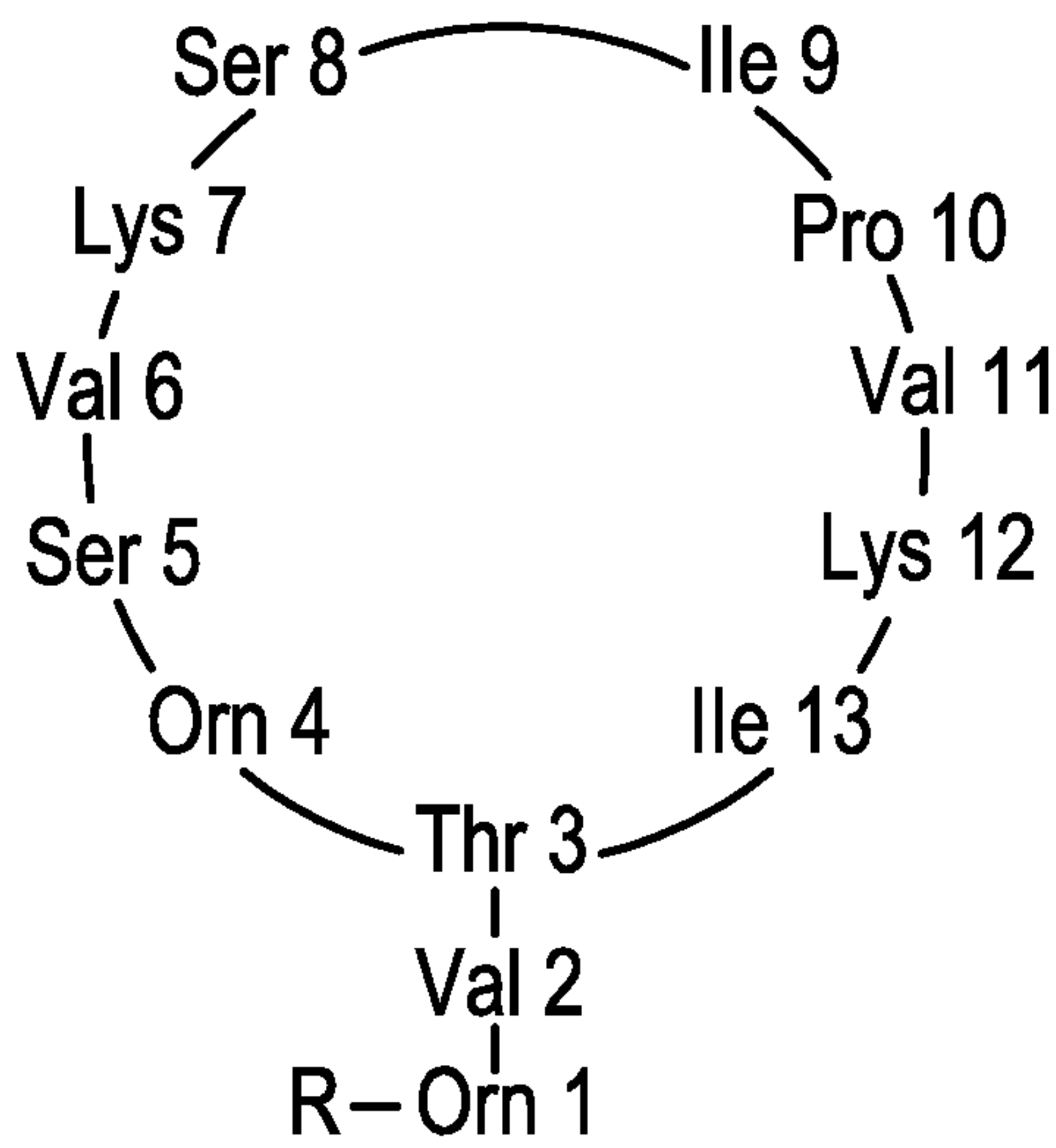
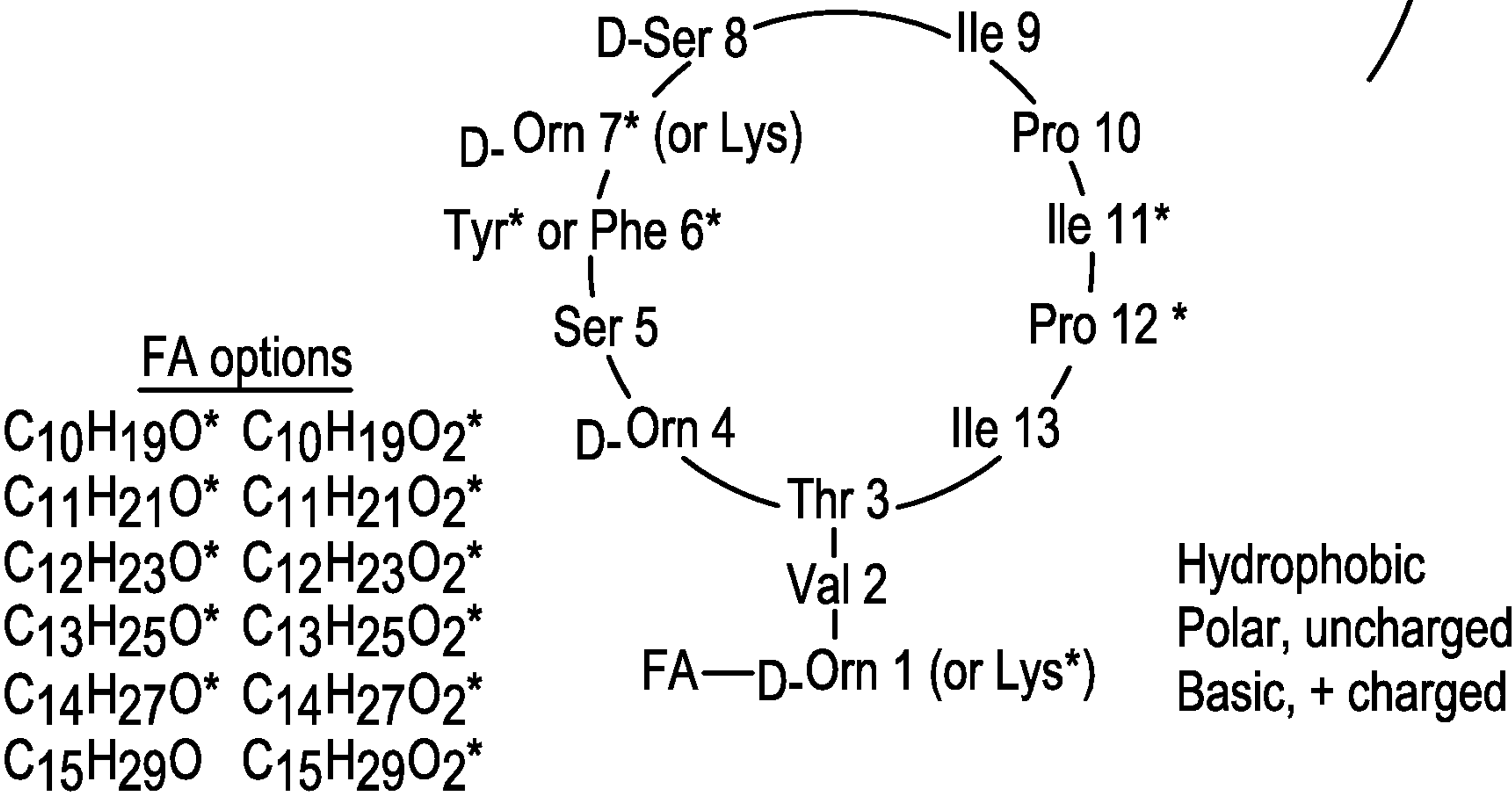


FIG. 8B

Compound of the present invention SEQ ID NO. 4

Compounds Identified in this Work



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FIG. 9

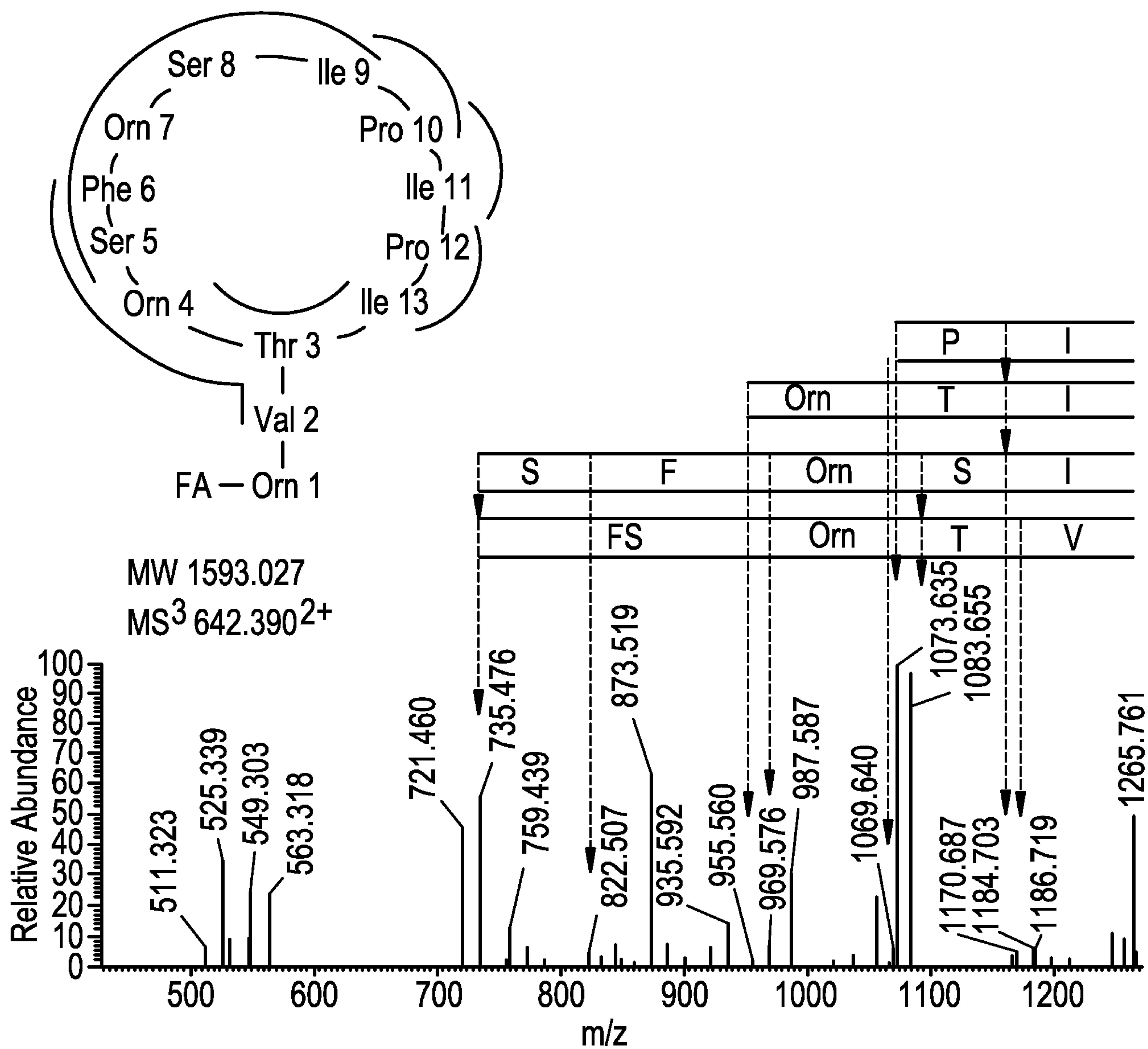
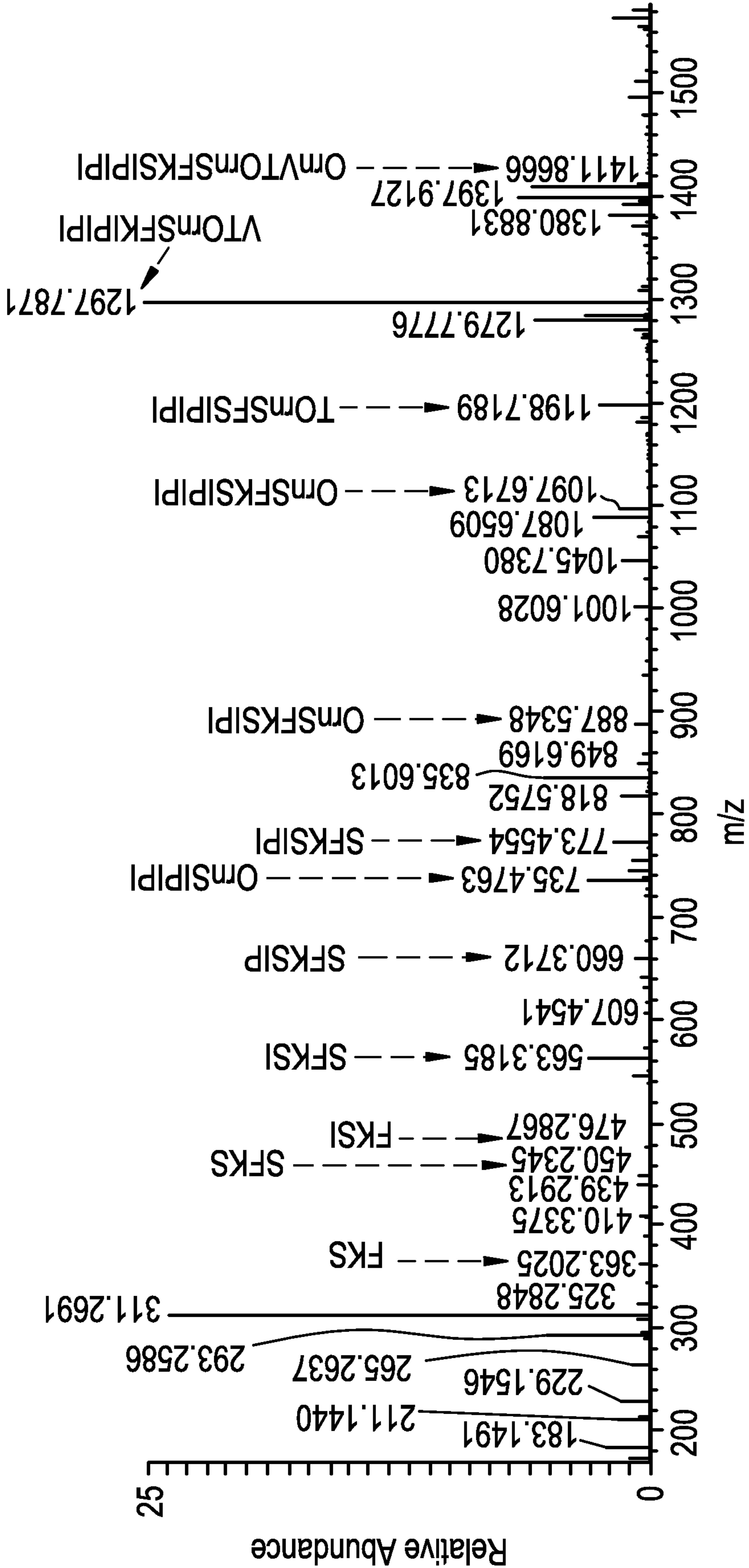


FIG. 10A

MV 1607, F



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FIG. 10B

MW 1623, Y

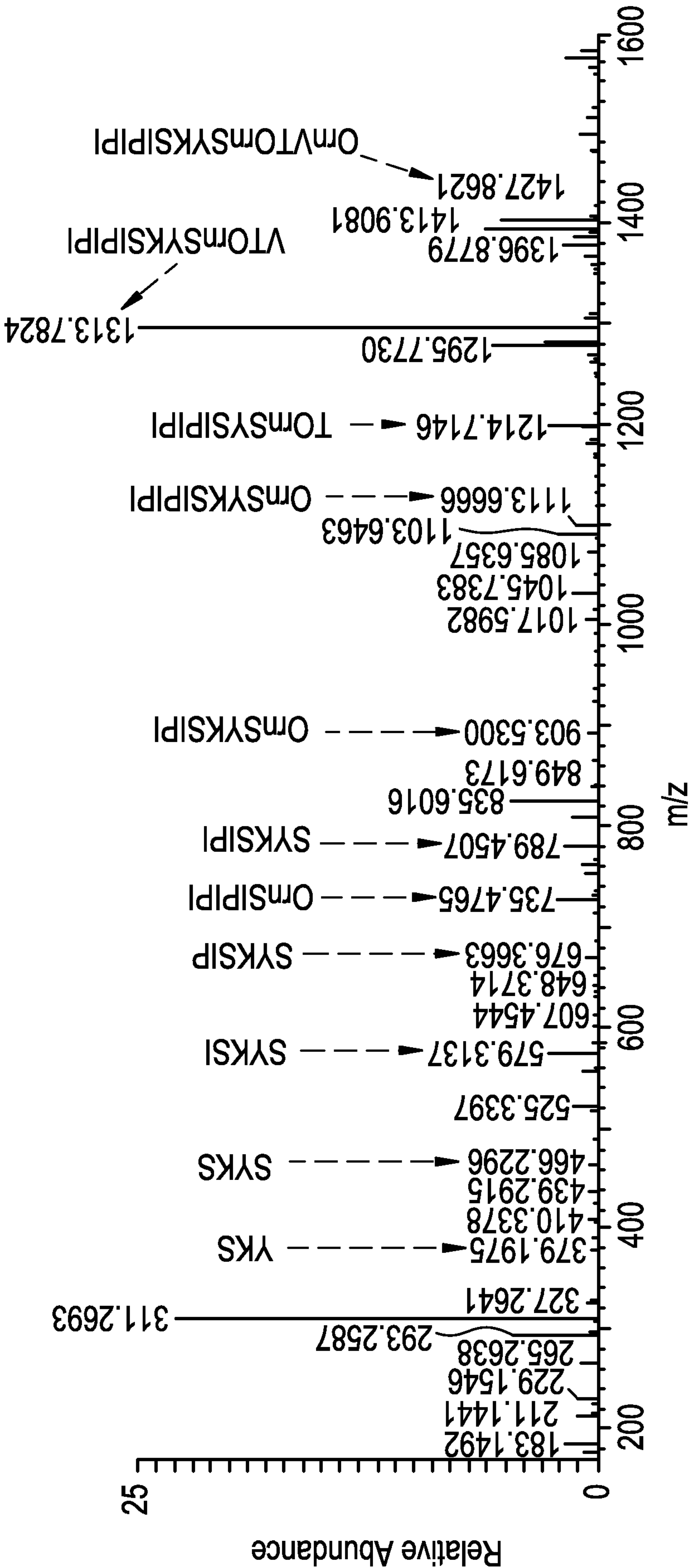


FIG. 11

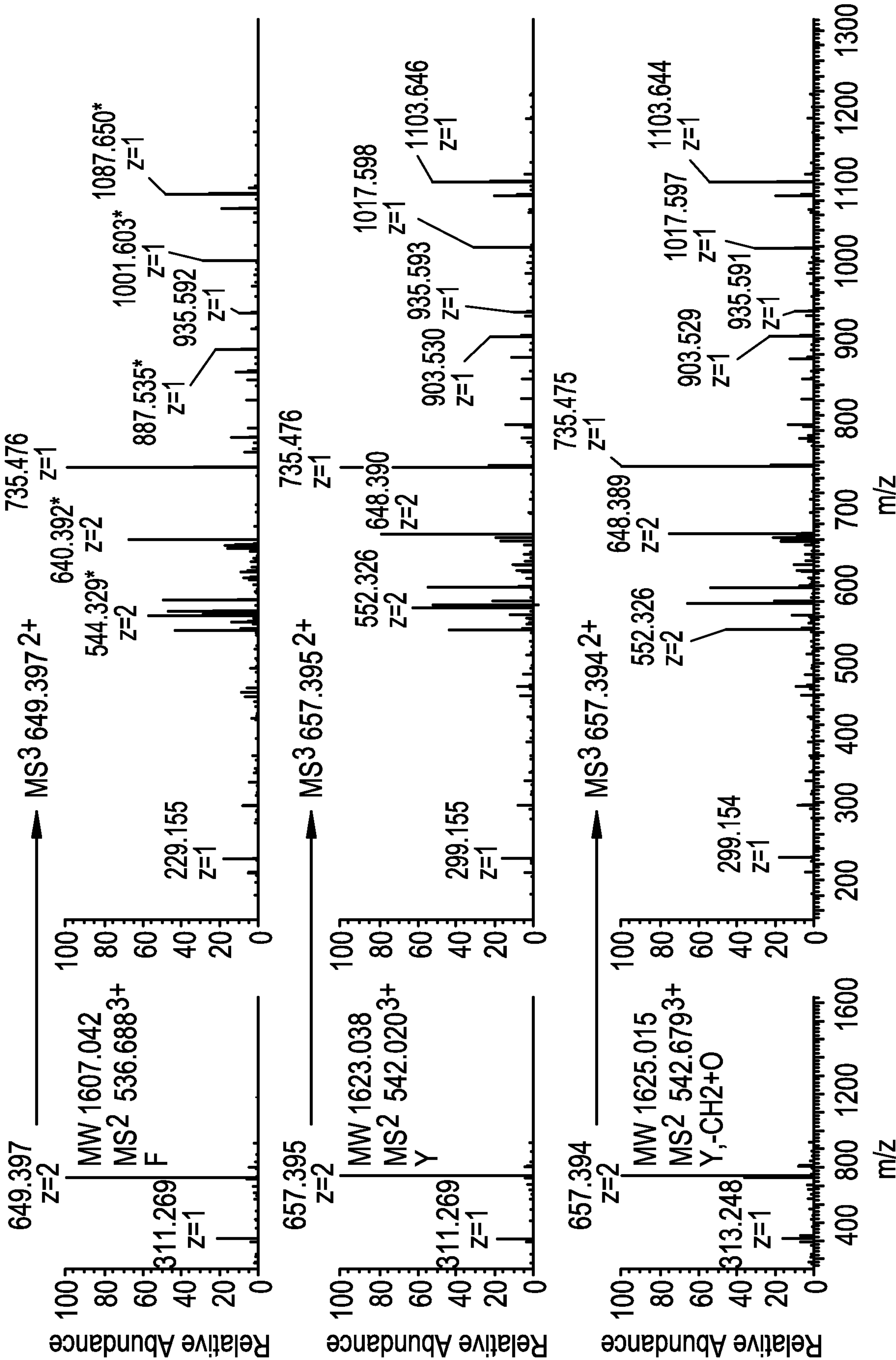
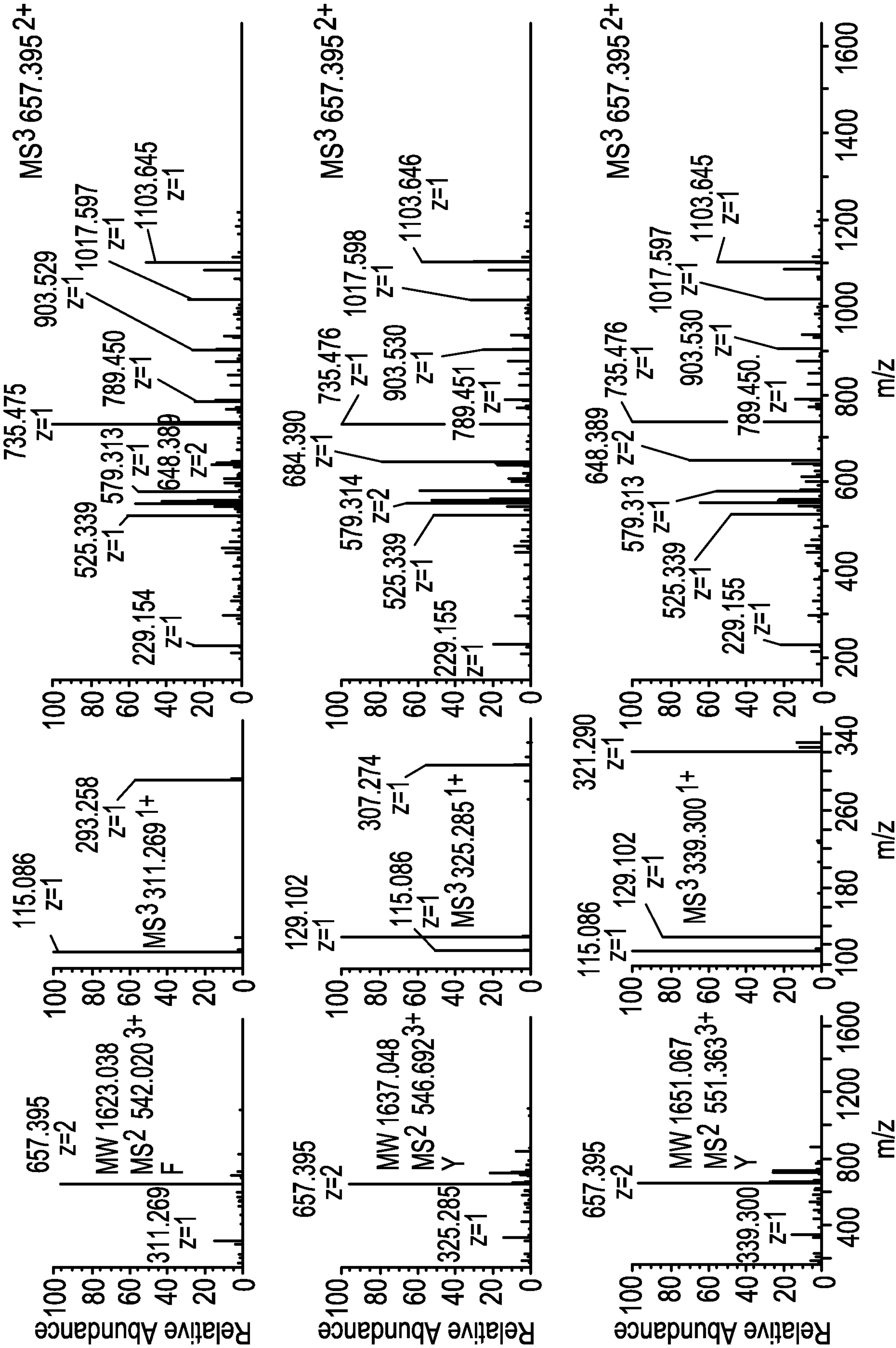


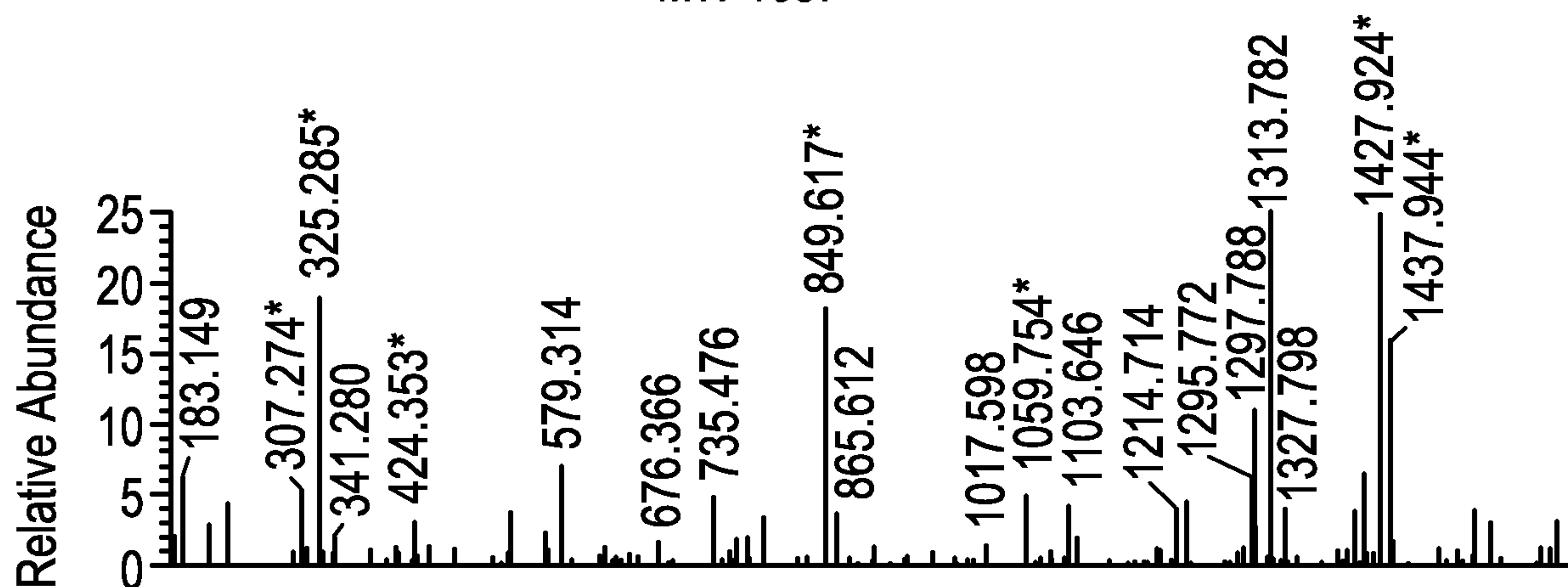
FIG. 12



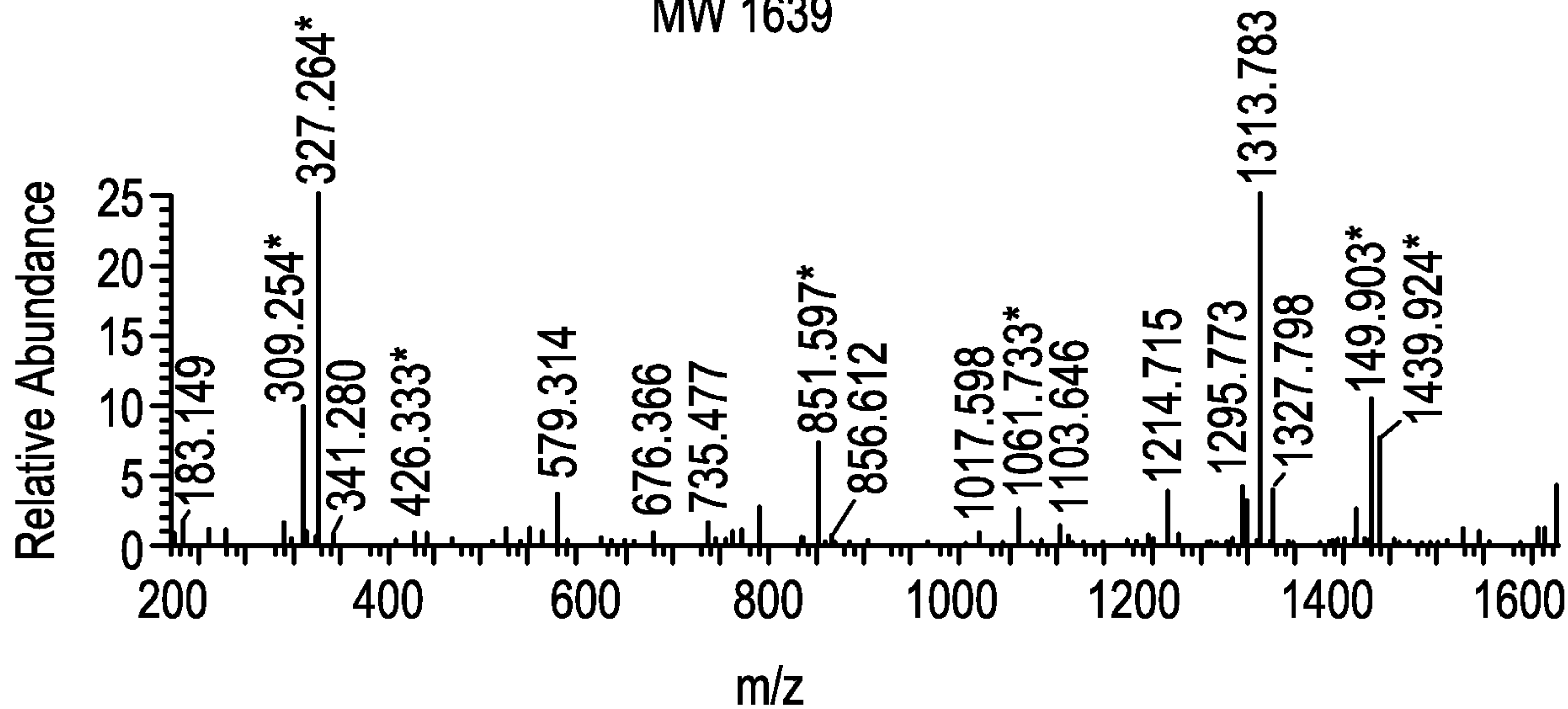
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**FIG. 13**

MW 1637

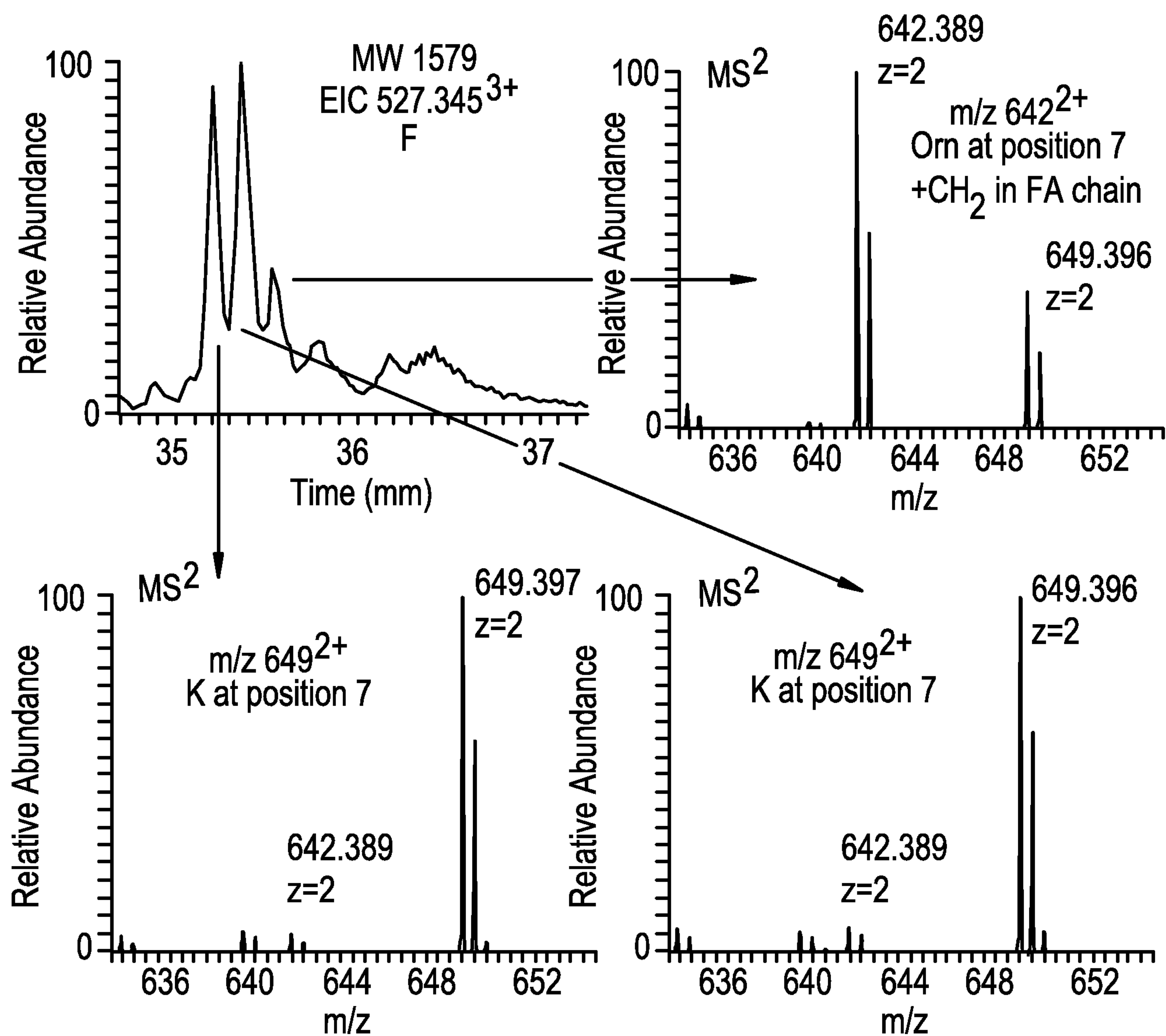


MW 1639



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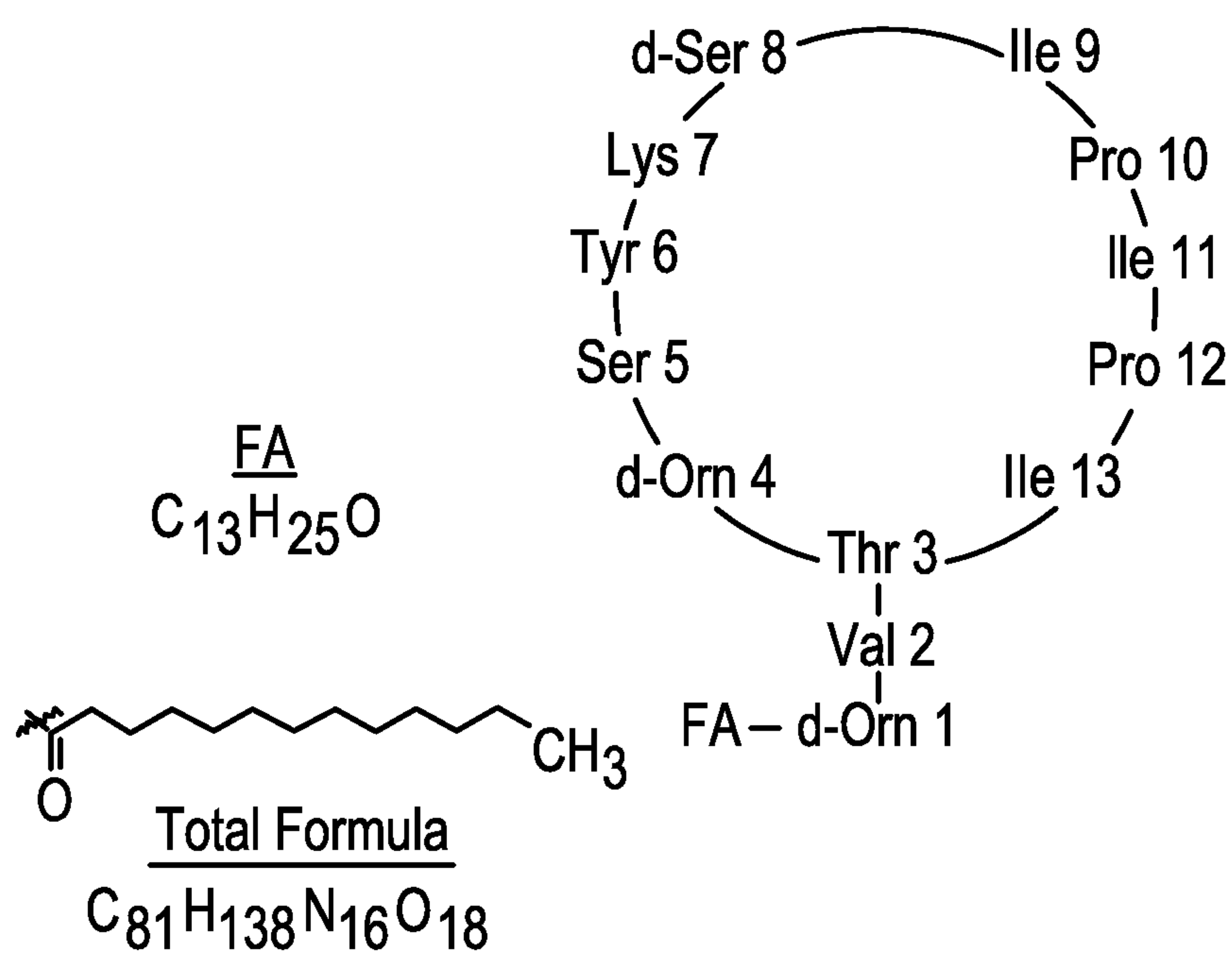
FIG. 14



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# FIG. 15

(SEQ ID NO. 77)



SUBSTITUTE SHEET (RULE 26)

FIG. 16B

|             |      |                                                                  |
|-------------|------|------------------------------------------------------------------|
| A6_61_pbtA  | 541  | VPIDPEYPEERILYMLEDSENARVLVSQSHLQTRSGYTGTVVLLBSENDYEAARDNLSESVN   |
| TS_15_pbtA  | 541  | VPIDPEYPEERILYMLEDSENARVLVSQSHLQTRSGYTGTVVLLBSENDYESSRDNLVFTVN   |
| OSY_SE_pbtA | 519  | VPIDPEYPEERILYMLEDSENARVLVSQSHLQTRSGYTGTVVLLBSENAFYSEDGCTNLESEN  |
| A6_61_pbtA  | 601  | EAHHLLAYVIYTSGETCKPKGVMIEHKQITALGDANKHAYQLDESCHRTLOWASFSFDVPT    |
| TS_15_pbtA  | 601  | EAHHLLAYVIYTSGETCKPKGVMIEHKQITALGDANKHAYQLDEFCGRTLOWASFSFDVPT    |
| OSY_SE_pbtA | 579  | QPSNLSYVIYTSGETCKPKGVMIEHESQVNAHANKSRVHELHEAGIEFELQWASFSFDVPT    |
| A6_61_pbtA  | 661  | GDMVRALLYGCGELIICPSEARANPEAICELIARHRIHIFESTPALVIPLMIEYVHECCKDV   |
| TS_15_pbtA  | 661  | GDMVRALLYGCGELIICPSEARANPEAICELIARHRIHIFESTPALVIPLMIEYVHECCKDV   |
| OSY_SE_pbtA | 639  | GDMVRALLYGCGELIICPSEARANPEAICELIARHRIHIFESTPALVIPLMIEYVHECCKDV   |
| A6_61_pbtA  | 721  | SSLRLLVVGSDDHCPAAEYRKLMERFSSQMRILNSYGVTEACVDACVYENCGSVDSITMLP    |
| TS_15_pbtA  | 721  | SSLRLLVVGSDDHCPAAEYRKLMERFSSQMRILNSYGVTEACVDACVYENCGSVDSITMLP    |
| OSY_SE_pbtA | 699  | HSLQLLVVGSDDHCPAAEYRKLMERFSSQMRILNSYGVTEACVDACVYENCGSVDSITMLP    |
| A6_61_pbtA  | 781  | IGKPLPSVSMYILDENKALQPIGIVGELIIGSAGVGRGYLNRDDLTAEKPVDDPYSQGX      |
| TS_15_pbtA  | 781  | IGKPLPSVSMYILDENKALQPIGIVGELIIGSAGVGRGYLNRDDLTAEKPVDDPYSQGX      |
| OSY_SE_pbtA | 758  | IGKPLPSVSMYILDENKALQPIGIVGELIIGSAGVGRGYLNRDDLTAEKPVDDPYSQGX      |
| A6_61_pbtA  | 840  | MYRTGDLARWLPPDGNIEYLGRLDDEQVKIRGNRIEIGELIETRMLOQTSLVREAVIVAREDEN |
| TS_15_pbtA  | 840  | MYRTGDLARWLPPDGNIEYLGRLDDEQVKIRGNRIEIGELIETRMLOQTSLVREAVIVAREDEN |
| OSY_SE_pbtA | 818  | MYRTGDLARWLPPDGNIEYLGRLDDEQVKIRGNRIEIGELIETRMLOQTSLVREAVIVAREDEN |
| A6_61_pbtA  | 900  | CLKALCAYYVADSEISVQQLRSTLAEQVPDYMIPSEYFMKLERLPLTNGKIDRNGCLPAP     |
| TS_15_pbtA  | 900  | CLKALCAYYVADSEISVQQLRSTLAEQVPDYMIPSEYFMKLERLPLTNGKIDRNGCLPAP     |
| OSY_SE_pbtA | 878  | CLKALCAYYVADSEISVQQLRSTLAEQVPDYMIPSEYFMKLERLPLTNGKIDRNGCLPAP     |
| A6_61_pbtA  | 960  | GQDYSGKIYVEPRNCAEQTLASIMKMLVLCYKRVGILDDHFFELGCDSEIKSIQVSSRMQQAC  |
| TS_15_pbtA  | 960  | GQDYSGKIYVEPRNCAEQTLASIMKMLVLCYKRVGILDDHFFELGCDSEIKSIQVSSRMQQAC  |
| OSY_SE_pbtA | 938  | GQDYSGKIYVEPRNCAEQTLASIMKMLVLCYKRVGILDDHFFELGCDSEIKSIQVSSRMQQAC  |
| A6_61_pbtA  | 1020 | YKLDIRDLFKYPTIEQISPHLVEVQKKAQCGEESSGEVGLTPILRWYFQRDEVSLHHYNOS    |
| TS_15_pbtA  | 1020 | YKLDIRDLFKYPTIEQISPHLVEVQKKAQCGEESSGEVGLTPILRWYFQRDEVSLHHYNOS    |
| OSY_SE_pbtA | 998  | YKLDIRDLFKYPTIEQISPHLVEVQKKAQCGEESSGEVGLTPILRWYFQRDEVSLHHYNOS    |

FIG. 16C

|        |      |      |                                                                |
|--------|------|------|----------------------------------------------------------------|
| A6_61  | Pbta | 1080 | IMLHRKAGPDEAALRNALSHKITEHHDALRMVFRKTEQCEYAAWNRRIEEGELYRLVLDI   |
| TS_15  | Pbta | 1080 | IMLHRKAGPDEAALRNALSHKITEHHDALRMVFRKTEQCEYAAWNRRIEEGELYRLVLDI   |
| OSY_SE | Pbta | 1058 | IMLYRKEGPDAAARKTIERIAEHHDALRMVFRKTES-YAAWNRRIEEGELYRLVMADE     |
| A6_61  | Pbta | 1140 | KERSAGVSESESLHNNLAAZANVIOGPHIEAGPLVGCAGLFRCPDGHLLIVIHHAVIDA    |
| TS_15  | Pbta | 1140 | KERSAGVSESESLHNNLAAZADAIOGCFMEEAGPLVGCAGLFRCPDGHLLIVIHHAVIDA   |
| OSY_SE | Pbta | 1117 | ENESACCP-----LIAQANEIOGIDIEGELVEAGLFCADGDHLLIVIHHTVIDE         |
| A6_61  | Pbta | 1200 | VSWRILLEDLATGYEQALCGSEIRLPCKIDSPRLWRRLSAYAQQSNMNEELKYMEQVAC    |
| TS_15  | Pbta | 1200 | VSWRILLEDLATGYEQALCGSEIRLPCKIDSPRLWRRLSAYAQQSNMNEELKYMQQVAC    |
| OSY_SE | Pbta | 1170 | VSWRILLEDMATGYEQALKGSEIRLPCKIDARTMSEERLASADSQTWINERAYMQARTO    |
| A6_61  | Pbta | 1260 | TTITPLPTDY-AGIALCGDSESVTVENSASETELLKQAHRAYNTOEMDDLLLTALCIAFR   |
| TS_15  | Pbta | 1260 | TTITPLPTDY-AGTALCGDSESVTVENSASETELLKQAHRAYNTOEMDDLLLTALCIAFR   |
| OSY_SE | Pbta | 1230 | TEMNPLPKDYADCSLODSESVINOMSEETECLLKHVHAYNTEEMDDLLLTALCTAVQ      |
| A6_61  | Pbta | 1319 | RWCCHERIRINLECHGRESILPDLDIRTVGMFTSEYPPQLLEVGSSEELPRIIKSVKEDL   |
| TS_15  | Pbta | 1319 | RWCCHERIRINLECHGRESILPDLDIRTVGMFTSEYPPQLLEVGSSEELPRIIKSVKEDL   |
| OSY_SE | Pbta | 1290 | RWSCRRRLINLECHGRESIADNDISRTVGMFTSEYPVLLLEEQAKGGSYRIKSVKEDL     |
| A6_61  | Pbta | 1379 | RSIPNKIGICYGICRYLSENTGICEVYNGTAPESVPNYLGQPDQDFONSGFSPYSTGSGNIG |
| TS_15  | Pbta | 1379 | RSIPNKIGICYGICRYLSDKSMQDNDGTAPESVPNYLGQPDQDFONSGFSPYSTGSGNIG   |
| OSY_SE | Pbta | 1350 | RQIPNKIGICYGICRYSEELPYEASNGANPESSPNYLGQPDQDFONSGMLSPDSGSGNTS   |
| A6_61  | Pbta | 1439 | GDQLRPYLLDMNGMVSDBCKLQDLISYGRTOYRAETIERLASLIRDELIERIIEHCVAKERN |
| TS_15  | Pbta | 1439 | GDQLRPYLLDMNGMVSDBCKLQDLISYGRTOYRAETIERLASLIRDSLLERIEHCVAKERN  |
| OSY_SE | Pbta | 1410 | GNQARQNALDNGMMDGSLVFDSEYGSXEXERRETIEDLACHECEIIRZETIAHCTAKERE   |
| A6_61  | Pbta | 1499 | ELTPSDVSLORISIQELEQIVERTSGIGEVEDIYALTPMQKGMWFHTAMDSQAGAYFEIT   |
| TS_15  | Pbta | 1499 | ELTPSDVSLORISIQELEQIVERTSGIGEVEDIYALTPMQKGMWFHTAMDSQAGAYFEIT   |
| OSY_SE | Pbta | 1470 | ELTPSDVSLQGSVELEQIVECTQHIGQENNYKLTTPMQKGMWFHTAMDRQAGAYFEIT     |
| A6_61  | Pbta | 1559 | RLTLEGTLNIEAPASWNEELAAAHAVPTNPLVDNNGEPLQVVFPSKRISVHEHEDLRSIN   |
| TS_15  | Pbta | 1559 | RLTLEGTLNIEAPASWNEELAAAHAVPTNPLVDNNGEPLQVVFPSKRISVHEHEDLRSIN   |
| OSY_SE | Pbta | 1530 | RFTLQCDLQVAPAKSWTALAAHHTVPTNPLHNGWKGEPLQVVFPSKRISVHEHEDLRSIN   |

FIG. 16D

|        |      |      |                  |             |             |             |                       |
|--------|------|------|------------------|-------------|-------------|-------------|-----------------------|
| A6_61  | pbta | 1619 | AYEQAVAIENEAAKER | EQCPDLENG   | VMRVSVLQTAD | VEVVLWISHHI | VMDGNCCLPLVA          |
| TS_15  | pbta | 1619 | SEEQAVAIENEAAKER | AQCPDLENG   | VMRVSVLQTAD | VEVVLWISHHI | VMDGNCCLPLVA          |
| OSY_SE | pbta | 1590 | PAKQEAHAIENAVNEE | EQCPDLENG   | VMRVSVLQTAD | VEVVLWISHHI | VMDGNCCLPLVA          |
| A6_61  | pbta | 1679 | AZVFNATYSALVEDKK | PILASVPSYNE | YIQWLERODES | AAAAAYNNN   | YLSGFEETTELPHSK       |
| TS_15  | pbta | 1679 | AZVFNATYSALVEDKK | PILASVPSYNE | YIQWLERODES | AAAAAYNNN   | YLSGFEETTELPHSK       |
| OSY_SE | pbta | 1650 | KRVFDATYSATVRH   | HNLEKT      | TVVPAT      | SOYIENLE    | QODEEAA               |
| A6_61  | pbta | 1729 | GERHSCQYEAGQVQ   | IDPCTSL     | SLALNDVAT   | QHQVTL      | NLLQASWGILLQKYNRTSDI  |
| TS_15  | pbta | 1739 | GERHSCQYEAGQVQ   | IDPCTSL     | SLALNDVAT   | QHQVTL      | NLLQASWGILLQKYNRTSDI  |
| OSY_SE | pbta | 1710 | DQGRSEAPAAEH     | IDCELGKD    | LSERENEA    | KRNLVLL     | SNLLQATNGILLQKYNRTSDI |
| A6_61  | pbta | 1799 | SVVSGRPAELVCI    | EEMICLFINT  | IPRVSSQA    | QERPA       | EVNTRMOEDALS          |
| TS_15  | pbta | 1799 | SVVSGRPAELVCI    | EEMICLFINT  | IPRVSSQA    | QERPA       | EVNTRMOEDALS          |
| OSY_SE | pbta | 1770 | GVVSGRPAELVCI    | EEMICLFINT  | IPRVSSQA    | QERPA       | EVNTRMOEDALS          |
| A6_61  | pbta | 1859 | IQAOCTLKQML      | THIMVLENY   | PMEOQDDQ    | PNSSD       | SGGLKLT               |
| TS_15  | pbta | 1859 | IQAOCTLKQML      | THIMVLENY   | PMEOQDDQ    | PNSSD       | SGGLKLT               |
| OSY_SE | pbta | 1830 | IQAOCTLKQML      | THIMVLENY   | PMEOQDDQ    | PNSSD       | SGGLKLT               |
| A6_61  | pbta | 1919 | DNIIVIRPDPNK     | QAL         | ESAD        | DMNVLK      | QELLHVLEQ             |
| TS_15  | pbta | 1919 | DNIIVIRPDPNK     | QAL         | ESAD        | DMNVLK      | QELLHVLEQ             |
| OSY_SE | pbta | 1890 | DEIVIRLDPNG      | GLVFD       | RTSE        | MEQLK       | CHILNNLEQ             |
| A6_61  | pbta | 1979 | DTFVAAYPREK      | SIHRLP      | PERRA       | ES          | PPDALAVVFC            |
| TS_15  | pbta | 1979 | DTFVAAYPREK      | SIHRLP      | PERRA       | ES          | PPDALAVVFC            |
| OSY_SE | pbta | 1950 | NRVVEYPREK       | SIHRLP      | PERRA       | ES          | PPDALAVVFC            |
| A6_61  | pbta | 2039 | ELVGCICADRS      | LEMVVG      | LAI         | IMK         | SEGA                  |
| TS_15  | pbta | 2039 | ELVGCICADRS      | LEMVVG      | LAI         | IMK         | SEGA                  |
| OSY_SE | pbta | 2010 | TLVGCICADRS      | LEMVVG      | LAI         | IMK         | SEGA                  |
| A6_61  | pbta | 2099 | WPEHFNVI         | MLD         | -           | VNETD       | VSNLMED               |
| TS_15  | pbta | 2099 | WPEHFNVI         | MLD         | -           | VNETD       | VSNLMED               |
| OSY_SE | pbta | 2070 | VPNSD            | SSVLLD      | AA          | AA          | RTIEG                 |

FIG. 16E

|     |    |      |      |         |    |    |     |     |     |    |    |    |    |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-----|----|------|------|---------|----|----|-----|-----|-----|----|----|----|----|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A6  | 61 | Pbta | 2158 | GVVRLVC | AA | TV | VEI | D   | SSD | VP | LQ | GS | T  | S  | F | D | A | T | F | E | I | N | G | S | L | I | N | G | A | A | L | I | L | P | S | C | N | V | S | L | T | D | M | S | E |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2157 | GVVRLVC | AA | TV | VEI | N   | SSD | VP | LQ | GS | T  | S  | F | D | A | T | F | E | I | N | G | S | L | I | N | G | A | A | L | I | L | P | P | C | N | V | S | L | T | D | M | S |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2126 | GVVRLV  | AD | AA | TV  | VEI | S   | K  | D  | VP | LQ | GS | T | S | F | D | A | T | F | E | I | N | G | S | L | I | N | G | A | A | L | I | L | P | P | C | N | V | S | L | T | D | M |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2218 | AIQEH   | RV | T  | T   | L   | N   | M  | T  | A  | C  | L  | F | Q | V | N | V | E | Q | I | E | C | F | Y | C | V | K | Q | L | L | V | G | C | D | V | V | S | P | T | H | V | R | K | V | M | E | K | H | N | G |
| TS  | 15 | Pbta | 2217 | AIQEH   | RV | T  | T   | L   | N   | M  | T  | A  | C  | L  | F | Q | V | N | V | E | Q | I | E | C | F | Y | C | V | K | Q | L | L | V | G | C | D | V | V | S | P | T | H | V | R | K | V | M | E | K | H | N |   |
| OSY | SE | Pbta | 2186 | AIQ     | CH | Q  | V   | T   | L   | N  | M  | T  | A  | C  | L | F | Q | V | N | V | E | Q | I | E | C | F | Y | C | V | K | Q | L | L | V | G | C | D | V | V | S | P | T | H | A | T | K | V | E | E | Y |   |   |
| A6  | 61 | Pbta | 2278 | GYG     | P  | T  | E   | N   | T   | T  | F  | T  | C  | C  | H | T | I | T | A | A | D | L | D | R | C | - | S | I | P | I | C | R | P | I | S | E | T | E | V | V | L | D | E | A | G | N | A | L | P |   |   |   |
| TS  | 15 | Pbta | 2277 | GYG     | P  | T  | E   | N   | T   | T  | F  | T  | C  | C  | H | T | I | T | A | A | D | L | D | R | C | - | S | I | P | I | C | R | P | I | S | E | T | E | V | V | L | D | E | A | G | N | A | L | P |   |   |   |
| OSY | SE | Pbta | 2246 | GYG     | P  | T  | E   | N   | T   | T  | F  | T  | C  | C  | H | E | L | I | S | A | A | D | E | R | F | - | S | I | P | I | C | R | P | I | S | E | T | E | V | V | L | D | E | A | G | N |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2338 | DGL     | A  | R  | C   | Y   | L   | N  | R  | P  | E  | L  | T | A | E | K | F | V | N | D | P | I | P | C | E | R | L | Y | R | T | G | D | L | A | E | N | L | P | D | G | S | I | E | F | I | C |   |   |   |   |
| TS  | 15 | Pbta | 2336 | DGL     | A  | R  | C   | Y   | L   | N  | R  | P  | E  | L  | T | A | E | K | F | V | N | D | P | I | P | C | E | R | L | Y | R | T | G | D | L | A | E | N | L | P | D | G | S | I | E |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2305 | DGL     | A  | R  | C   | Y   | L   | N  | R  | P  | E  | L  | T | A | E | K | F | V | N | D | P | I | P | A | T | R | L | I | R | T | G | D | L | A | E | N | L | P | D |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2398 | I       | E  | P  | C   | E   | V   | L  | A  | Y  | L  | L  | R | I | D | E | V | G | E | A | A | V | I | A | R | E | D | S | S | G | Q | K | E | L | C | A | Y | F | T | I | E | A |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2396 | I       | E  | P  | C   | E   | V   | L  | A  | Y  | L  | L  | R | I | D | E | V | G | E | A | A | V | I | A | R | E | D | S | S | G | Q | K | E | L | C | A | Y | F | T | A |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2365 | I       | E  | L  | G   | E   | V   | E  | A  | H  | L  | L  | V | E | F | M | Q | S | A | A | V | I | A | R | K | E | D | S | G | Q | N | L | C | A | Y | F | A |   |   |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2458 | I       | P  | S  | H   | P   | I   | Q  | I  | E  | E  | L  | P | L | T | P | N | G | K | V | D | R | R | A | L | P | - | Q | P | E | C | E | C | H | E | N | I | Q | - | I |   |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2456 | I       | P  | S  | H   | P   | I   | Q  | I  | E  | E  | L  | P | L | T | P | N | G | K | V | D | R | R | A | L | P | - | P | E | C | E | C | H | E | N | I | Q | - | I |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2425 | I       | P  | H  | F   | Q   | V   | E  | R  | P  | L  | T  | P | N | G | K | V | D | R | R | A | L | P | E | P | E | C | E | R | I | N | T | G | H | E | H | V |   |   |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2517 | V       | E  | V  | I   | D   | S   | F  | F  | E  | L  | G  | C | H | S | L | R | A | T | T | L | V | S | K | V | H | R | E | L | S | V | V | P | L | Q | D | V | F | R | I | P |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2515 | V       | E  | V  | I   | D   | S   | F  | F  | E  | L  | G  | C | H | S | L | R | A | T | T | L | V | S | K | V | H | R | E | L | S | V | V | P | L | Q | D | V | F | R |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2485 | V       | E  | V  | I   | D   | S   | F  | F  | E  | L  | G  | C | H | S | L | R | A | T | T | L | V | S | K | V | H | R | E | L | S | V | S | P | L | E | V |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2577 | I       | P  | R  | E   | D   | R   | E  | W  | I  | P  | V  | S | S | A | Q | K | R | L | F | V | L | H | O | N | E | G | A | E | L | S | N | M | P | G | V | M | A | I | E | G |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2575 | I       | P  | R  | E   | D   | R   | E  | W  | I  | P  | V  | S | S | A | Q | K | R | L | F | V | L | H | O | N | E | G | A | E | L | S | N | M | P | G | V | M | A | I |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2545 | I       | P  | Q  | V   | C   | R   | E  | C  | I  | P  | V  | S | S | A | Q | K | R | L | F | V | L | H | O | N | E | G | A | E | L | S | N | M | P | G | V | M | A |   |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbta | 2637 | E       | V  | L  | R   | T   | G   | F  | E  | M  | N  | C  | E | P | M | O | R | I | S | D | V | E | T | V | E | N | I | V | G | A | A | S | E | A | S | V | I | R |   |   |   |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbta | 2635 | E       | V  | L  | R   | T   | G   | F  | E  | M  | N  | C  | E | P | M | O | R | I | S | D | V | E | T | V | E | N | I | V | G | A | A | S | E | A | S | V | I |   |   |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbta | 2605 | E       | T  | L  | R   | T   | G   | F  | E  | M  | N  | C  | E | P | M | O | R | I | S | D | V | E | T | V | E | N | I | V | G | A | A | S | E | A | S | V |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

FIG. 16F

|        |      |      |                                                                   |
|--------|------|------|-------------------------------------------------------------------|
| A6 61  | Pbta | 2697 | IEVANGRHLLLFDMHHIISDCASMGILLDEFVALYSGEQLPELRLOVEDYASWQHEEAYL      |
| TS 15  | Pbta | 2695 | IEVDNRHLLLFDMHHIISDCASMGILLDEFVALYSGEELPELRLOKDYASWQOQSEYLL       |
| OSY SE | Pbta | 2664 | IEGAKRHLLLFDMHHIISDCASMGILLDEFVALYSGEELPELRLOKDYASWQOQSEYLL       |
| A6 61  | Pbta | 2757 | SMEEQKAYNLETLRGELPVLOLPVDYTHPAFRSPAGSTLEFIYPADKTDQKQKQCGESD       |
| TS 15  | Pbta | 2755 | SMEEQKAYNLETLRGELPVLOLPVDYTHPAFRSPAGSTLEFIYPADKADQKQKQCGESD       |
| OSY SE | Pbta | 2724 | DMSKQSEAYNLETLRGELPVLEFIYTHPAFRSPAGSTLEFIYQRRERLELQOLAEESG        |
| A6 61  | Pbta | 2817 | ATMYMVLALYTALLHKYITGQEDVIIVGMPVIACTHADIETPLIGMPVNTLPLRHYPAGEKT    |
| TS 15  | Pbta | 2815 | ATMYMVLALYTALLHKYITGQEDVIIVGMPVIACTHADIETPLIGMPVNTLPLRHYPAGEKT    |
| OSY SE | Pbta | 2784 | ATMYMVLALYTALLHKYITGQEDVIIVGMPVIACTHADIETPLIGMPVNTLPLRHYPAGEKT    |
| A6 61  | Pbta | 2877 | FRSFLGEVRSQSTLOAYEHQEQYPPFEELVDHIQPTEDVSRNPIFDITVLVLQNTTEKGAWSIDG |
| TS 15  | Pbta | 2875 | FRSFLGEVRSQSTLOAYEHQEQYPPFEELVDHIQPTEDVSRNPIFDITVLVLQNTTEKGAWSIDG |
| OSY SE | Pbta | 2844 | FRSFLGEVRSQSTLOAYEHQEQYPPFEELVDHIQPTEDVSRNPIFDITVLVLQNTTEKGAWSIDG |
| A6 61  | Pbta | 2937 | LAVTPNPPIEHAFAKFDLTLHVEEEDGLACSIIEYATALLYRETIERLACHFNQLEAVIS      |
| TS 15  | Pbta | 2935 | LAVTPNPPIEHAFAKFDLTLHVEEEDGLACSIIEYATALLYRETIERLACHFNQLEAVIS      |
| OSY SE | Pbta | 2904 | LAVTPNPPIEHAFAKFDLTLHVEEEDGLACSIIEYATALLYRETIERLACHFNQLEAVIS      |
| A6 61  | Pbta | 2997 | NPSARLEQOLGIIITETEKQOLPECPNDTSADYPRDKTIHRLFEQOVERTPPDAIATCTDQCF   |
| TS 15  | Pbta | 2995 | NPSARLEQOLGIIITETEKQOLPECPNDTSADYPRDKTIHRLFEQOVERTPPDAIATCTDQCF   |
| OSY SE | Pbta | 2964 | NPSARLEQOLGIIITETEKQOLPECPNDTSADYPRDKTIHRLFEQOVERTPPDAIATCTDQCF   |
| A6 61  | Pbta | 3057 | LTYYQELNERANSLANVLRAEGICADKLVGIMAEETTMMLVGLIAILKACGAYVPIIDPEYP    |
| TS 15  | Pbta | 3055 | LTYYQELNERANSLANVLRAEGICADKLVGIMAEETTMMLVGLIAILKACGAYVPIIDPEYP    |
| OSY SE | Pbta | 3024 | LTYYQELNERANSLANVLRAEGICADKLVGIMAEETTMMLVGLIAILKACGAYVPIIDPEYP    |
| A6 61  | Pbta | 3117 | DEERISYMLSDSCADILLPRHLRQVAYEGTVLELDDEQTYSGDKSNPFSVNKPESDLAYV      |
| TS 15  | Pbta | 3115 | DEERISYMLSDSCADILLPRHLRQVAYEGTVLELDDEQTYSGDKSNPFSVNKPESDLAYV      |
| OSY SE | Pbta | 3084 | DEERISYMLSDSCADILLPRHLRQVAYEGTVLELDDEQTYSGDKSNPFSVNKPESDLAYV      |
| A6 61  | Pbta | 3177 | IYTSGETTGKPKGTLLIEHKNVVRLLFNERNLFDPRSTDTNTLPHSFCFDFSVWEMYGALLY    |
| TS 15  | Pbta | 3175 | IYTSGETTGKPKGTLLIEHKNVVRLLFNERNLFDPRSTDTNTLPHSFCFDFSVWEMYGALLY    |
| OSY SE | Pbta | 3144 | IYTSGETTGKPKGTLLIEHKNVVRLLFNERNLFDPRSTDTNTLPHSFCFDFSVWEMYGALLY    |

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FIG. 16G

|        |      |      |                                                                   |
|--------|------|------|-------------------------------------------------------------------|
| A6_61  | Pbta | 3237 | GGRLVVVPQLTAKNPAMPFLQLLAEEERVITLHQTYFYQLIREALIDGSPSELNIRMVIFG     |
| TS_15  | Pbta | 3235 | GGRLVVVPQLTAKNPAMPFLQLLAEEERVITLHQTYFYQLIREALADGSPSELNIRMVIFG     |
| OSY_SE | Pbta | 3204 | GGRLVVVPQLTAKNPAMPFLQLLAEEERVITLHQTYFYQLIREALADGSPSELNIRMVIFG     |
| A6_61  | Pbta | 3297 | GEALSPQLLKDWRAKYERTQLINMYGITEETTVHVYTYKKEITETAEIEQARSNIGPPIPTLRI  |
| TS_15  | Pbta | 3295 | GEALSPQLLKDWRAKYERTQLINMYGITEETTVHVYTYKKEITETAEIEQARSNIGPPIPTLRI  |
| OSY_SE | Pbta | 3264 | GEALNPQLLKDWRAKYERTQLINMYGITEETTVHVYTYKKEITETAEIEQARSNIGPPIPTLRI  |
| A6_61  | Pbta | 3357 | YILDANRQCVPPIGVAGEMFVAGEGLARGYLNRPELTADRFVDNPFEPGSKMYKTGDLAKN     |
| TS_15  | Pbta | 3355 | YILDANRQCVPPIGVAGEMFVAGEGLARGYLNRPELTADRFVDNPFEPGSKMYKTGDLAKN     |
| OSY_SE | Pbta | 3324 | YILDANRQCVPPIGVAGEMFVAGEGLARGYLNRPELTADRFVDNPFEPGSKMYKTGDLAKN     |
| A6_61  | Pbta | 3417 | LPDGNIEYLGRIDHQVKIRGYRIELGEVEAQVTXVESVREAVVAREE-NCEKLLCAYPV       |
| TS_15  | Pbta | 3415 | LPDGNIEYLGRIDHQVKIRGYRIELGEVEAQVTXVESVREAVVAREE-NCEKLLCAYPV       |
| OSY_SE | Pbta | 3384 | LPDGNIEYLGRIDHQVKIRGYRIELGEVEAQVTXVESVREAVVAREE-NCEKLLCAYPV       |
| A6_61  | Pbta | 3476 | ADRQLTVGEMRTELACQLFTYMIPTSYFVQERRMPLTSNGKVDRKALPAPEGGINIGKEYV     |
| TS_15  | Pbta | 3474 | ADRQLTVGEMRTELACQLFTYMIPTSYFVQERRMPLTSNGKVDRKALPAPEGGINIGKEYV     |
| OSY_SE | Pbta | 3444 | ADRELTVGEMRTELACQLFTYMIPTSYFVQERRMPLTSNGKVDRKALPAPEGGINIGKEYV     |
| A6_61  | Pbta | 3536 | APRTPMASLARMWELLGIEQVGVTDNPFELGCHSLRATALVNRVHOENNIQLPLRDVF        |
| TS_15  | Pbta | 3534 | APRTPMASLARMWELLGIEQVGVTDNPFELGCHSLRATALVNRVHOENNIQLPLRDVF        |
| OSY_SE | Pbta | 3504 | APRTPMASLARMWELLGIEQVGVTDNPFELGCHSLRATALVNRVHOENNIQLPLRDVF        |
| A6_61  | Pbta | 3596 | RPSTIERELAAAMSEMAEESYSSIPVAEVQDHYVPVSSACKRLYLILHQLLEGAEQGINMPGIM  |
| TS_15  | Pbta | 3594 | RPSTIERELAAAMSEMAEESYSSIPVAEVQDHYVPVSSACKRLYLILHQLLEGAEQGINMPGIM  |
| OSY_SE | Pbta | 3564 | RPSTIERELAAAMSEMAEESYSSIPVAEVQDHYVPVSSACKRLYLILHQLLEGAEQGINMPGIM  |
| A6_61  | Pbta | 3656 | LEGEELDRSRPEAARFKLIARHDIILRTGFEVYGEAVQRIHDTVDFAIEYRKYVEEQEVQQ     |
| TS_15  | Pbta | 3654 | LEGEELDRSRPEAARFKLIARHDIILRTGFEVYGEAVQRIHDTVDFAIEYRKYVEEQEVQQ     |
| OSY_SE | Pbta | 3624 | LEGEELDRSRPEAARFKLIARHDIILRTGFEVYGEAVQRIHDTVDFAIEYRKYVEEQEVQQ     |
| A6_61  | Pbta | 3716 | QVRFQPIRTFELDKPPLLRVGLIEIACTKEQHVLLFDMHHIISDQVSGISIGIVLQEIIMRHYEG |
| TS_15  | Pbta | 3714 | QVRFQPIRTFELDKPPLLRVGLIEIACTKEQHVLLFDMHHIISDQVSGISIGIVLQEIIMRHYEG |
| OSY_SE | Pbta | 3684 | QVRFQPIRTFELDKPPLLRVGLIEIACTKEQHVLLFDMHHIISDQVSGISIGIVLQEIIMRHYEG |

FIG. 16H

|        |      |      |                                                                  |
|--------|------|------|------------------------------------------------------------------|
| A6_61  | Pbta | 3776 | EQVPPPLHIQYKDYAANQCSQAQKEQLKHQKAYWLCQFQGGELPILLEPFTDYARPAQQYCS   |
| TS_15  | Pbta | 3774 | EEVPPPLHIQYKDYAANQCSQAQKEQLKHQKAYWLCQFQGGELPILLEPFTDYARPAQQYCS   |
| OSY_SE | Pbta | 3742 | AAEEPLFIQYKDYAANQCSQAQKEQLKHQKAYWLCQFQGGELPILLEPFTDYARPAQQYCS    |
| A6_61  | Pbta | 3836 | LTLEFPRIDKDVADGLNRIADTGTLLYMLLAAYTMLHKYTCQEDIVVGTPIAGRTHRE       |
| TS_15  | Pbta | 3834 | LTLEFPRIDKDVADGLNRIADTGTLLYMLLAAYTMLHKYTCQEDIVVGTPIAGRTHRE       |
| OSY_SE | Pbta | 3802 | STLEFPRIDKDVADGLNRIADTGTLLYMLLAAYTMLHKYTCQEDIVVGTPIAGRTHRE       |
| A6_61  | Pbta | 3896 | LQPLIGMPFVNTLAIRAYPEGAKAPRSYLDSEIRSTMIGAYEHQOQYPFEEELVEGLQLTRRLS |
| TS_15  | Pbta | 3894 | LQPLIGMPFVNTLAIRAYPEGAKAPRSYLDSEIRSTMIGAYEHQOQYPFEEELVEGLQLTRRLS |
| OSY_SE | Pbta | 3862 | LQPLIGMPFVNTLAIRAYPEGAKAPRSYLDSEIRSTMIGAYEHQOQYPFEEELVEGLQLTRRLS |
| A6_61  | Pbta | 3956 | RNPLFDTMPALDNTDMKADSLGELCMKPYPLEYTIISKFDVSLDVKADEAGLDCSPEYATS    |
| TS_15  | Pbta | 3954 | RNPLFDTMPALDNTDMKADSLGELCMKPYPLEYTIISKFDVSLDVKADEAGLDCSPEYATS    |
| OSY_SE | Pbta | 3922 | RNPLFDTMPALDNTDMKADSLGELCMKPYPLEYTIISKFDVSLDVKADEAGLDCSPEYATS    |
| A6_61  | Pbta | 4016 | LFKSETIHRMAEHPSQLLKDIYNHPPDAQGLGELCMLTVQESSEILQVFNPTSHSKAENETI   |
| TS_15  | Pbta | 4014 | LFKSETIHRMAEHPSQLLKDIYNHPPDAQGLGELCMLTVQESSEILQVFNPTSHSKAENETI   |
| OSY_SE | Pbta | 3982 | LFKSETIHRMAEHPSQLLKDIYNHPPDAQGLGELCMLTVQESSEILQVFNPTSHSKAENETI   |
| A6_61  | Pbta | 4076 | HRLPFEQAERTPEQPAVVFCEMRNTYSELNERANKLARTLRACGVEPDDILICVMADRSID    |
| TS_15  | Pbta | 4074 | HRLPFEQAERTPEQPAVVFCEMRNTYSELNERANKLARTLRACGVEPDDILICVMADRSID    |
| OSY_SE | Pbta | 4042 | HRLPFEQAERTPEQPAVVFCEMRNTYSELNERANKLARTLRACGVEPDDILICVMADRSID    |
| A6_61  | Pbta | 4136 | MVVAVMAYLXSGGAYVPIDPEYEDRIRYMLEDAKARILLTQCHLODKVPECTWVLLLED      |
| TS_15  | Pbta | 4134 | MVVAVMAYLXSGGAYVPIDPEYEDRIRYMLEDAKARILLTQCHLODKVPECTWVLLLED      |
| OSY_SE | Pbta | 4102 | MVVAVMAYLXSGGAYVPIDPEYEDRIRYMLEDAKARILLTQCHLODKVPECTWVLLLED      |
| A6_61  | Pbta | 4196 | EAASYHEDDNTNLEPCEPCHLCYVIYTSCTTGNPKGVMIERHQLAAMASANKAEYELHEPG    |
| TS_15  | Pbta | 4194 | EAASYHEDDNTNLEPCEPCHLCYVIYTSCTTGNPKGVMIERHQLAAMASANKAEYELHEPG    |
| OSY_SE | Pbta | 4162 | EAASYHEDDNTNLEPCEPCHLCYVIYTSCTTGNPKGVMIERHQLAAMASANKAEYELHEPG    |
| A6_61  | Pbta | 4256 | IRWLQNASFSPDVFSGDLARTLLHGGELILCPSPDTRANPGALAEELLRSSGICOMFESTPAL  |
| TS_15  | Pbta | 4254 | IRWLQNASFSPDVFSGDLARTLLHGGELILCPSPDTRANPGALAEELLRSSGICOMFESTPAL  |
| OSY_SE | Pbta | 4222 | IRWLQNASFSPDVFSGDLARTLLHGGELILCPSPDTRANPGALAEELLRSSGICOMFESTPAL  |

FIG. 16I

|        |      |      |                                                               |
|--------|------|------|---------------------------------------------------------------|
| A6_61  | Pbta | 4316 | VIPLMEHVYERCHDIDSLRLLLIGSDLCPADPFRKLDRFSESMRIINSYGVTEACVDSS   |
| TS_15  | Pbta | 4314 | VIPLMEHVYERCHDIDSLRLLLIGSDLCPADPFRKLDRFSESMRIINSYGVTEACVDSS   |
| OSY_SE | Pbta | 4282 | VIPFMQYVYNNMDISLILLIGSDHCPTAEPRKLTERRCCSHMRIINSYGVTEACVDAC    |
| A6_61  | Pbta | 4376 | YYEPESDSVRSVPICKPLPYVSMYILGENLSLOPVGLAGELYIAGAGVGRGYNRPENT    |
| TS_15  | Pbta | 4374 | YYEPESDSVRSVPICKPLPYVSMYILGENLSLOPVGLAGELYIAGAGVGRGYNRPENT    |
| OSY_SE | Pbta | 4342 | YYERTPPDAERPPICKPLPYVSMYILDENESLOPVCHTCELYIAGAGVGRGYNRPENT    |
| A6_61  | Pbta | 4436 | ADKPVDRPPADGQRMVRTGDLAKWLPDGNIELIGRTDHQVKIRGYRIEIGEVESKLOETP  |
| TS_15  | Pbta | 4434 | ADKPVDRPPADGQRMVRTGDLAKWLPDGNIELIGRTDHQVKIRGYRIEIGEVESKLOETP  |
| OSY_SE | Pbta | 4402 | VKKPVDMPPFPGARMVRTGDLAKWLPDGNIEYACRIIDHQVKIRGYRIEIGEVESKLLAA  |
| A6_61  | Pbta | 4496 | HIREAAVVAKEDGSGRKKVLCAYITSRELTAGEWRAALAKELPAYMIPSHFMRLERMPLT  |
| TS_15  | Pbta | 4494 | DIREAAVVAKEDGSGRKKVLCAYITSRELTAGEWRAALAKELPAYMIPSHFMRLERMPLT  |
| OSY_SE | Pbta | 4462 | GIREAAVVAKEDGSGRKKVLCAYEVADSAITVGELEKASAAQQLPEYMIPEHFCLERMPLT |
| A6_61  | Pbta | 4556 | PNCKLDRKGLPAPEGAAITGTEIEAPRTDASIALAAANQSVLHVERVGTNDHFFELGSDS  |
| TS_15  | Pbta | 4554 | PNCKLDRKGLPAPEGAAITGTEIEAPRTDASIALAAANQSVLHVERVGTNDHFFELGSDS  |
| OSY_SE | Pbta | 4522 | PNCKLDRKGLPAPEGAAITGTEIEAPRTDASIALAAANQSVLHVERVGTNDHFFELGSDS  |
| A6_61  | Pbta | 4616 | IKSIQVSSRLHQAGYKLEIRDLFKYPTIAQLSPQLQPIGRIADQGEVSGEVELTPIQGWY  |
| TS_15  | Pbta | 4614 | IKSIQVSSRLHQAGYKLEIRDLFKYPTIAQLSPQLQPIGRIADQGEVSGEVELTPIQGWY  |
| OSY_SE | Pbta | 4582 | IKSIQVSSRLHQAGYKLEIRDLFKYPTIAELSEHMQPIGRKADQGEVSGEVALTPIQGWY  |
| A6_61  | Pbta | 4676 | FGLDLDDMHYHQSFMLYRQCGFNEEALERTLKHSLVCHHDALRMVFKESAGVTAWNRAT   |
| TS_15  | Pbta | 4674 | FGLDLDDMHYHQSFMLYRQCGFNEEALERTLKHSLVCHHDALRMVFKESAGVTAWNRAT   |
| OSY_SE | Pbta | 4642 | FGQRFADPHHYNQSFMLYRQCGFNEEALERTLKHSLVCHHDALRMVFKESAGVTAWNRAT  |
| A6_61  | Pbta | 4736 | EECELEFDPLADIANSGDREQVIEAKANDIOASINLQCGPLVKAGLFRCEQCHHLLIAIH  |
| TS_15  | Pbta | 4734 | EECELEFDPLADIANSGDREQVIEAKANDIOASINLQCGPLVKAGLFRCEQCHHLLIAIH  |
| OSY_SE | Pbta | 4702 | CECELESLNVABFTDDPACYRAIEAKANEIQSCINLQCGPLVKAGLFRCEQCHHLLIAIH  |
| A6_61  | Pbta | 4796 | HAVTDCVSNRILLEDIAGCYEQACKGDDIRLPKTDSYAANWSRLVEYAEETDLCHERSY   |
| TS_15  | Pbta | 4794 | HAVTDCVSNRILLEDIAGCYEQACKGDDIRLPKTDSYAANWSRLVEYAEETDLCHERSY   |
| OSY_SE | Pbta | 4762 | HAVTDCVSNRILLEDIAGCYEQACKGDDIRLPKTDSYAANWSRLVEYAEETDLCHERSY   |

FIG. 16J

|        |      |      |                                                                         |
|--------|------|------|-------------------------------------------------------------------------|
| A6_61  | Pbta | 4856 | WRHVLRAGTNPFPKDPDTESSLOQDSNSVTVANNOQDTEHLLKRVHRA YNTDMNEILLAA           |
| TS_15  | Pbta | 4854 | WRHVLRAGTNPFPKDPDTESSLOQDSNSVTVANNOQDTEHLLKRVHRA YNTDMNEILLAA           |
| OSY_33 | Pbta | 4822 | WQRAQSENTPFPKDPDTESSLOQDSNSVTVANNOQDTEHLLKRVHRA YNTDMNEILLAA            |
| A6_61  | Pbta | 4916 | LAIAIQKWSCHNQILVNLECHGCKREPIAGDLDISRTVCMPTSETYPVLLKAEKDRGLAYHIK         |
| TS_15  | Pbta | 4914 | LAIAIQKWSCHNQILVNLECHGCKREPIAGDLDISRTVCMPTSETYPVLLKAEKDRGLAYHIK         |
| OSY_33 | Pbta | 4882 | LAIAIQKWSCHNQILVNLECHGCKREPIAGDLDISRTVCMPTSETYPVLLKAEKDRGLAYHIK         |
| A6_61  | Pbta | 4976 | RAKEELRQIPNKGICGICRYLSERPQDSLENGCAPEISFNILQDFDQDSESGMMLSPYS             |
| TS_15  | Pbta | 4974 | RAKEELRQIPNKGICGICRYLSERPQDSLENGCAPEISFNILQDFDQDSESGMMLSPYS             |
| OSY_33 | Pbta | 4942 | RAKEELRQIPNKGICGICRYLSERPQDSLENGCAPEISFNILQDFDQDSESGMMLSPYS             |
| A6_61  | Pbta | 5036 | KGSDGSALHTRQYVLDINGAITDGLILLDMSYSEKRYRKEKTMELLACHFEESLLEIIDHC           |
| TS_15  | Pbta | 5034 | KGSDGSALHTRQYVLDINGAITDGLILLDMSYSEKRYRKEKTMELLACHFEESLLEIIDHC           |
| OSY_33 | Pbta | 5002 | KGSDGSALHTRQYVLDINGAITDGLILLDMSYSEKRYRKEKTMELLACHFEESLLEIIDHC           |
| A6_61  | Pbta | 5096 | VSRQTELTTPSDLLQGLSIEQLEQIAEETBELGIIENMYMLTPMOKGMWPHNALDQOEG             |
| TS_15  | Pbta | 5094 | VSRQTELTTPSDLLQGLSIEQLEQIAEETBELGIIENMYMLTPMOKGMWPHNALDQOEG             |
| OSY_33 | Pbta | 5062 | VSRQTELTTPSDLLQGLSIEQLEQIAEETBELGIIENMYMLTPMOKGMWPHNALDQOEG             |
| A6_61  | Pbta | 5156 | AGAYFEQTRFTLRGELDPALPAQSLHELAAHHSVLKTNFCS - LDGEPVQVFPREGKITP           |
| TS_15  | Pbta | 5154 | AGAYFEQTRFTLRGELDPALPAQSLHELAAHHSVLKTNFCS - LDGEPVQVFPREGKITP           |
| OSY_33 | Pbta | 5120 | AGAYFEQTRFTLRGELDPALPAQSLHELAAHHSVLKTNFCS - LDGEPVQVFPREGKITP           |
| A6_61  | Pbta | 5215 | TYEDLSQLPAEQAAVIERVASDKLQSPDLERDPLVRVTLNRTEASSCHVLNSSHILM               |
| TS_15  | Pbta | 5213 | TYEDLSQLPAEQAAVIERVASDKLQSPDLERDPLVRVTLNRTEASSCHVLNSSHILM               |
| OSY_33 | Pbta | 5179 | TYEDLSQLPAEQAAVIERVASDKLQSPDLERDPLVRVTLNRTEASSCHVLNSSHILM               |
| A6_61  | Pbta | 5275 | DCWCLPQLTDELPRISAVTNHAACTTEATGTGTCIP - - - - -GSAESNNKEANLP - - - - -DY |
| TS_15  | Pbta | 5273 | DCWCLPQLTDELPRISAVTNHAACTTEATGTGTCIP - - - - -GSAESNNKEANLP - - - - -DY |
| OSY_33 | Pbta | 5239 | DCWCLPQLTDELPRISAVTNHAACTTEATGTGTCIP - - - - -GSAESNNKEANLP - - - - -DY |
| A6_61  | Pbta | 5327 | SRYIENLAEQDMSAAAETWNGYLAGEYEQTRLPNGKITVNDKPPVLEQASRKLGLITISR            |
| TS_15  | Pbta | 5328 | SRYIENLAEQDMSAAAETWNGYLAGEYEQTRLPNGKITVNDKPPVLEQASRKLGLITISR            |
| OSY_33 | Pbta | 5276 | SRYIENLAEQDMSAAAETWNGYLAGEYEQTRLPNGKITVNDKPPVLEQASRKLGLITISR            |

FIG. 16K

|             |      |                                                                |
|-------------|------|----------------------------------------------------------------|
| A6_61_Pb1A  | 5387 | MIRIAKQHQVTLNTLLQAAAGIIVLQKYNCTQDVVPCGVVSCRPAADVPGVESMIGLPINTY |
| T8_15_Pb1A  | 5388 | MIRIAKQHQVTLNTLLQAAAGIIVLQKYNCTQDVVPCGVVSCRPAADVPGVESMIGLPINTY |
| OSY_SE_Pb1A | 5336 | MSQIAKQHQVTLNTLLQAAAGIIVLQKYNCTQDVVPCGVVSCRPAADVPGVESMIGLPINTY |
| A6_61_Pb1A  | 5447 | PVRVSCACASFSFSDVMEQLQNAALAESCRDYVPLYEIQSRTSQKSELISHIMVFENYPLD  |
| T8_15_Pb1A  | 5448 | PVRVSNACASFSFSDVMEQLQNAALAESCRDYVPLYEIQSRTSQKSELISHIMVFENYPLD  |
| OSY_SE_Pb1A | 5396 | PVRVACAAETEFQVVERLQECALDSGRDYVPLYEIQCAQKQKSELISHIMVFENYPLD     |
| A6_61_Pb1A  | 5507 | ERMEQGTGENDGALALTDVQAAEQTNYPNLMVVPGBELIIRPDFNSSEVYDRCHMERLHR   |
| T8_15_Pb1A  | 5508 | ERMEQGTGENDGALALTDVQAAEQTNYPNLMVVPGBELIIRPDFNSSEVYDRCHMERLHR   |
| OSY_SE_Pb1A | 5456 | EQMEQGTGENDGALALTDVQAAEQTNYPNLMVVPGBELIIRPDFNSSEVYDRCHMERLHR   |
| A6_61_Pb1A  | 5567 | HLMBVLREQVTGNPAISIAEVOLSTAEKAEVQSAPNDTVVDYPREQTIHMMFEEQVQRTT   |
| T8_15_Pb1A  | 5568 | HLMBVLREQVTGNPAISIAEVOLSTAEKAEVQSAPNDTVVDYPREQTIHMMFEEQVQRTT   |
| OSY_SE_Pb1A | 5516 | HLMBVLREQVTGNPAISIAEVOLSTAEKAEVQSAPNDTVVDYPREQTIHMMFEEQVQRTT   |
| A6_61_Pb1A  | 5627 | DAAAVLYGDDVITTYRELNERANRLARTLRAAGVPEPDQIVGIMAESLELMVGIMGILKAG  |
| T8_15_Pb1A  | 5628 | DAAAVLYGDDVITTYRELNERANRLARTLRAAGVPEPDQIVGIMAESLELMVGIMGILKAG  |
| OSY_SE_Pb1A | 5576 | DAAAVLYGDDVITTYRELNERANRLARTLRAAGVPEPDQIVGIMAESLELMVGIMGILKAG  |
| A6_61_Pb1A  | 5687 | GAIVPIAPDYPPEERIRYMLDSDSQAQVLLVQGSAGEAVDFVGRINLDDAEAYDEESNPE   |
| T8_15_Pb1A  | 5688 | GAIVPIAPDYPPEERIRYMLDSDSQAQVLLVQGSAGEAVDFVGRINLDDAEAYDEESNPE   |
| OSY_SE_Pb1A | 5636 | GAIVPIAPDYPPEERIRYMLDSDSQAQVLLVQGSAGEAVDFVGRINLDDAEAYDEESNPE   |
| A6_61_Pb1A  | 5747 | PVNEPTDIAIYIYTSCTTCRPGVMVEHTSVINRLLNMOKRYPICSEDTIMQKTAITFDV    |
| T8_15_Pb1A  | 5748 | PVNEPTDIAIYIYTSCTTCRPGVMVEHTSVINRLLNMOKRYPICSEDTIMQKTAITFDV    |
| OSY_SE_Pb1A | 5696 | PVNEPTDIAIYIYTSCTTCRPGVMVEHTSVINRLLNMOKRYPICSEDTIMQKTAITFDV    |
| A6_61_Pb1A  | 5807 | SVWELFWWAFVCSKVLMLSVGCEKNPFAIVDAIERHRIITMHPVPSMLHAPLEHVEQITD   |
| T8_15_Pb1A  | 5808 | SVWELFWWAFVCSKVLMLSVGCEKNPFAIVDAIERHRIITMHPVPSMLHAPLEHVEQITD   |
| OSY_SE_Pb1A | 5756 | SVWELFWWAFVCSKVLMLSVGCEKNPFAIVDAIERHRIITMHPVPSMLHAPLEHVEQITD   |
| A6_61_Pb1A  | 5867 | AERERGLAPLROVFTSCEALLASQVERPFRHYIAPASGAQLINLYCPTTEATVDVTYFDCEP |
| T8_15_Pb1A  | 5868 | AERERGLAPLROVFTSCEALLASQVERPFRHYIAPASGAQLINLYCPTTEATVDVTYFDCEP |
| OSY_SE_Pb1A | 5816 | AERERGLAPLROVFTSCEALLASQVERPFRHYIAPASGAQLINLYCPTTEATVDVTYFDCEP |

FIG. 16L

|             |      |                                                                 |
|-------------|------|-----------------------------------------------------------------|
| A6_61_Pbta  | 5927 | GQTVSVPIGKPIDNTSIIYVNEHMQVQPIGVAGELCIAGVCLARGYNNRPDLTAEKFT      |
| TS_15_Pbta  | 5928 | GQTVSVPIGKPIDNTSIIYVNEHMQVQPIGVAGELCIAGVCLARGYNNRPDLTAEKFT      |
| OSY_SE_Pbta | 5976 | GQFTSVPIGKPIDNTQIYIVNRQDQPIGVAGELCIAGVCLARGYNNRPDLTAEKFT        |
| A6_61_Pbta  | 5987 | IPSV - GERNYRTGDLARWLPDGNIEYLGRIDHQVKIRGYRIELGELERALLNNVQZIRETV |
| TS_15_Pbta  | 5988 | IPSV - GERNYRTGDLARWLPDGNIEYLGRIDHQVKIRGYRIELGELERALLNNVQZIRETV |
| OSY_SE_Pbta | 5936 | IPFTPGERNYRTGDLARWLPDGNIEYLGRIDHQVKIRGYRIELGELERALLNNVQZIRETV   |
| A6_61_Pbta  | 6046 | VVAREEDGQKSLCAYYVADGDPVCEMLRAALAAELPSYMIPIPSYFIQLEQMP LAPNGKLD  |
| TS_15_Pbta  | 6047 | VVAREEDGQKSLCAYYVADGDPVCEMLRAALAAELPSYMIPIPSYFIQLEQMP LAPNGKLD  |
| OSY_SE_Pbta | 5996 | VVAREDESQKALCAYEADSELPVSELSALAVELPGYMIPIPSYFIQLEQMP LAPNGKLD    |
| A6_61_Pbta  | 6106 | RKALPAPKPDVIQTGTDHAPRTALEVKLVRIWQEVLGLDQIGVKDDPFELGCHSLRATAL    |
| TS_15_Pbta  | 6107 | RKALPAPKPDVIQTGTDHAPRTALEVKLVRIWQEVLGLDQIGVKDDPFELGCHSLRATAL    |
| OSY_SE_Pbta | 6056 | RKALPAPGCSRRCKZHHAPRELLLEVVKLVRIWQEVLGLAHVSVKDDPFELGCHSLRATL    |
| A6_61_Pbta  | 6168 | ASKVSKEMHVALPLRDIPHYSTLEAMAQAIGELEKQEHRAIPIAPMAEHYPLASAQKRLY    |
| TS_15_Pbta  | 6167 | ASKVSKEMHVALPLRDIPHYSTLEAMAQAIGELEKQEHRAIPIAPMAEHYPLASAQKRLY    |
| OSY_SE_Pbta | 6116 | VSKLHRENNINPLRDIPFRSILEDMALAIQRTSQEETQTIPOVEASQYYPLESAQKRLY     |
| A6_61_Pbta  | 6226 | ILHQAECAQOSYNMPCAMSVSCHIDNRRLAALLLELIARHDTLRTSTFEMVDGEPVQVHQ    |
| TS_15_Pbta  | 6227 | ILHQAECAQOSYNMPCAMSVSCHIDNRRLAALLLELIARHDTLRTSTFEMVDGEPVQVHQ    |
| OSY_SE_Pbta | 6176 | ILVQVVEGAEOSYNMPGAMSEERCOEDENQFHAATRCGLIARHVEVETSTFEMVCGEPVQVHQ |
| A6_61_Pbta  | 6286 | HVDPALEYSTAREKDSEOVAQCFVRDPDFLEQPPLELVGLVQLEQSEHQHLLLEDNHHIISD  |
| TS_15_Pbta  | 6287 | HVDPALEYSTAREKDSEOVAQCFVRDPDFLEQPPLELVGLVQLEQSEHQHLLLEDNHHIISD  |
| OSY_SE_Pbta | 6236 | DTAFAMEYMQHSEEEAEANAQCFVRTFDLEQPSLLRVGLLELDR - EHHHLLFDNHHIISD  |
| A6_61_Pbta  | 6346 | GISMDILVDELARLYDGEELPPLEIQYKDYVLWQCAEASSEQMKKEHEEYMLRTLGNELPL   |
| TS_15_Pbta  | 6347 | GISMDILVDELARLYDGEELPPLEIQYKDYVLWQCAEASSEQMKKEHEEYMLRTLGNELPL   |
| OSY_SE_Pbta | 6295 | GISMGILVDEEARLYSGEELPPLEIQYKDYALWQCSSEACSEERKQCEAYMLDALDGEELPO  |

FIG. 16M

|     |    |    |    |      |                                                                |
|-----|----|----|----|------|----------------------------------------------------------------|
| A6  | 61 | Pb | tA | 6406 | LELPTEFARCEQORSYDGDCKLHPAIDGQNLNEKIQRLASQSGATLYMVLLAAYTTLHKYSC |
| TS  | 15 | Pb | tA | 6407 | LELPTEFARCEQORSYDGDCKLHPAIDGQNLNEKIQRLASQSGATLYMVLLAAYTTLHKYSC |
| OSY | SE | Pb | tA | 6355 | LELPTEFARPAHQSHGCDTDDVIDSHMSGGLQRLAEEHSTLYMVLLAAYTTLHKYSD      |
| A6  | 61 | Pb | tA | 6466 | QNDLVVGTPIAGRTHVDVEPLIGMPVNSLAIRNYPNDDKTFRSYLLEEVKESTLSAFEHQD  |
| TS  | 15 | Pb | tA | 6467 | QNDLVVGTPIAGRTHVDVEPLIGMPVNSLAIRNYPNDDKTFRSYLLEEVKESTLSAFEHQD  |
| OSY | SE | Pb | tA | 6415 | QEDLVVGTPIAGRTHVDVEPLIGMPVNSLAIRNYPNDDKTFRSYLLEEVKESTLSAFEHQD  |
| A6  | 61 | Pb | tA | 6526 | YPPDKLVEQLEDAMVPCRNPFVDTMPVLQNAKARTINLCELAPPEPLIPSHTVAKFDLTLE  |
| TS  | 15 | Pb | tA | 6527 | YPPDKLVEQLEDAMVPCRNPFVDTMPVLQNAKARTINLCELAPPEPLIPSHTVAKFDLTLE  |
| OSY | SE | Pb | tA | 6475 | YPPAEELVEHVCQAVMSPSRNPFVDTMPVLQNTEDRNVRFGELTIEPYTQHNNVAKFDLTLE |
| A6  | 61 | Pb | tA | 6586 | MAIEDGMLSCQPEYCTILFSANNIANFAEDFLEILSQACEQPDIRLEDIQLSCSAYQEEEE  |
| TS  | 15 | Pb | tA | 6587 | MAIEDGMLSCQPEYCTILFSANNIANFAEDFLEILSQACEQPDIRLEDIQLSCSAYQEEEE  |
| OSY | SE | Pb | tA | 6535 | MAIEDGMLSCQPEYCTILFSANNIANFAEDFLEILSQACEQPDIRLEDIQLSCSAYQEEEE  |
| A6  | 61 | Pb | tA | 6646 | --LEEEIDFAP                                                    |
| TS  | 15 | Pb | tA | 6647 | --LEEEIDFAP                                                    |
| OSY | SE | Pb | tA | 6595 | ASDAERIDPVP                                                    |

A6 6i PtbA is SEQ ID NO. 11  
TS-15 PtbA is SEQ ID NO. 14  
OSY SE PtbA is SEQ ID NO. 17

FIG. 17A

|     |    |      |     |     |   |   |   |   |   |   |    |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-----|----|------|-----|-----|---|---|---|---|---|---|----|---|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|---|---|---|---|---|---|---|---|---|---|---|---|---|----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A6  | 61 | Pbcb | 1   | --M | A | F | D | K | E | I | E  | F | N  | K | A | K | I | D | E | D | T | P | T | L | P | T | S | S | E  | A | A | R | H | Y | S | V | T | M | P | A | E | I | S  | E | R | I | I | R | M | S | K | G | S |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbcb | 1   | --M | A | F | D | K | E | I | E  | F | N  | K | A | K | I | D | E | D | T | P | T | L | P | T | S | S | E  | A | A | R | H | Y | S | V | T | M | P | A | E | I | S  | E | R | I | I | R | M | S | K | G | S |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 1   | M   | N | A | F | E | K | E | T  | E | F  | N | K | A | O | F | D | A | E | D | E | A | I | L | P | E | S  | T | A | S | T | V | T | A | R | D | H | S | E | S | E  | S | A | D | E | S | O | R | I | S | H | M | S | E | S |   |   |   |   |
| A6  | 61 | Pbcb | 59  | H   | Q | A | F | N | I | L | L  | G | G  | I | Q | C | L | L | H | K | Y | T | S | E | N | R | I | V | I  | G | M | P | I | V | K | A | G | E | K | R | L | P | I  | N | Q | V | V | L | L | K | E | N | V | N | E | L | T | F | K |   |   |
| TS  | 15 | Pbcb | 59  | H   | Q | A | F | N | I | L | L  | G | G  | I | Q | C | L | L | H | K | Y | T | S | E | N | R | I | V | I  | G | M | P | I | V | K | A | G | E | K | R | L | P | I  | N | Q | V | V | L | L | K | E | N | V | N | E | L | T | F | K |   |   |
| OSY | SE | Pbcb | 61  | H   | Q | A | F | N | I | L | L  | G | G  | I | Q | C | L | L | H | K | Y | T | S | E | N | R | I | V | I  | G | M | P | I | V | K | A | G | E | K | R | L | P | I  | N | Q | V | V | L | L | K | E | N | V | N | E | L | T | F | K |   |   |
| A6  | 61 | Pbcb | 119 | L   | L | T | S | L | K | O | S  | F | T  | E | A | I | R | H | O | E | I | P | P | R | L | I | T | E | Q  | M | N | V | O | E | K | N | G | L | P | V | I | N | T  | M | A | L | K | N | I | H | T | V | N | F | I | P | T | V | V | A | D |
| TS  | 15 | Pbcb | 119 | L   | L | T | S | L | K | O | S  | F | T  | E | A | I | R | H | O | E | I | P | P | R | L | I | T | E | Q  | M | N | V | O | E | K | N | G | L | P | V | I | N | T  | M | A | L | K | N | I | H | T | V | N | F | I | P | T | V | V | A | D |
| OSY | SE | Pbcb | 121 | L   | L | T | E | L | K | T | E  | L | T  | A | I | N | H | O | N | I | P | P | R | K | T | E | E | L | H  | E | A | V | M | C | P | V | N | T | M | V | S | K | E  | I | H | T | E | F | S | Q | S | V | V | E |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 179 | L   | P | O | F | E | P | E | A  | E | N  | L | L | S | V | V | N | E | R | V | D | S | V | F | I | S | O  | I | I | E | H | L | O | R | V | L | S | I | V | L | L  | E | P | N | T | N | L | G | D | L | R | L | S | D | E |   |   |   |   |
| TS  | 15 | Pbcb | 179 | L   | P | O | F | E | P | E | A  | E | N  | L | L | S | V | V | N | E | R | V | D | S | V | F | I | S | O  | I | I | E | H | L | O | R | V | L | S | I | V | L | L  | E | P | N | T | N | L | G | D | L | R | L | S |   |   |   |   |   |   |
| OSY | SE | Pbcb | 181 | L   | P | O | F | E | P | E | A  | E | N  | L | L | S | V | V | N | E | R | V | D | S | V | F | I | S | O  | I | I | N | H | E | S | E | P | A | D | V | L | T | P  | E | R | V | L | O | D | N | L | S |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 239 | S   | I | L | L | H | G | E | N  | T | A  | A | E | X | P | R | D | R | T | I | H | E | L | F | T | E | Q  | A | R | T | P | D | A | V | A | A | V | G | O | O | L  | T | Y | A | E | L | N | G | E | R | A | N | R | L |   |   |   |   |   |
| TS  | 15 | Pbcb | 239 | S   | I | L | L | H | G | E | N  | T | A  | A | E | X | P | R | D | R | T | I | H | E | L | F | T | E | Q  | A | R | T | P | D | A | V | A | A | V | L | G | O | O  | L | T | Y | A | E | L | N | G | E | R |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 241 | A   | Q | L | L | T | E | E | N  | T | A  | A | E | X | P | R | D | R | T | I | H | E | L | F | T | E | Q  | A | R | T | P | D | A | V | A | V | E | E | D | K | O  | L | T | Y | A | E | L | N | G | E |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 299 | Q   | N | A | G | V | R | S | D  | O | L  | V | G | I | M | A | E | R | S | L | E | M | I | V | G | L | L  | A | I | M | K | A | G | C | A | Y | V | P | I | D | P  | E | P | Q | E | R | I | R | Y | M | L | E | D |   |   |   |   |   |   |
| TS  | 15 | Pbcb | 299 | Q   | N | A | G | V | R | S | D  | O | L  | V | G | I | M | A | E | R | S | L | E | M | I | V | G | L | L  | A | I | M | K | A | G | C | A | Y | V | P | I | D | P  | E | P | Q | E | R | I | R | Y | M | L |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 301 | R   | E | E | G | V | A | R | C  | T | L  | V | G | I | C | V | E | R | S | L | E | M | I | G | L | L | C  | I | E | R | A | G | C | A | Y | V | P | I | D | P | E  | P | E | R | T | N | A | L | L |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 359 | L   | Q | D | H | L | R | E | R  | V | -- | S | Y | E | G | T | I | V | D | M | N | S | E | H | N | I | G  | D | E | C | T | E | L | A | S | V | S | D | E | S | -- | N | L | A | Y | V | I | T | S | G | T |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbcb | 359 | L   | Q | D | H | L | R | E | R  | V | -- | S | Y | E | G | T | I | V | D | M | N | S | E | H | N | I | G  | D | E | C | T | E | L | A | S | V | S | D | E | S | -- | N | L | A | Y | V | I | T | S |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 361 | T   | Q | A | E | L | Q | T | S  | P | N  | S | I | D | S | V | E | D | A | A | E | T | A | L | E | G | S  | W | F | N | I | T | D | A | A | C | E | A | D | D | A  | I | I | I | T | S | G | T |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 416 | I   | E | H | R | S | A | V | N  | A | L  | L | N | R | I | T | Y | G | L | S | S | D | R | E | L | Q | L  | P | S | F | S | F | D | G | F | V | M | S | A | F | C  | S | L | L | S | G | A | G | L |   |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbcb | 416 | I   | E | H | R | S | A | V | N  | A | L  | L | N | R | I | T | Y | G | L | S | S | D | R | E | L | Q | L  | P | S | F | S | F | D | G | F | V | M | S | A | F | C  | S | L | L | S | G | A | G |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 421 | V   | T | E | R | G | V | R | -- | L | E  | A | A | N | Y | V | D | E | S | S | K | D | V | F | L | Q | G  | S | I | S | P | D | A | T | F | E | I | N | G | S | L  | L | N | G | A | L |   |   |   |   |   |   |   |   |   |   |   |   |   |
| A6  | 61 | Pbcb | 476 | P   | L | A | H | G | A | I | S  | O | S  | G | I | T | H | E | P | I | C | V | P | N | L | I | C | A | L  | L | N | V | M | O | A | E | S | V | S | T | L | R | T  | V | T | L | A | G | E | S | V |   |   |   |   |   |   |   |   |   |   |
| TS  | 15 | Pbcb | 476 | P   | L | A | H | G | A | I | S  | O | S  | G | I | T | H | E | P | I | C | V | P | N | L | I | C | A | L  | L | N | V | M | O | A | E | S | V | S | T | L | R | T  | V | T | L | A | G | E | S |   |   |   |   |   |   |   |   |   |   |   |
| OSY | SE | Pbcb | 479 | L   | T | E | N | T | E | A | I  | Q | H  | Q | H | I | L | W | L | T | A | G | L | E | H | V | N | E | -- | N | O | L | A | E | Q | G | V | Q | Q | L | L | G | G  | V | S | K | T | H | A |   |   |   |   |   |   |   |   |   |   |   |   |

FIG. 17B

|             |      |                       |                                               |
|-------------|------|-----------------------|-----------------------------------------------|
| A6_61_pbtB  | 536  | PNVKLFNBYCPTENSVAATC  | ---AIGLEKDDQRTTICTPIENASVLINNTSGELQPLHVPC     |
| TS_15_pbtB  | 536  | PNVKLFNBYCPTENSVAATC  | ---AIGLEKDDQRTTICTPIENASVLINNTSGELQPLHVPC     |
| OSY_SE_pbtB | 538  | QDDELVNGYCPTENPIFTCCH | EISADTERLSIPICERPIANTCVYLDZAGKLLPFCVVC        |
| A6_61_pbtB  | 593  | ELCIAGEGLARGYLNRPELT  | TEKPAAHFPVPCERIYETCD SARWLNSTIEYLGRIDHGV      |
| TS_15_pbtB  | 593  | ELCIAGEGLARGYLNRPELT  | TEKPAAHFPVPCERIYETCD SARWLNSTIEYLGRIDHGV      |
| OSY_SE_pbtB | 598  | ELYTGGGLARGYLNRPELT   | TEKPVDSFPVPCTRRYETCD SARWLNSTIEYLGRIDHGV      |
| A6_61_pbtB  | 653  | KIRGPRIELGSEIESSLKE   | MACVAREVIVDARPDGNGCQMLCAYMVADAEITVTELREALS    |
| TS_15_pbtB  | 653  | KIRGPRIELGSEIESSLKE   | MACVAREVIVDARPDGNGCQMLCAYMVADAEITVTELREALS    |
| OSY_SE_pbtB | 658  | KICGPRIELGSEIESSLKE   | MACVAREVIVDARPDGNGCQMLCAYMVADAEITVTELREALS    |
| A6_61_pbtB  | 713  | NLPDYMIPSHRFVQMEQLP   | LTPTSGKLDKSLPDPQANLAIGTEYIAPRTPLEARLAQINQE    |
| TS_15_pbtB  | 713  | NLPDYMIPSHRFVQMEQLP   | LTPTSGKLDKSLPDPQANLAIGTEYIAPRTPLEARLAQINQE    |
| OSY_SE_pbtB | 718  | ELPAMIPSHRFVQMEQLP    | LTPTSGKLDKSLPDPQANLAIGTEYIAPRTPLEARLAQINQE    |
| A6_61_pbtB  | 773  | SLGVEEVGCIKDNFFALG    | CHSLRAATLASKLHKELVNVHVPLEBDLFRNPTIEELALLMDGME |
| TS_15_pbtB  | 773  | SLGVEEVGCIKDNFFALG    | CHSLRAATLASKLHKELVNVHVPLEBDLFRNPTIEELALLMDGME |
| OSY_SE_pbtB | 778  | VLCGEKVEKDSFPEFEG     | CHSLRAATLASKLHKELVNVHVPLEBDLFRNPTIEELALLMDGME |
| A6_61_pbtB  | 833  | QQEFSAIERVKESSEYYS    | VSSACKRLYVLOOLEGAEQSYNMPGAMLLIEGLDREERLEASFR  |
| TS_15_pbtB  | 833  | QQEFSAIERVKESSEYYS    | VSSACKRLYVLOOLEGAEQSYNMPGAMLLIEGLDREERLEASFR  |
| OSY_SE_pbtB | 838  | RQEEQCLPLDEREYYPV     | SSACKRLYVLOOLEGAEQSYNMPGAMLLIEGLDREERLEASFR   |
| A6_61_pbtB  | 893  | KLIARHETLRTGTFELMD    | GEVPVKVYQVSEPAIEMQASEEAAQKAREPIRAFOLMTPTPL    |
| TS_15_pbtB  | 893  | KLIARHETLRTGTFELMD    | GEVPVKVYQVSEPAIEMQASEEAAQKAREPIRAFOLMTPTPL    |
| OSY_SE_pbtB | 898  | SLIQRHETLRTGTFELMD    | GEVPVKVYQVSEPAIEMQASEEAAQKAREPIRAFOLMTPTPL    |
| A6_61_pbtB  | 953  | LRVGLIEMAPDRHVLLYD    | MHHIISDCASMGVVEEFARLYGSEELPPLRIQYKDFAAWQQ     |
| TS_15_pbtB  | 953  | LRVGLIEMAPDRHVLLYD    | MHHIISDCASMGVVEEFARLYGSEELPPLRIQYKDFAAWQQ     |
| OSY_SE_pbtB | 958  | LRVGLIEMAPDRHVLLYD    | MHHIISDCASMGVVEEFARLYGSEELPPLRIQYKDFAAWQQ     |
| A6_61_pbtB  | 1013 | SEAAQKRSKQCEYVWLQ     | TFGGELPVLELPTDYARPAIQSYEGEYETFTVDSDISTALQRL   |
| TS_15_pbtB  | 1013 | SEAAQKRSKQCEYVWLQ     | TFGGELPVLELPTDYARPAIQSYEGEYETFTVDSDISTALQRL   |
| OSY_SE_pbtB | 1018 | SEAAQKRSKQCEYVWLQ     | TFGGELPVLELPTDYARPAIQSYEGEYETFTVDSDISTALQRL   |

FIG. 17C

|        |      |      |                                                                 |
|--------|------|------|-----------------------------------------------------------------|
| AS_61  | pbcb | 1073 | AADSGTLLYMLLAAAYTVLLHKYTCQEDIVVCTTNAGRMHDDLOQLICMFVNTLAIRNYP    |
| TS_15  | pbcb | 1073 | AADSGTLLYMLLAAAYTVLLHKYTCQEDIVVCTTNAGRMHDDLOQLICMFVNTLAIRNYP    |
| OSY_SE | pbcb | 1073 | AADSGTLLYMLLAAAYTVLLHKYTCQEDIVVCTTNAGRMHDDLOQLICMFVNTLAIRNYP    |
| AS_61  | pbcb | 1133 | ACESTFRAYLEQVKEQALAAFEHQEYPPFEELVEKLEVTTRDMSRNPLPDTMFSLQNMENKD  |
| TS_15  | pbcb | 1133 | ACESTFRAYLEQVKEQALAAFEHQEYPPFEELVEKLEVTTRDMSRNPLPDTMFSLQNMENKD  |
| OSY_SE | pbcb | 1133 | ACESTFRAYLEQVKEQALAAFEHQEYPPFEELVEKLEVTTRDMSRNPLPDTMFSLQNMENKD  |
| AS_61  | pbcb | 1193 | FELPCLQLKPYCFEHQISKFDLSLDVAEGADCLACSLAYASSLYRQDTIVRMAKHVYRQLL   |
| TS_15  | pbcb | 1193 | FELPCLQLKPYCFEHQISKFDLSLDVAEGADCLACSLAYASSLYRQDTIVRMAKHVYRQLL   |
| OSY_SE | pbcb | 1193 | FELPCLQLKPYCFEHQISKFDLSLDVAEGADCLACSLAYASSLYRQDTIVRMAKHVYRQLL   |
| AS_61  | pbcb | 1253 | ESIAQSPEAQISVLGMLTPGEGEQIRFKFNHDPSSMEQKHTVHQLCEEQAAITPERTAVV    |
| TS_15  | pbcb | 1253 | ESIAQSPEAQISVLGMLTPGEGEQIRFKFNHDPSSMEQKHTVHQLCEEQAAITPERTAVV    |
| OSY_SE | pbcb | 1253 | ESIAQSPEAQISVLGMLTPGEGEQIRFKFNHDPSSMEQKHTVHQLCEEQAAITPERTAVV    |
| AS_61  | pbcb | 1313 | HEHEQLSIRRELNERANRLARTLRQHGVQPEQLVGIADRSLDIMIVGIMAILKAGCAYVPI   |
| TS_15  | pbcb | 1313 | HEHEQLSIRRELNERANRLARTLRQHGVQPEQLVGIADRSLDIMIVGIMAILKAGCAYVPI   |
| OSY_SE | pbcb | 1313 | HEHEQLSIRRELNERANRLARTLRQHGVQPEQLVGIADRSLDIMIVGIMAILKAGCAYVPI   |
| AS_61  | pbcb | 1373 | DPKYPEERIIRYMLSDSKANVLVTQSHLOSLSSFPDGTWVLLDEESSYAEADAANLVSI     |
| TS_15  | pbcb | 1373 | DPKYPEERIIRYMLSDSKANVLVTQSHLOSLSSFPDGTWVLLDEESSYAEADAANLVSI     |
| OSY_SE | pbcb | 1373 | DPKYPEERIIRYMLSDSKANVLVTQSHLOSLSSFPDGTWVLLDEESSYAEADAANLVSI     |
| AS_61  | pbcb | 1433 | HLAYVIYTSCTTQPKGAMIEHRQLTVMAKAWEREYRLREESIIRMMQNASFSPDVPFSCDL   |
| TS_15  | pbcb | 1433 | HLAYVIYTSCTTQPKGAMIEHRQLTVMAKAWEREYRLREESIIRMMQNASFSPDVPFSCDL   |
| OSY_SE | pbcb | 1433 | HLAYVIYTSCTTQPKGAMIEHRQLTVMAKAWEREYRLREESIIRMMQNASFSPDVPFSCDL   |
| AS_61  | pbcb | 1493 | IRALLHGGCELVLCPERANRANPAEIEELIRKKHRLHMPDCTPSIYIPLMEYVVENKLDISSL |
| TS_15  | pbcb | 1493 | IRALLHGGCELVLCPERANRANPAEIEELIRKKHRLHMPDCTPSIYIPLMEYVVENKLDISSL |
| OSY_SE | pbcb | 1493 | IRALLHGGCELVLCPERANRANPAEIEELIRKKHRLHMPDCTPSIYIPLMEYVVENKLDISSL |
| AS_61  | pbcb | 1553 | KLVAVGSDYCPPDEFCKMLDRFGSQPRIINSYGVTEETCIDASYIEPTTPTVPRALPICKP   |
| TS_15  | pbcb | 1553 | KLVAVGSDYCPPDEFCKMLDRFGSQPRIINSYGVTEETCIDASYIEPTTPTVPRALPICKP   |
| OSY_SE | pbcb | 1553 | KLVAVGSDYCPPDEFCKMLDRFGSQPRIINSYGVTEETCIDASYIEPTTPTVPRALPICKP   |

FIG. 17D

|        |      |      |                                                                |
|--------|------|------|----------------------------------------------------------------|
| A6_61  | pbcb | 1613 | LPGVYIMDQQRSLLPVGVIGELYIGGPCVGRGYWNRSEMTNKKFYDPPFLQDYMRYPT     |
| TS_15  | pbcb | 1613 | LPGVYIMDQQRSLLPVGVIGELYIGGPCVGRGYWNRSEMTNKKFYDPPFLQDYMRYPT     |
| OSY_SE | pbcb | 1618 | LPGVYIMDQQRSLLPVGVIGELYIGGPCVGRGYWNRSEMTNKKFYDPPFLQDYMRYPT     |
| A6_61  | pbcb | 1673 | GDLARMPDGNIEYLGRIDHQAIRGYRIEIGEVESKLLKVEYVRESVVARQDPNCTKA      |
| TS_15  | pbcb | 1673 | GDLARMPDGNIEYLGRIDHQAIRGYRIEIGEVESKLLKVEYVRESVVARQDPNCTKA      |
| OSY_SE | pbcb | 1678 | GDLARMPDGNIEYLGRIDHQAIRGYRIEIGEVESKLLKVEYVRESVVARQDPNCTKA      |
| A6_61  | pbcb | 1733 | LCAYFVADENLTVSELRSALADELPAYMIPSYFVQLDRPLTPNCKVDRKALPAPEAGAE    |
| TS_15  | pbcb | 1733 | LCAYFVADENLTVSELRSALADELPAYMIPSYFVQLDRPLTPNCKVDRKALPAPEAGAE    |
| OSY_SE | pbcb | 1738 | LCAYFVADENLTVSELRSALADELPAYMIPSYFVQLDRPLTPNCKVDRKALPAPEAGAE    |
| A6_61  | pbcb | 1793 | TGIEYVAPRTESEELALANVMQTVLGIERVGVGDHFFELGGDSIKSIQVASRLQQAGYKLE  |
| TS_15  | pbcb | 1793 | TGIEYVAPRTESEELALANVMQTVLGIERVGVGDHFFELGGDSIKSIQVASRLQQAGYKLE  |
| OSY_SE | pbcb | 1798 | TGIEYVAPRTESEELALANVMQTVLGIERVGVGDHFFELGGDSIKSIQVASRLQQAGYKLE  |
| A6_61  | pbcb | 1853 | IRDLFKYPTIAQLGSEHLQASKVADQGEVSGDVPLTPILGWFFEQQPADAHYINQSIMLY   |
| TS_15  | pbcb | 1853 | IRDLFKYPTIAQLGSEHLQASKVADQGEVSGDVPLTPILGWFFEQQPADAHYINQSIMLY   |
| OSY_SE | pbcb | 1858 | IRDLFKYPTIAQLGSEHLQASKVADQGEVSGDVPLTPILGWFFEQQPADAHYINQSIMLY   |
| A6_61  | pbcb | 1913 | KREGPDAAIRNVLQAATVTEHHDALRIVPRRNDQGDYTTANNEAIEEGELPHLEVLNLTGEP |
| TS_15  | pbcb | 1913 | KREGPDAAIRNVLQAATVTEHHDALRIVPRRNDQGDYTTANNEAIEEGELPHLEVLNLTGEP |
| OSY_SE | pbcb | 1918 | KREGPDAAIRNVLQAATVTEHHDALRIVPRRNDQGDYTTANNEAIEEGELPHLEVLNLTGEP |
| A6_61  | pbcb | 1973 | SGDHEQNVHQIIEAKAEIQREDFDLHDGELARAGLCTDEGDHLLLVNHHGVVDGVSWEI    |
| TS_15  | pbcb | 1973 | SGDHEQNVHQIIEAKAEIQREDFDLHDGELARAGLCTDEGDHLLLVNHHGVVDGVSWEI    |
| OSY_SE | pbcb | 1977 | SGDHEQNVHQIIEAKAEIQREDFDLHDGELARAGLCTDEGDHLLLVNHHGVVDGVSWEI    |
| A6_61  | pbcb | 2033 | LLEDIAAGYEOALKEGPVRLPAKTDSFRTWANGLASVARSSEAMIEECQFWEQACANATSI  |
| TS_15  | pbcb | 2033 | LLEDIAAGYEOALKEGPVRLPAKTDSFRTWANGLASVARSSEAMIEECQFWEQACANATSI  |
| OSY_SE | pbcb | 2031 | LLEDIAAGYEOALKEGPVRLPAKTDSFRTWANGLASVARSSEAMIEECQFWEQACANATSI  |
| A6_61  | pbcb | 2093 | LPLEKDFEASTSLQQDSESVVWNSREETDMLLKXVHRAINTDNDILLALALQALQQWC     |
| TS_15  | pbcb | 2093 | LPLEKDFEASTSLQQDSESVVWNSREETDMLLKXVHRAINTDNDILLALALQALQQWC     |
| OSY_SE | pbcb | 2090 | LPLEKDFEASTSLQQDSESVVWNSREETDMLLKXVHRAINTDNDILLALALQALQQWC     |

FIG. 17E

|     |    |      |      |                     |                 |      |      |      |      |      |       |       |      |     |      |     |
|-----|----|------|------|---------------------|-----------------|------|------|------|------|------|-------|-------|------|-----|------|-----|
| A6  | 61 | pbtB | 2153 | GHEKALVTLECHGRENIMP | ELDI            | ERTV | GWFT | SERY | PFLL | ESDP | PKSLS | SYRI  | KRM  | KEN | LRR  | I   |
| TS  | 15 | pbtB | 2153 | GHEKALVTLECHGRENIMP | ELDI            | ERTV | GWFT | SERY | PFLL | ESDP | PKSLS | SYRI  | KRM  | KEN | LRR  | I   |
| OSY | SE | pbtB | 2149 | GRD                 | VLVTLECHGRENIMP | ELDI | ERTV | GWFT | SERY | PFLL | ESDP  | PKSLS | SYRI | KRM | KEN  | LRR |
| A6  | 61 | pbtB | 2213 | PNKGIGYGIHRYLS      | SGM             | SGT  | ENV  | SRSE | ASAO | PEIS | FN    | YLCG  | OFDD | LON | NEME | VS  |
| TS  | 15 | pbtB | 2213 | PNKGIGYGIHRYLS      | SGM             | SGT  | ENV  | SRSE | ASAO | PEIS | FN    | YLCG  | OFDD | LON | NEME | VS  |
| OSY | SE | pbtB | 2209 | PNKGIGYGIHRYLS      | SGM             | SGT  | ENV  | SRSE | ASAO | PEIS | FN    | YLCG  | OFDD | LON | NEME | VS  |
| A6  | 61 | pbtB | 2273 | AEISVRQARN          | TTLD            | FN   | GMIS | ACV  | LAL  | EV   | SY    | SS    | KO   | YRR | DTI  | DR  |
| TS  | 15 | pbtB | 2273 | AEISVRQARN          | TTLD            | FN   | GMIS | ACV  | LAL  | EV   | SY    | SS    | KO   | YRR | DTI  | DR  |
| OSY | SE | pbtB | 2263 | ME                  | SRQARN          | THAL | DING | AD   | CS   | LAL  | EV    | SY    | SS   | KO  | YRR  | DTI |
| A6  | 61 | pbtB | 2333 | KDKPELT             | PSD             | VL   | VN   | GL   | IED  | LER  | IA    | EQ    | TR   | D   | LG   | DI  |
| TS  | 15 | pbtB | 2333 | KDKPELT             | PSD             | VL   | VN   | GL   | IED  | LER  | IA    | EQ    | TR   | D   | LG   | DI  |
| OSY | SE | pbtB | 2323 | KDKPELT             | PSD             | VL   | VN   | GL   | IED  | LER  | IA    | EQ    | TR   | D   | LG   | DI  |
| A6  | 61 | pbtB | 2393 | PEOTRPT             | IQG             | EL   | D    | V    | Q    | L    | P     | A     | S    | S   | L    | D   |
| TS  | 15 | pbtB | 2393 | PEOTRPT             | IQG             | EL   | D    | V    | Q    | L    | P     | A     | S    | S   | L    | D   |
| OSY | SE | pbtB | 2383 | PEOTRPT             | IQG             | EL   | D    | V    | Q    | L    | P     | A     | S    | S   | L    | D   |
| A6  | 61 | pbtB | 2453 | DELPE               | DEK             | Q    | DR   | VE   | AM   | AQ   | AD    | ER    | CG   | FD  | LE   | CD  |
| TS  | 15 | pbtB | 2453 | DELPE               | DEK             | Q    | DR   | VE   | AM   | AQ   | AD    | ER    | CG   | FD  | LE   | CD  |
| OSY | SE | pbtB | 2443 | CALPE               | AE              | ET   | HE   | VE   | TE   | Q    | ED    | ER    | CG   | FD  | LE   | CD  |
| A6  | 61 | pbtB | 2513 | POLTQEW             | LET             | YS   | DS   | VN   | GR   | SS   | SS    | SS    | SS   | SS  | SS   | SS  |
| TS  | 15 | pbtB | 2513 | POLTQEW             | LET             | YS   | DS   | VN   | GR   | SS   | SS    | SS    | SS   | SS  | SS   | SS  |
| OSY | SE | pbtB | 2503 | POLTQEW             | LET             | YS   | DS   | VN   | GR   | SS   | SS    | SS    | SS   | SS  | SS   | SS  |
| A6  | 61 | pbtB | 2573 | PQKSS               | GR              | SD   | VY   | I    | AD   | N    | V     | F     | E    | L   | G    | E   |
| TS  | 15 | pbtB | 2573 | PQKSS               | GR              | SD   | VY   | I    | AD   | N    | V     | F     | E    | L   | G    | E   |
| OSY | SE | pbtB | 2563 | PQKSS               | GR              | SD   | VY   | I    | AD   | N    | V     | F     | E    | L   | G    | E   |
| A6  | 61 | pbtB | 2623 | AVFGGV              | V               | S    | GR   | PA   | IP   | CI   | ES    | NI    | GL   | FI  | NI   | PI  |
| TS  | 15 | pbtB | 2623 | AVFGGV              | V               | S    | GR   | PA   | IP   | CI   | ES    | NI    | GL   | FI  | NI   | PI  |
| OSY | SE | pbtB | 2623 | AVFGGV              | V               | S    | GR   | PA   | IP   | CI   | ES    | NI    | GL   | FI  | NI   | PI  |

FIG. 17F

|     |    |    |      |                                                                  |
|-----|----|----|------|------------------------------------------------------------------|
| A6  | 61 | Pb | 2693 | PLYDIQALSTHKQDLINHLVFNYPMEEQMEQAC - DERGQLNITDVRVAEQTSYDPRNLV    |
| TS  | 15 | Pb | 2693 | PLYDIQALSTHKQDLINHLVFNYPMEEQMEQAC - DERGQLNITDVRVAEQTSYDPRNLV    |
| OSY | SE | Pb | 2683 | PLYDIQALSTHKQDLINHLVFNYPMEEQMEQAC - DERGQLNITDVRVAEQTSYDPRNLV    |
| A6  | 61 | Pb | 2752 | VMPGEDMMIRLEYNAVMYDRADMER RQHLIHVLEQVTADPAIAVKDVRLATDDEKABELL    |
| TS  | 15 | Pb | 2752 | VMPGEDMMIRLEYNAVMYDRADMER RQHLIHVLEQVTADPAIAVKDVRLATDDEKABELL    |
| OSY | SE | Pb | 2743 | VMPGEDMMIRLEYNAVMYDRADMER RQHLIHVLEQVTADPAIAVKDVRLATDDEKABELL    |
| A6  | 61 | Pb | 2812 | TAFNDTESEYPREQMIHMPFEQVQRTPDATAVI CGAAAMTYREMMERANQLARTLRAAG     |
| TS  | 15 | Pb | 2812 | TAFNDTESEYPREQMIHMPFEQVQRTPDATAVI CGAAAMTYREMMERANQLARTLRAAG     |
| OSY | SE | Pb | 2803 | TAFNDTESEYPREQMIHMPFEQVQRTPDATAVI CGAAAMTYREMMERANQLARTLRAAG     |
| A6  | 61 | Pb | 2872 | VVPDQIIVGIMAEERSELMVGIMCILKAGCAVYPIAPDYPSEERIRYMLDDSSAQVLIYQGS   |
| TS  | 15 | Pb | 2872 | VVPDQIIVGIMAEERSELMVGIMCILKAGCAVYPIAPDYPSEERIRYMLDDSSAQVLIYQGS   |
| OSY | SE | Pb | 2863 | VVPDQIIVGIMAEERSELMVGIMCILKAGCAVYPIAPDYPSEERIRYMLDDSSAQVLIYQGS   |
| A6  | 61 | Pb | 2932 | AGEAIDPAGRVINLDDADSYDQDSSNLEEMVNKPTDIAYIYTSGTIGRKPQVMVEHTSVI     |
| TS  | 15 | Pb | 2932 | AGEAIDPAGRVINLDDADSYDQDSSNLEEMVNKPTDIAYIYTSGTIGRKPQVMVEHTSVI     |
| OSY | SE | Pb | 2923 | AGEAIDPAGRVINLDDADSYDQDSSNLEEMVNKPTDIAYIYTSGTIGRKPQVMVEHTSVI     |
| A6  | 61 | Pb | 2992 | NRLLMQKRYPIGADDTIMOKTAITFDVSVMELFWAFVGSKVLMPLVGSSEKNPAAIVEA      |
| TS  | 15 | Pb | 2992 | NRLLMQKRYPIGADDTIMOKTAITFDVSVMELFWAFVGSKVLMPLVGSSEKNPAAIVEA      |
| OSY | SE | Pb | 2983 | NRLLMQKRYPIGADDTIMOKTAITFDVSVMELFWAFVGSKVLMPLVGSSEKNPAAIVEA      |
| A6  | 61 | Pb | 3052 | IEQYHISTMHFVPSMLHAFLEHIEQLPEAEERER - LSPLQVFTSGEALLASQVERPHQYV   |
| TS  | 15 | Pb | 3052 | IEQYHISTMHFVPSMLHAFLEHIEQLPEAEERER - LSPLQVFTSGEALLASQVERPHQYV   |
| OSY | SE | Pb | 3043 | IEQYHISTMHFVPSMLHAFLEHIEQLPEAEERER - LSPLQVFTSGEALLASQVERPHQYV   |
| A6  | 61 | Pb | 3111 | VPASGARLINLYCPTATVDVTYFPDCEPGQTYVSPICKPIDNTIRIIVNEMHQVQPIGV      |
| TS  | 15 | Pb | 3111 | VPASGARLINLYCPTATVDVTYFPDCEPGQTYVSPICKPIDNTIRIIVNEMHQVQPIGV      |
| OSY | SE | Pb | 3103 | VPASGARLINLYCPTATVDVTYFPDCEPGQTYVSPICKPIDNTIRIIVNEMHQVQPIGV      |
| A6  | 61 | Pb | 3171 | AGELCIAGVGLARGVWNRPELTIEEKFFVLVP - SVGERMYRTGDLARWLPDGNIEYLGRIDR |
| TS  | 15 | Pb | 3171 | AGELCIAGVGLARGVWNRPELTIEEKFFVLVP - SVGERMYRTGDLARWLPDGNIEYLGRIDR |
| OSY | SE | Pb | 3163 | AGELCIAGVGLARGVWNRPELTIEEKFFVLVP - SVGERMYRTGDLARWLPDGNIEYLGRIDR |

FIG. 17G

|             |      |                                                                  |
|-------------|------|------------------------------------------------------------------|
| A6_61_PbCb  | 3230 | QVKIRGYRIELGHELETAALLSIDAVRETVVAREDESGQKSLCAYVADGEATSSDLRAAL     |
| TS_15_PbCb  | 3230 | QVKIRGYRIELGHELETAALLKIDAVRETVVAREDESGQKSLCAYVADGEATSSDLRAAL     |
| OSY_SE_PbCb | 3223 | QVKIRGYRIELGHELETAALLKIDAVRETVVAREDESGQKSLCAYVADGEATSSDLRAAL     |
| A6_61_PbCb  | 3290 | AAELPSYMIIPSYFVRLIQMPLAPNGKLDKALPAPERSLQVESYVAPRTEAEQMLATVW      |
| TS_15_PbCb  | 3290 | AAELPSYMIIPSYFVRLIQMPLAPNGKLDKALPAPERSLQVESYVAPRTEAEQMLATVW      |
| OSY_SE_PbCb | 3283 | AAELPSYMIIPSYFVRLIQMPLAPNGKLDKALPAPERSLQVESYVAPRTEAEQMLATVW      |
| A6_61_PbCb  | 3350 | QAVLCIERVCGITDHFPELGGDSIKSIQVAARMQOQACFKLEIRDLFKYPTVTOLVPPYMOPI  |
| TS_15_PbCb  | 3350 | QAVLCIERVCGITDHFPELGGDSIKSIQVAARMQOQACFKLEIRDLFKYPTVTOLVPPYMOPI  |
| OSY_SE_PbCb | 3343 | QAVLCIERVCGITDHFPELGGDSIKSIQVAARMQOQACFKLEIRDLFKYPTVTOLVPPYMOPI  |
| A6_61_PbCb  | 3410 | NRTADQGEVVGCEVPMTPILHWFPEHQOQFANPHHFNQSVMLYRKDGCFVADAVCKALHKLVEH |
| TS_15_PbCb  | 3410 | NRTADQGEVVGCEVPMTPILHWFPEHQOQFANPHHFNQSVMLYRKDGCFVADAVCKALHKLVEH |
| OSY_SE_PbCb | 3403 | NRTADQGEVVGCEVPMTPILHWFPEHQOQFANPHHFNQSVMLYRKDGCFVADAVCKALHKLVEH |
| A6_61_PbCb  | 3470 | HDALRIVIQRTQCEYSELNRRSLVEGELFSMEIDLTQSDPFAAIEAEANHIQGSIDLQ       |
| TS_15_PbCb  | 3470 | HDALRIVIQRTQCEYSELNRRSLVEGELFSMEIDLTQSDPFAAIEAEANHIQGSIDLQ       |
| OSY_SE_PbCb | 3463 | HDALRIVIQRTQCEYSELNRRSLVEGELFSMEIDLTQSDPFAAIEAEANHIQGSIDLQ       |
| A6_61_PbCb  | 3530 | ACPLVKAGLFHGSDDGPHLLVVIHHAVIDGVSWRILLLEDLAACGYEQALNQKQVRLPMTDS   |
| TS_15_PbCb  | 3530 | ACPLVKAGLFHGSDDGPHLLVVIHHAVIDGVSWRILLLEDLAACGYEQALNQKQVRLPMTDS   |
| OSY_SE_PbCb | 3522 | ACPLVKAGLFHGSDDGPHLLVVIHHAVIDGVSWRILLLEDLAACGYEQALNQKQVRLPMTDS   |
| A6_61_PbCb  | 3590 | FRTWAEQLVEYANSPANDKESAYNLSVAQTEVAALPKDSECTVSLQRDSESVVLEWMSD      |
| TS_15_PbCb  | 3590 | FRTWAEQLVEYANSPANDKESAYNLSVAQTEVAALPKDSECTVSLQRDSESVVLEWMSD      |
| OSY_SE_PbCb | 3583 | FRTWAEQLVEYANSPANDKESAYNLSVAQTEVAALPKDSECTVSLQRDSESVVLEWMSD      |
| A6_61_PbCb  | 3650 | TERLLKHVHRAYNTEMDDILLTALGRALMKWRCIGIRLVLTLGCHGRESILQDMDITRTVG    |
| TS_15_PbCb  | 3650 | TERLLKHVHRAYNTEMDDILLTALGRALMKWRCIGIRLVLTLGCHGRESILQDMDITRTVG    |
| OSY_SE_PbCb | 3643 | TERLLKHVHRAYNTEMDDILLTALGRALMKWRCIGIRLVLTLGCHGRESILQDMDITRTVG    |
| A6_61_PbCb  | 3710 | WFTTEYFPFELGMEANDSLGSGQIKKVKVEDLRIPNKGIGYGLFRYLSNSGKQAWNDAPTQ    |
| TS_15_PbCb  | 3710 | WFTTEYFPFELGMEANDSLGSGQIKKVKVEDLRIPNKGIGYGLFRYLSNSGKQAWNDAPTQ    |
| OSY_SE_PbCb | 3703 | WFTTEYFPFELGMEANDSLGSGQIKKVKVEDLRIPNKGIGYGLFRYLSNSGKQAWNDAPTQ    |

FIG. 17H

|     |    |    |      |                    |                         |                |         |
|-----|----|----|------|--------------------|-------------------------|----------------|---------|
| A6  | 61 | Pb | 3770 | IRYNVLCQFPDADLNNKE | SVSPYASGSSEISDEQERKYPDL | INGVIAEGQTLGLS | SVKE    |
| TS  | 15 | Pb | 3770 | IRYNVLCQFPDADLNNKE | SVSPYASGSSEISDEQERKYPDL | INGVIAEGQTLGLS | SVKE    |
| OSY | SE | Pb | 3763 | IRYNVLCQFPDADLNNKE | SVSPYASGSSEISDEQERKYPDL | INGVIAEGQTLGLS | SVKE    |
| A6  | 61 | Pb | 3830 | YRKETMEEELGDF      | LTESLKEII               | AHCE           | QERTQ   |
| TS  | 15 | Pb | 3830 | YRKETMEEELGDF      | LTESLKEII               | AHCE           | QERTQ   |
| OSY | SE | Pb | 3823 | YRKETMEEELGDF      | LTESLKEII               | AHCE           | QERTQ   |
| A6  | 61 | Pb | 3890 | ENVYALT            | PMQKGMWFS               | AMDEL          | TGAYHEQ |
| TS  | 15 | Pb | 3890 | ENVYALT            | PMQKGMWFS               | AMDEL          | TGAYHEQ |
| OSY | SE | Pb | 3883 | ENVYALT            | PMQKGMWFS               | AMDEL          | TGAYHEQ |
| A6  | 61 | Pb | 3950 | FISCPQGE           | PVQV                    | FRNK           | PIGFS   |
| TS  | 15 | Pb | 3950 | FISCPQGE           | PVQV                    | FRNK           | PIGFS   |
| OSY | SE | Pb | 3943 | FISCPQGE           | PVQV                    | FRNK           | PIGFS   |
| A6  | 61 | Pb | 4010 | SAIRTC             | ELSC                    | RVL            | NS      |
| TS  | 15 | Pb | 4010 | SAIRTC             | ELSC                    | RVL            | NS      |
| OSY | SE | Pb | 4003 | SAIRTC             | ELSC                    | RVL            | NS      |
| A6  | 61 | Pb | 4069 | WLGQODE            | EA                      | AGTY           | NS      |
| TS  | 15 | Pb | 4069 | WLGQODE            | EA                      | AGTY           | NS      |
| OSY | SE | Pb | 4063 | WLGQODE            | EA                      | AGTY           | NS      |
| A6  | 61 | Pb | 4129 | ARQH               | QVTL                    | N              | TL      |
| TS  | 15 | Pb | 4129 | ARQH               | QVTL                    | N              | TL      |
| OSY | SE | Pb | 4122 | ARQH               | QVTL                    | N              | TL      |
| A6  | 61 | Pb | 4189 | KCE                | ST                      | SP             | AE      |
| TS  | 15 | Pb | 4189 | KCE                | ST                      | SP             | AE      |
| OSY | SE | Pb | 4182 | KCE                | ST                      | SP             | AE      |
| A6  | 61 | Pb | 4249 | QAG                | CD                      | EH             | CM      |
| TS  | 15 | Pb | 4249 | QAG                | CD                      | EH             | CM      |
| OSY | SE | Pb | 4242 | QAG                | CD                      | EH             | CM      |

FIG. 17I

|             |      |                                                                 |
|-------------|------|-----------------------------------------------------------------|
| A6_61_pbtB  | 4309 | ILSQIVDMPRAVEDLELATEAEKSEVQSFNDTFTNYPRDMLHLPEEQAEHPDAVA         |
| TS_15_pbtB  | 4309 | ILSQIVDMPRAVEDLELATEAEKSEVQSFNDTFTNYPRDMLHLPEEQAEHPDAVA         |
| OSY_SE_pbtB | 4302 | ILEQIARAFQVTVSELELATEAEQAEITSIENNAETEPYPRDKTDEHLPEEQAEHPDAVA    |
| A6_61_pbtB  | 4369 | ISPRDFQMTYRDINDRVNHLARTLRAVGVGTDXLVGLMSERSPDMLICILAILKAGCGYV    |
| TS_15_pbtB  | 4369 | ISPRDFQMTYRDINDRVNHLARTLRAVGVGTDXLVGLMSERSPDMLICILAILKAGCGYV    |
| OSY_SE_pbtB | 4362 | VMYENSCQETRELNERANRLARTLRADCAQADLVGLMVESLDMVYGLAILKAGCGYV       |
| A6_61_pbtB  | 4429 | PIDPEYPCERIRYMLEDSCARIMLAQQHLTGKIPVMDASPLDAIINIDTETSVDNCGSNL    |
| TS_15_pbtB  | 4429 | PIDPEYPCERIRYMLEDSCARIMLAQQHLTGKIPVMDASPLDAIINIDTETSVDNCGSNL    |
| OSY_SE_pbtB | 4422 | PIDPEYPCERIRYMLEDSCATCTHETCTQERHLCERIPQACTRYV---LDDSEHESDSENL   |
| A6_61_pbtB  | 4489 | EAQTDASSENLAQVIYTSCTTGCKPKGNLTTHRNIVKVVRETEYIDITNHDNVVLQMSYAP   |
| TS_15_pbtB  | 4489 | EAQTDASSENLAQVIYTSCTTGCKPKGNLTTHRNIVKVVRETEYIDITNHDNVVLQMSYAP   |
| OSY_SE_pbtB | 4477 | DLNNGPA--DLAYVIYTSCTTGCKPKGNLTTHRNIVRVRVQCAQYIDICEQDNVVLQMSYAP  |
| A6_61_pbtB  | 4549 | DGSTEDIYGALLNGAKLVIVPHETLLLEVVRQLAEKLVQEKISVMFITTAFFNVVLVDVQASC |
| TS_15_pbtB  | 4549 | DGSTEDIYGALLNGAKLVIVPHETLLLEVVRQLAEKLVQEKISVMFITTAFFNVVLVDVQASC |
| OSY_SE_pbtB | 4535 | DGSTEDFYGALLNGAKLVIVPQETLLVEERLAELIEREISVMFITTAFFNVVLVDVQASC    |
| A6_61_pbtB  | 4609 | LSNIRAILFGCGERVSVSHVRKALNHVAPGSLKHVYCGPTSESTVPATCHDVHEVTENAVTVP |
| TS_15_pbtB  | 4609 | LSNIRAILFGCGERVSVSHVRKALNHVAPGSLKHVYCGPTSESTVPATCHDVHEVTENAVTVP |
| OSY_SE_pbtB | 4595 | LSNIRAILFGCGERVSVSHVRKALNHVAPGSLKHVYCGPTSESTVPATCHDVHEVTENAVTVP |
| A6_61_pbtB  | 4669 | IGRPISNTSEIYIVDANNILOPVGAGELCVAGDGLARGYLMRPDLTAEEKFVDSPIVQGER   |
| TS_15_pbtB  | 4669 | IGRPISNTSEIYIVDANNILOPVGAGELCVAGDGLARGYLMRPDLTAEEKFVDSPIVQGER   |
| OSY_SE_pbtB | 4655 | IGRPISNTSEIYIVNNEENCLQPGVAGELCVAGDGLARGYLMRPDLTAEEKFVDSPIVQGER  |
| A6_61_pbtB  | 4729 | MYRTGDLAKWLPDGSIEYVGRIDQQVKIRCYRIELGELIEAQLNVEDVQEAUVVARDTDT    |
| TS_15_pbtB  | 4729 | MYRTGDLAKWLPDGSIEYVGRIDQQVKIRCYRIELGELIEAQLNVEDVQEAUVVARDTDT    |
| OSY_SE_pbtB | 4715 | MYRTGDLAKWLPDGSIEYVGRIDQQVKIRCYRIELGELIEAQLNVEDVQEAUVVARDTDT    |
| A6_61_pbtB  | 4789 | GEKQLCAYIVAMRPLEANHLREVMCOAMPSEYMLPAHPFQLEQLPLTFNGKVDKALPAPPE   |
| TS_15_pbtB  | 4789 | GEKQLCAYIVAMRPLEANHLREVMCOAMPSEYMLPAHPFQLEQLPLTFNGKVDKALPAPPE   |
| OSY_SE_pbtB | 4775 | GEKQLCAYIVAMRPLEANHLREVMCOAMPSEYMLPAHPFQLEQLPLTFNGKVDKALPAPPE   |

|             |      |                                                                 |
|-------------|------|-----------------------------------------------------------------|
| A6_61_pbtB  | 4849 | EC-RSGETPVLPPTPLEAQLVQIQWQVLCISSESVTQHFELGCHSLKATLLVMRLHQEL     |
| TS_15_pbtB  | 4849 | EC-RSGETPVAPRTPLEAQLVQIQWQVLCISSESVTQHFELGCHSLKATLLVMRLHQEL     |
| OSY_SE_pbtB | 4835 | BHVQSGTEVTPAPRTPCEQDARINQCEVLCSEKQGVNDNPFELGCHSLKATLLVMRLHQEL   |
| A6_61_pbtB  | 4908 | NIELPLKDVQYPTLEVMAKRLSNAGSGSHVSIIPVAAPSQHYPVSSAQKRLYILHQLEGA    |
| TS_15_pbtB  | 4908 | NIELPLKDVQYPTLEAMAKRLSNAGSGSHVSIIPVAAPSQHYPVSSAQKRLYILHQLEGA    |
| OSY_SE_pbtB | 4895 | SHIELPLKDVQYKPTLEAMAKRLSNAGSGSHVSIIPVAAPSQHYPVSSAQKRLYILHQLEGA  |
| A6_61_pbtB  | 4968 | ELSYNMPNMLLEGQAVDLGRLEAPFRLIERHETLRTGPELVNGEPVQRIYPEVDFAIER     |
| TS_15_pbtB  | 4968 | ELSYNMPNMLLEGQAVDLGRLEAPFRLIERHETLRTGPELVNGEPVQRIYPEVDFAIER     |
| OSY_SE_pbtB | 4955 | ELSYNMPNMLLEGQAVDLGRLEAPFRLIERHETLRTGPELVNGEPVQRIYPEVDFAIER     |
| A6_61_pbtB  | 5028 | VLAEEGASGLMQQFVRSFQLEKPPLLRIGCIELSEERSILMFDNMHIIISDGTSMGILIN    |
| TS_15_pbtB  | 5028 | VLAEEGASGLMQQFVRSFQLEKPPLLRIGCIELSEERSILMFDNMHIIISDGTSMGILIN    |
| OSY_SE_pbtB | 5015 | MQASEEEMEARERQFVRSFQLEKPPLLRIGCIELSEERSILMFDNMHIIISDGTSMGILIN   |
| A6_61_pbtB  | 5088 | EFVHLYSGARELTPLRIQYKDYAVWQOQSDTQGMANKLQEGYNLKVLCGCELPVLEMPDTSIR |
| TS_15_pbtB  | 5088 | EFVHLYSGARELTPLRIQYKDYAVWQOQSDTQGMANKLQEGYNLKVLCGCELPVLEMPDTSIR |
| OSY_SE_pbtB | 5075 | EFVHLYSGARELTPLRIQYKDYAVWQOQSDTQGMANKLQEGYNLKVLCGCELPVLEMPDTSIR |
| A6_61_pbtB  | 5148 | PTTQSPFGDLLOPDLDPVRSAGLRRIAENGATMYMVLALYKTMHLYKSCQEDIIIVGTP     |
| TS_15_pbtB  | 5148 | PTTQSPFGDLLOPDLDPVRSAGLRRIAENGATMYMVLALYKTMHLYKSCQEDIIIVGTP     |
| OSY_SE_pbtB | 5135 | PAVQSPFGDLLOPDLDPVRSAGLRRIAENGATMYMVLALYKTMHLYKSCQEDIIIVGTP     |
| A6_61_pbtB  | 5208 | IACRNHGDLPQLLCMFVNTLAIRSYPAASKTFLSYLSEIKETTLGAFENQNYPFPEALVEO   |
| TS_15_pbtB  | 5208 | IACRNHGDLPQLLCMFVNTLAIRSYPAASKTFLSYLSEIKETTLGAFENQNYPFPEALVEO   |
| OSY_SE_pbtB | 5195 | IACRNHGDLPQLLCMFVNTLAIRSYPAASKTFLSYLSEIKETTLGAFENQNYPFPEALVEO   |
| A6_61_pbtB  | 5268 | VQVMRDMSRNVPVDTMFIQNADQGEKIDGRLQSVPRNHTVSKFDLTFQAREDEAEIIV      |
| TS_15_pbtB  | 5268 | VQVMRDMSRNVPVDTMFIQNADQGEKIDGRLQSVPRNHTVSKFDLTFQAREDEAEIIV      |
| OSY_SE_pbtB | 5255 | VQVMRDMSRNVPVDTMFIQNADQGEKIDGRLQSVPRNHTVSKFDLTFQAREDEAEIIV      |
| A6_61_pbtB  | 5328 | CSIEYATDLPERGCTIERMARHFEQQLVDAVLDNPPQASLSNLSMVTNSEKALLQDKFNDTDM |
| TS_15_pbtB  | 5328 | CSIEYATDLPERGCTIERMARHFEQQLVDAVLDNPPQASLSNLSMVTNSEKALLQDKFNDTDM |
| OSY_SE_pbtB | 5315 | CSIEYATDLPERGCTIERMARHFEQQLVDAVLDNPPQASLSNLSMVTNSEKALLQDKFNDTDM |

FIG. 17K

|             |      |                                                                |
|-------------|------|----------------------------------------------------------------|
| A6_61_PbCb  | 5388 | APPSDKTVHELPAEQVETPDAVAVVSGCCEQLSYGCELNRKANQLANKLREYGVTAEQPVG  |
| TS_15_PbCb  | 5388 | APPSDKTVHELPAEQVETPDAVAVVSGCCEQLSYGCELNRKANQLANKLREYGVTAEQPVG  |
| OSY_SE_PbCb | 5375 | GYREKTHQFEQVETPDAVAVVSGCCEQLSYGCELNRKANQLANKLREYGVTAEQPVG      |
| A6_61_PbCb  | 5448 | IIVERTLDTVVAVAVLKAAGTGFVPIIDPEYPTTRIRYMLADSGAKLVLAQSELPGLIIPDD |
| TS_15_PbCb  | 5448 | IIVERTLDTVVAVAVLKAAGTGFVPIIDPEYPTTRIRYMLADSGAKLVLAQSELPGLIIPDD |
| OSY_SE_PbCb | 5435 | IIVERTLDTVVAVAVLKAAGTGFVPIIDPEYPTTRIRYMLADSGAKLVLAQSELPGLIIPDD |
| A6_61_PbCb  | 5508 | VRLIDVRDESLYQGDGADVPNGSKPSENLIIYTSCTTGNPKGVMLERGNMNVNLLHYQOK   |
| TS_15_PbCb  | 5508 | VRLIDVRDESLYQGDGADVPNGSKPSENLIIYTSCTTGNPKGVMLERGNMNVNLLHYQOK   |
| OSY_SE_PbCb | 5495 | VRLIDVRDESLYQGDGADVPNGSKPSENLIIYTSCTTGNPKGVMLERGNMNVNLLHYQOK   |
| A6_61_PbCb  | 5568 | GTNIEMPERILOYASGSEFDVCYQEMPSALLFGGGLYXVDNEMRKDPVRLPQEIIEKHEIDV |
| TS_15_PbCb  | 5568 | GTNIEMPERILOYASGSEFDVCYQEMPSALLFGGGLYXVDNEMRKDPVRLPQEIIEKHEIDV |
| OSY_SE_PbCb | 5555 | GTNIEMPERILOYASGSEFDVCYQEMPSALLFGGGLYXVDNEMRKDPVRLPQEIIEKHEIDV |
| A6_61_PbCb  | 5628 | LYIPVAPLIKFIAPPEPNAEAPPKCVRHIIITAGEQLVVTVPQVQACLRDLICLHNHYGPSE |
| TS_15_PbCb  | 5628 | LYIPVAPLIKFIAPPEPNAEAPPKCVRHIIITAGEQLVVTVPQVQACLRDLICLHNHYGPSE |
| OSY_SE_PbCb | 5615 | LYIPVAPLIKFIAPPEPNAEAPPKCVRHIIITAGEQLVVTVPQVQACLRDLICLHNHYGPSE |
| A6_61_PbCb  | 5688 | THVVTIYTIMTPEDHAGVGLPPIGPIANTAIYIENDRLLELQPIGAGELIYSGDCVGRGYN  |
| TS_15_PbCb  | 5688 | THVVTIYTIMTPEDHAGVGLPPIGPIANTAIYIENDRLLELQPIGAGELIYSGDCVGRGYN  |
| OSY_SE_PbCb | 5675 | THVVTIYTIMTPEDHAGVGLPPIGPIANTAIYIENDRLLELQPIGAGELIYSGDCVGRGYN  |
| A6_61_PbCb  | 5748 | GRIDLTEERKFLDNPPVPGERLYKTGDVARNWLPDGSIEYVGRSDHQVKIRGPRIELGEVES |
| TS_15_PbCb  | 5748 | GRIDLTEERKFLDNPPVPGERLYKTGDVARNWLPDGSIEYVGRSDHQVKIRGPRIELGEVES |
| OSY_SE_PbCb | 5735 | GRIDLTEERKFLDNPPVPGERLYKTGDVARNWLPDGSIEYVGRSDHQVKIRGPRIELGEVES |
| A6_61_PbCb  | 5808 | QLLHVPAVQEATVVALEDHAGQKQLCAYFTAEISLTAGELRAVLSQELPGYMIPISEYFVQL |
| TS_15_PbCb  | 5808 | QLLHVPAVQEATVVALEDHAGQKQLCAYFTAEISLTAGELRAVLSQELPGYMIPISEYFVQL |
| OSY_SE_PbCb | 5795 | QLLHVPAVQEATVVALEDHAGQKQLCAYFTAEISLTAGELRAVLSQELPGYMIPISEYFVQL |
| A6_61_PbCb  | 5868 | ERLPLTPNGKIDRRALPKPEGGIEGTCTEYVAPRTTEARLARIWQDVLCGLSVGVKDNFF   |
| TS_15_PbCb  | 5868 | ERLPLTPNGKIDRRALPKPEGGIEGTCTEYVAPRTTEARLARIWQDVLCGLSVGVKDNFF   |
| OSY_SE_PbCb | 5855 | ERLPLTPNGKIDRRALPKPEGGIEGTCTEYVAPRTTEARLARIWQDVLCGLSVGVKDNFF   |

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FIG. 17L

|        |      |      |                                                                |                                       |
|--------|------|------|----------------------------------------------------------------|---------------------------------------|
| A6_61  | pbte | 5928 | ELGCHSLRATTTLVSRLYKEMNVNPLRGVFRHPTIERMSQAISQMETS               | MYTAIPIAEEQE                          |
| TS_15  | pbte | 5928 | ELGCHSLRATTTLVSRLYKEMNVNPLRGVFRHPTIERMSQAISQMETS               | LYTAIPIAEEQE                          |
| OSY_SE | pbte | 5915 | ELGCHSLRATTTLASSTTKKEMEVNPLRTPVPCPTIEEMAGMIAEMEQE              | NYTAIPIAEESE                          |
| A6_61  | pbte | 5988 | YVPLESSAQLRLYIMSQLGEGSEL SYNMPGNLVLEGCQLNRDQPPQTAFKL           | LIARHETLRTGFE                         |
| TS_15  | pbte | 5988 | YVPLESSAQLRLYIMSQLGEGSEL SYNMPGNLVLEGCQLNRDQPPQTAFKL           | LIARHETLRTGFE                         |
| OSY_SE | pbte | 5975 | VVPLESSAQLRLYIMSQLGEGSEL SYNMPGNLVLEGCQLNRDQPPQTAFKL           | LIARHETLRTGFE                         |
| A6_61  | pbte | 6048 | MVDGEPNQRIRHNTTEFAIDYRQVSE                                     | -DEVPEIIGQPIRQFDLEHPPPLLRVGLFEVCGQDRH |
| TS_15  | pbte | 6048 | MVDGEPNQRIRHNTTEFAIDYRQVSE                                     | -DEVPEIIGQPIRQFDLEHPPPLLRVGLFEVCGQDRH |
| OSY_SE | pbte | 6035 | MVDGEPNQRIRHNTTEFAIDYRQVSE                                     | -DEVPEIIGQPIRQFDLEHPPPLLRVGLFEVCGQDRH |
| A6_61  | pbte | 6107 | ILVFDNMHHIISDGVSMNSNLVDEFTRLYANEEERPPRLRIQYKDIAVMQCA           | RENLERKKRQED                          |
| TS_15  | pbte | 6107 | ILVFDNMHHIISDGVSMNSNLVDEFTRLYANEEERPPRLRIQYKDIAVMQCA           | RENLERKKRQED                          |
| OSY_SE | pbte | 6095 | ILVFDNMHHIISDGVSMNSNLVDEFTRLYANEEERPPRLRIQYKDIAVMQCA           | RENLERKKRQED                          |
| A6_61  | pbte | 6167 | YVMSVLOGDLFPNAELPDDYDRTAVRSFSGEQIEFEINPVVTGQLNQLASNHECTLYMVL   |                                       |
| TS_15  | pbte | 6167 | YVMSVLOGDLFPNAELPDDYDRTAVRSFSGEQIEFEINPVVTGQLNQLASNHECTLYMVL   |                                       |
| OSY_SE | pbte | 6155 | YVMSVLOGDLFPNAELPDDYDRTAVRSFSGEQIEFEINPVVTGQLNQLASNHECTLYMVL   |                                       |
| A6_61  | pbte | 6227 | SAVQILLSEKYCCGDDIIVGTPVAGRNHADLEPLIGMPVNTLAIRNRPOGDKTFQSPFLAEV |                                       |
| TS_15  | pbte | 6227 | SAVQILLSEKYCCGDDIIVGTPVAGRNHADLEPLIGMPVNTLAIRNRPOGDKTFQSPFLAEV |                                       |
| OSY_SE | pbte | 6215 | SAVQILLSEKYCCGDDIIVGTPVAGRNHADLEPLIGMPVNTLAIRNRPOGDKTFQSPFLAEV |                                       |

FIG.17M

|             |      |                                                                                                        |
|-------------|------|--------------------------------------------------------------------------------------------------------|
| A6 6i PbtB  | 6227 | SA YQ ILLSKYCGQDDII VGT P VAC R N H A D L E P L I G M F V N T L A I R N R P Q G D K T F Q S F L A E V  |
| TS 15 PbtB  | 6227 | SA YQ ILLSKYCGQDDII VGT P VAC R N H A D L E P L I G M F V N T L A I R N R P Q G D K T F Q S F L A E V  |
| OSY SE PbtB | 6215 | SA Y T ILLSKYSGQDDII VGT P VAC R N H A D L E P L I G M F V N T L A I R N R P Q G D K T F L S L L E E V |

|             |      |                                                                                                                       |
|-------------|------|-----------------------------------------------------------------------------------------------------------------------|
| A6 6i PbtB  | 6287 | KE ST L G A P E H Q E Y P F E E L I D L L K L Q M E T S R N P L F D T V F V L O N T E E R E A G I C G L T I S P Y V T |
| TS 15 PbtB  | 6287 | KE ST L G A P E H Q E Y P F E E L I D L L K L Q M E T S R N P L F D T V F V L O N T E E R E A G I C G L T I S P Y V T |
| OSY SE PbtB | 6275 | KE T A L G A P E H Q E Y P F E E L I E R L N Q M D A N R N P F D T V F V L O N T E S H E V R E E L T S P Y V L        |

|             |      |                                                                                                                     |
|-------------|------|---------------------------------------------------------------------------------------------------------------------|
| A6 6i PbtB  | 6347 | DD SV S A K P D L T L S V S E E D D G M K G S P L Y A S K L P K A G I H R M M R D Y L S I L S Q V C E N P R I R I O |
| TS 15 PbtB  | 6347 | DD SV S A K P D L T L S V S E E D D G M K G S P L Y A S K L P K A G I H R M M R D Y L S I L S Q V C E N P R I R I O |
| OSY SE PbtB | 6335 | D N P E B A K P D L T L F V S E E D D V I K G C F Q Y E E K L F K A A M H B I M M R D L L L A Q I V E D P H I R R   |

|             |      |                                             |
|-------------|------|---------------------------------------------|
| A6 6i PbtB  | 6407 | D I S I S G Q Q T O E K S K I D T I E P A P |
| TS 15 PbtB  | 6407 | D I S I S G Q Q T O E K S K I D T I E P A P |
| OSY SE PbtB | 6395 | D I K C N E Q S V N Q R S H E T I E P A P   |

A6 6i PtbB is SEQ ID NO. 12  
TS-15 PtbB is SEQ ID NO. 15  
OSY SE PtbB is SEQ ID NO. 18

FIG. 18A

|             |     |                                                                 |                     |                |      |
|-------------|-----|-----------------------------------------------------------------|---------------------|----------------|------|
| A6_61_pbtC  | 1   | MKSVEKEEA YWNGMCDSDSDMSILPYCSTSCREANADTNAAKVSMI                 | ~ ~ ~               | RALP           | ELSD |
| TS_15_pbtC  | 1   | MKSVEKEKEEA YWNGMCDSDSDMSILPYCSTHGREANADTNAAKVSMI               | ~ ~ ~               | RALP           | ELSD |
| OSY_SE_pbtC | 1   | MKSVEKEKEEA YWNEKFDSDSDMSILPYSENE ~ ~ ~                         | SNMSEENNTWGVINRTLP  | PP             | ELSQ |
| A6_61_pbtC  | 57  | RMNTLANGSDALYMI GLAGVTCLLHHYTHRENVLVGMTIDES                     | EDDSSP              | RDVLIMKTN      |      |
| TS_15_pbtC  | 57  | RMNTLANGSDALYMI GLAGVTCLLHHYTHRENVLVGMTIDES                     | EDDSSP              | RDVLIMKTN      |      |
| OSY_SE_pbtC | 55  | RMNTLANGSDALYMI VLACVNSLLYK YTHRENVLVCMFA YTALHGEHP             | THDP                | FLYIENN        |      |
| A6_61_pbtC  | 116 | LTRGESPFSVLGSIKTA VCGCALEHHRHLPFRKKYVHNLNLEMDTNGCLPVMNTVVS      | ESA IHTA            |                |      |
| TS_15_pbtC  | 116 | LTRGESPFSVLGSIKTA VCGCALEHHRHLPFRKMVHNLNLEMDTNGCLPVMNTVVS       | YSA IHTA            |                |      |
| OSY_SE_pbtC | 115 | VNEKSTPESLGCQKKA SVEEALDEHQHLPFRKMFROUNLCQVDP                   | QCLPVMNTVVS         | YSA IHTA       |      |
| A6_61_pbtC  | 176 | SIDLSVESSDVPRFDAKDDGCHLEVLVDSESYDASYIATLFECCERLLHFFVLFPDQPIG    |                     |                |      |
| TS_15_pbtC  | 176 | SIDLSVESSDVPRFDAKDDGCHLEVLVDSESYDASYIATLFEHFFRLLHFFVLFPDQPIG    |                     |                |      |
| OSY_SE_pbtC | 175 | SLEQSA AAEAAFCPEFVNDKIQLRMSZDNNRVSDDIVESMLAEFFRLLSVLFPQPELEIG   |                     |                |      |
| A6_61_pbtC  | 236 | MTLLSAEEERHLLHEFNDVNTDPPRQATLYQPIEECHAEKQPDALAVSEYEDTKLTYSRLN   |                     |                |      |
| TS_15_pbtC  | 236 | MAVLLSEEEKHRLLEHFNVDVNTDPPRQATLHQPIEEHAEKQPDALAVSEYEDTKLTYSRLN  |                     |                |      |
| OSY_SE_pbtC | 235 | KVSELLSEHECHHLLAILNDTTHETPROTTLHQLFEECAERMPDAAAL                | EDKELTYAELN         |                |      |
| A6_61_pbtC  | 296 | ARANRLARTLRSEGVCTEALVGLMAERSIDMI VGM L AVLKACGGYVAIDPSYPEERVRYM |                     |                |      |
| TS_15_pbtC  | 296 | ARANRLARTLRSEGVCTEALVGLMAERSIDMI VGM L AVLKACGGYVAIDPSYPEERVRYM |                     |                |      |
| OSY_SE_pbtC | 295 | AAANRLARLLRDEGVVRGT LVGFCAEKSEEMTGCLGLKACGMVPEIDPSYPCERINAM     |                     |                |      |
| A6_61_pbtC  | 356 | LEDSGARVILLVQQHLQNRVPNTESAA RLTLTDDEQSYHEDASNI                  | ~                   | ESSTAVDLACVIYT |      |
| TS_15_pbtC  | 356 | LEDSGARVILLVQQHLQNRVPNTESAA RLTLTDDEQSYHEDASNI                  | ~                   | ESSTAVDLACVIYT |      |
| OSY_SE_pbtC | 355 | LEDTAISVMLTQAHLC TGVPMELDSV - LIDTAAREMTLECSWPNITD              | TAATADE             | YAYIIT         |      |
| A6_61_pbtC  | 415 | SCITGNPKGNLTTHRMIVRIYKNTNITIEIQDKVQLQLSSYSFDESAPDIFGALTNGAQL    |                     |                |      |
| TS_15_pbtC  | 415 | SCITGNPKGNLTTHRMIVRIYKNTNITIEIQDKVQLQLSSYSFDESAPDIFGALTNGAQL    |                     |                |      |
| OSY_SE_pbtC | 414 | SCSTGIPKGVCVTHRCVNRGVVAANNVCHISEMDVFLQCSITISFDAAT               | FEI                 | GESLNGAAL      |      |
| A6_61_pbtC  | 475 | VLVPHHTLLDAEKLAELIETEEISVMILITAYFNVLVDVNN                       | SCLEHIRAILFCGERSSVA |                |      |
| TS_15_pbtC  | 475 | VLVPHHTLLDAEKLAELIETEEISVMILITAYFNVLVDVNN                       | SCLEHIRAILFCGERSSVA |                |      |
| OSY_SE_pbtC | 474 | ATLEPFGN - LSLTEWTOAQOQHCVTLEWELAALEHVVVENQLQALQGCQCLLV         | SSVVSQT             |                |      |

FIG. 18B

|             |      |                                                                                                                                                                                                                                                 |
|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A6_61_pbtC  | 535  | HVR <del>AL</del> EQTOPGRLRHA <del>Y</del> GPSESTVIATWHDVTEISE <del>CA</del> VSVPICRPISNTAIIYVNERN                                                                                                                                              |
| TS_15_pbtC  | 535  | HVR <del>CA</del> LEQTOPGRLRHA <del>Y</del> GPSESTVIATWHDVTEISE <del>CA</del> VSVPICRPISNTAIIYVNERN                                                                                                                                             |
| OSY_SE_pbtC | 533  | HAA <del>Y</del> VLERVYKDI <del>EL</del> VN <del>Q</del> SGPHE <del>N</del> TE <del>T</del> CC <del>EE</del> ESAADMER <del>ES</del> PIGEPHANT <del>Q</del> Y <del>ED</del> DEAG                                                                 |
| A6_61_pbtC  | 595  | DLQPIGVSGELCVAGEGLVRGYLNRPELT <del>EQ</del> KFVDNRPFPGERMYRTCDLARWLPDGTIE                                                                                                                                                                       |
| TS_15_pbtC  | 595  | DLQPIGVSGELCVAGEGLVRGYLNRPELT <del>ACK</del> FVDNRPFPGERMYRTCDLARWLPDGTIE                                                                                                                                                                       |
| OSY_SE_pbtC | 593  | K <del>LD</del> Y <del>GV</del> YGE <del>LY</del> TC <del>GE</del> GLAC <del>GV</del> YNNRPELT <del>AE</del> KFVDNRPFPCT <del>EE</del> IR <del>TC</del> DLARWLPDGTIE                                                                            |
| A6_61_pbtC  | 655  | YVGRMD <del>Q</del> VKIRGHRIEIGEVEAQLLKVA <del>FI</del> QKATIVVRCREDGEKQLCAYYVADRLL <del>PA</del>                                                                                                                                               |
| TS_15_pbtC  | 655  | YVGRMD <del>Q</del> VKIRGHRIEIGEVEAQLLKVA <del>L</del> QKATIVVRCREDGEKQLCAYYVADRLL <del>SA</del>                                                                                                                                                |
| OSY_SE_pbtC | 653  | YVGRMD <del>Q</del> VKIRGHRIEIGEVEAQLLKVA <del>ES</del> LD <del>IV</del> Y <del>AK</del> Q <del>DES</del> CK <del>TL</del> CAY <del>Y</del> TAA <del>EL</del> MA                                                                                |
| A6_61_pbtC  | 715  | GEIR <del>TM</del> LAKELPSYNI <del>PAY</del> FIQLEOMPLTTNGCKVDKRALPEPEEHVQAE <del>TE</del> YVAPRSE <del>QE</del>                                                                                                                                |
| TS_15_pbtC  | 715  | GEIR <del>TM</del> LAKELPSYNI <del>PAY</del> FIQLEOMPLTTNGCKVDKRALPEPEEHVQAE <del>TE</del> YVAPRSE <del>QE</del>                                                                                                                                |
| OSY_SE_pbtC | 713  | GEIR <del>AA</del> LSCELPVYNI <del>P</del> THL <del>Q</del> CEOMPLTFNGCKVD <del>RA</del> LPEPEGL <del>MT</del> GI <del>EH</del> VAPRSE <del>FL</del> E                                                                                          |
| A6_61_pbtC  | 775  | IRLARV <del>MQ</del> EV <del>LG</del> LSRVGAKDHPFELGGHSLRAT <del>TL</del> VSKLHKKEENISLSLRDVFRNP <del>TL</del> EA                                                                                                                               |
| TS_15_pbtC  | 775  | IRLARV <del>MQ</del> EV <del>LG</del> LSRVGAKDHPFELGGHSLRAT <del>TL</del> VSKLHKKEENISLSLRDVFRNP <del>TL</del> EA                                                                                                                               |
| OSY_SE_pbtC | 773  | SKLAR <del>MQ</del> EV <del>LG</del> LE <del>EV</del> SVKDS <del>PF</del> ELGGHSLRAT <del>TL</del> ASKLHK <del>EL</del> HN <del>SL</del> LRD <del>FR</del> NP <del>TE</del> RE                                                                  |
| A6_61_pbtC  | 835  | MAAL <del>ME</del> DAQCR <del>KE</del> FAPIPTVEEKDVYFVSSVQKR <del>LF</del> ILHQLEGAEQSYNMP <del>CA</del> LLLEGVD                                                                                                                                |
| TS_15_pbtC  | 835  | MAAL <del>ME</del> DAQCR <del>TF</del> SPIPTVEEKDVYFVSSVQKR <del>LF</del> ILHQLEGAEQSYNMP <del>CA</del> LLLEGVD                                                                                                                                 |
| OSY_SE_pbtC | 833  | DAR <del>LT</del> DCMERQA <del>Y</del> Q <del>LP</del> LE <del>EE</del> ED <del>MY</del> PVSSA <del>Q</del> KR <del>LF</del> ILHQLEGAEQSYNMP <del>CA</del> LLLEGVD                                                                              |
| A6_61_pbtC  | 895  | RNRLE <del>YAF</del> RQ <del>LI</del> TRHET <del>LR</del> TCFEMVNGEPVQRIYPTV <del>MP</del> FVVEEMSA <del>EE</del> CS <del>SE</del> VE <del>EE</del> QIRQPI                                                                                      |
| TS_15_pbtC  | 895  | RNRLE <del>YAF</del> RQ <del>LI</del> TRHET <del>LR</del> TCFEMVNGEPVQRIYPTV <del>MP</del> FVVEEMSA <del>EE</del> CS <del>SE</del> VE <del>EE</del> QIRQPI                                                                                      |
| OSY_SE_pbtC | 893  | RNR <del>FE</del> EA <del>FG</del> SLICR <del>HE</del> TL <del>RT</del> CFEMVNGEPVQRIYPTV <del>MP</del> FVVEEMSA <del>EE</del> CS <del>SE</del> VE <del>EE</del> QIRQPI                                                                         |
| A6_61_pbtC  | 955  | RAPDLSTAPLFRAGL <del>IK</del> LAPQRHILLDFDMHHIISD <del>Q</del> TSIGIMIEEPTSLYS <del>GN</del> ELEP <del>LR</del> I                                                                                                                               |
| TS_15_pbtC  | 955  | RAPDLSTPPLFRAGL <del>IE</del> LAPQRHILLDFDMHHIISD <del>Q</del> TSIGIMIEEPTSLYS <del>GN</del> ELEP <del>LR</del> I                                                                                                                               |
| OSY_SE_pbtC | 952  | R <del>PP</del> DL <del>EE</del> EP <del>PL</del> LV <del>EL</del> IEL <del>Q</del> CD <del>R</del> HILL <del>DM</del> H <del>HI</del> ISD <del>Q</del> VE <del>EE</del> GL <del>Y</del> VE <del>RY</del> LY <del>CE</del> ELP <del>PR</del> RI |
| A6_61_pbtC  | 1015 | QYKDFAA <del>ANQ</del> SE <del>EE</del> QIEQLK <del>R</del> Q <del>EE</del> Y <del>N</del> LQ <del>Q</del> MEGVLPVLELPTDYVRPAVQSHD <del>CA</del> LFE <del>FS</del> ED                                                                           |
| TS_15_pbtC  | 1015 | QYKDFAA <del>ANQ</del> SE <del>EE</del> QIEQLK <del>S</del> Q <del>EE</del> Y <del>N</del> LQ <del>Q</del> MEGVLPVLELPTDYVRPAVQSHD <del>CA</del> LFE <del>FS</del> ED                                                                           |
| OSY_SE_pbtC | 1012 | QYKDFAA <del>ANQ</del> CS <del>EP</del> Q <del>EL</del> EN <del>Q</del> Q <del>EE</del> Y <del>N</del> LQ <del>Q</del> SE <del>GL</del> PVLEL <del>PA</del> D <del>VA</del> RPVQ <del>ST</del> EG <del>DT</del> FE <del>EA</del> ED             |

FIG. 18C

|        |      |      |                                                                 |
|--------|------|------|-----------------------------------------------------------------|
| A6_61  | pbtc | 1075 | REQSQDLRKHAADTRTTLVMVLLAAAYTII LHKYSGQEDIVVGTPIAGRTHDDVQPLICMF  |
| TS_15  | pbtc | 1075 | REQSQDLRKHAADTRTTLVMVLLAAAYTII LHKYSGQEDIVVGTPIAGRTHDDVQPLICMF  |
| OSY_SE | pbtc | 1072 | PRISEALHCGAAEEGCTTLYMVLLAAAYTII LHKYSGQEDIVVGTPIAGRTHDDVQPLICMF |
| A6_61  | pbtc | 1135 | VNTLAIERNYPGSGKSVLTYLEEIKETTLGAPENODYPPEELVENVCISRDMSRHPVFDTM   |
| TS_15  | pbtc | 1135 | VNTLAIERNYPGSGKSVLTYLEEIKETTLGAPENODYPPEELVENVCISRDMSRHPVFDTM   |
| OSY_SE | pbtc | 1132 | VNTLAIERNYPGSGKSVLTYLEEIKETTLGAPENODYPPEELVENVCISRDMSRHPVFDTM   |
| A6_61  | pbtc | 1195 | PALENTERRRFDLGLQVKKPYCAEYGMKAFDNLNLTVTEDGDDGLYCTMEYATALYNRSTIE  |
| TS_15  | pbtc | 1195 | PALENTERRRFDLGLQVKKPYCAEYGMKAFDNLNLTVTEDGDDGLYCTMEYATALYNRSTIE  |
| OSY_SE | pbtc | 1192 | PALQNMDDLDLELACLREKPYPAEYGMKAFDNLNLTVTEDGDDGLYCTMEYATALYNRSTIE  |
| A6_61  | pbtc | 1255 | RLCCHPFLQVVGEMTHNPQAAISSLOMVTSEKKAQLOHFNSTVMEESSDKTVHELFAEQV    |
| TS_15  | pbtc | 1255 | RLCCHPFLQVVGEMTHNPQAAISSLOMVTSEKKAQLOHFNSTVMEESSDKTVHELFAEQV    |
| OSY_SE | pbtc | 1252 | RRAKHFGRELEAYAHPEPARRAASLEEMTTEEEEQRRHYFNPTAGRSQNTVPELPEEQV     |
| A6_61  | pbtc | 1315 | ERTPDAAVAVVSGSEQLSYCEINRKANQLAMKLECYGTAKQPVGLIVERTLDTVVAVAV     |
| TS_15  | pbtc | 1315 | ERTPDAAVAVVSGSEQLSYCEINRKANQLAMKLECYGTAKQPVGLIVERTLDTVVAVAV     |
| OSY_SE | pbtc | 1312 | ERTPDAAVAVVSGSEQLSYCEINRKANQLAMKLECYGTAKQPVGLIVERTLDTVVAVAV     |
| A6_61  | pbtc | 1375 | LKASCTFVPIDPEYPETRIRYMLADSCAKLVLAQSLLPGIISDDVRLIDVRDZSLYQGDG    |
| TS_15  | pbtc | 1375 | LKASCTFVPIDPEYPETRIRYMLADSCAKLVLAQSLLPGIISDDVRLIDVRDZSLYQGDG    |
| OSY_SE | pbtc | 1372 | LKSGCAVVPIDPCQIPEORIHMLDMSNAQVLLAQRHLQARAASFSGRRMLDEEAFVGGDG    |
| A6_61  | pbtc | 1435 | ADVPMGSKPSNLLYIITYSGTGNPKGVNLEHCNNVNLCHYQCCNCTNIHPSPS-HILQYAS   |
| TS_15  | pbtc | 1435 | ADVPMGSKPSNLLYIITYSGTGNPKGVNLEHCNNVNLCHYQCCNCTNIHPSPS-HILQYAS   |
| OSY_SE | pbtc | 1432 | SNDEERVNCPERHLSYIITYSGTGNPKGVNLEHCNNVNLCHYQCCNCTNIHPSPS-HILQYAS |
| A6_61  | pbtc | 1494 | GSFDVVCYQEMFSALLFGGSLVMVDNEMRRKDPVRLPQEIEXKHEIDVMYIIF--VAPLKPI  |
| TS_15  | pbtc | 1494 | GSFDVVCYQEMFSALLFGGSLVMVDNEMRRKDPVRLPQEIEXKHEIDVMYIIF--VAPLKPI  |
| OSY_SE | pbtc | 1492 | FSFDVVFSGGIZRALLHGGSEIICFPEZANANPAEELIEXKHEIDVMYIIF--VAPLKPI    |
| A6_61  | pbtc | 1550 | PAPEWAAEAPPCVRHIIITAGEQLVVTPTQVOACLKRI--DILCHNHYGPFSETHVVTITM   |
| TS_15  | pbtc | 1550 | PAPEWAAEAPPCVRHIIITAGEQLVVTPTQVOACLKRI--DILCHNHYGPFSETHVVTITM   |
| OSY_SE | pbtc | 1552 | YENK-----LDISSMKCAVVSADHCPKEEFQKLERFSGQMRVNSYGVETTDSCVFE        |

FIG. 18D

|        |      |      |                                                                 |
|--------|------|------|-----------------------------------------------------------------|
| A6_61  | PbTc | 1608 | TRVIEVCLPPIGKPIANTSIYIVNDSEFELQPIGVKCELYVSGACVGRGYNWGRITDLTEEK  |
| TS_15  | PbTc | 1608 | MPVIEVCLPPIGKPIANTSIYIVNDSEFELQPIGVKCELYVSGASVGRGYNWGRITDLTEEK  |
| OSY_SE | PbTc | 1607 | QASTEGRVPIGKPPGVVYIIDDQCHSLPQETSELIYCGPCVGRGYNWGRITDLTEEK       |
| A6_61  | PbTc | 1668 | FLDNPPAPGERLYKIGDVARWLPDGSLEYVGRSDHQVKIRGFRIELGEVESQLLEVPAYO    |
| TS_15  | PbTc | 1668 | FLDNPPAPGERLYKIGDVARWLPDGSLEYVGRSDHQVKIRGFRIELGEVESQLLEVPAYO    |
| OSY_SE | PbTc | 1667 | FLDNPPAPGERLYKIGDVARWLPDGSLEYVGRSDHQVKIRGFRIELGEVESQLLEVPAYO    |
| A6_61  | PbTc | 1728 | SEATVVALEDHAGQKQOLCAYFAAERSLTAGELRCALSOQLPCYMNIPSYFVQLERLPLTPNG |
| TS_15  | PbTc | 1728 | SEATVVALEDHAGQKQOLCAYFAAERSLTAGELRCALSOQLPCYMNIPSYFVQLERLPLTPNG |
| OSY_SE | PbTc | 1727 | SEATVVALEDHAGQKQOLCAYFAAERSLTAGELRCALSOQLPCYMNIPSYFVQLERLPLTPNG |
| A6_61  | PbTc | 1788 | KIDRRALPKPECGIETCTEYVAPRTCTEALARIWQDVLCGLPSVGVKDNPPFELGCHSLRA   |
| TS_15  | PbTc | 1788 | KIDRRALPKPECGIETCTEYVAPRTCTEALARIWQDVLCGLPSVGVKDNPPFELGCHSLRA   |
| OSY_SE | PbTc | 1787 | KIDRRALPKPECGIETCTEYVAPRTCTEALARIWQDVLCGLPSVGVKDNPPFELGCHSLRA   |
| A6_61  | PbTc | 1848 | TTLVSRLYKEMNVNPPFLRGVFRHPTIEEMAKAITEMHQELYTEIPIAEKKAYYPLSSAQK   |
| TS_15  | PbTc | 1848 | TTLVSRLYKEMNVNPPFLRGVFRHPTIEEMAKAITEMHQELYTEIPIAEKKAYYPLSSAQK   |
| OSY_SE | PbTc | 1847 | TTLVSRLYKEMNVNPPFLRGVFRHPTIEEMAKAITEMHQELYTEIPIAEKKAYYPLSSAQK   |
| A6_61  | PbTc | 1908 | RLFIVSQLTGAEVSYNNMPGVLLILEGELDRARFERAPQKLLIDRHESLRTSFETVRCPEVQR |
| TS_15  | PbTc | 1908 | RLFIVSQLTGAEVSYNNMPGVLLILEGELDRARFERAPQKLLIDRHESLRTSFETVRCPEVQR |
| OSY_SE | PbTc | 1907 | RLFIVSQLTGAEVSYNNMPGVLLILEGELDRARFERAPQKLLIDRHESLRTSFETVRCPEVQR |
| A6_61  | PbTc | 1968 | IHSQVEPAIEYHLAAECDAEALITHPVRRPQKQAPLLRVGLIETCHERHILMFDMHHII     |
| TS_15  | PbTc | 1968 | IHSQVEPAIEYHLAAECDAEALITHPVRRPQKQAPLLRVGLIETCHERHILMFDMHHII     |
| OSY_SE | PbTc | 1967 | IHSQVEPAIEYHLAAECDAEALITHPVRRPQKQAPLLRVGLIETCHERHILMFDMHHII     |
| A6_61  | PbTc | 2028 | SDGVTMGHVNVNEPSRIYACDQQLPALRIQYKDYAIVWQDSNEYAEKLAHQESYWLKQLDGEL |
| TS_15  | PbTc | 2028 | SDGVTMGHVNVNEPSRIYACDQQLPALRIQYKDYAIVWQDSNEYAEKLAHQESYWLKQLDGEL |
| OSY_SE | PbTc | 2027 | SDGVTMGHVNVNEPSRIYACDQQLPALRIQYKDYAIVWQDSNEYAEKLAHQESYWLKQLDGEL |
| A6_61  | PbTc | 2088 | PTLELPTDIYVRPAVQQFEGDVALLFTLTNSQAEQLQRLAANYGATLYMVLLAAAYTVLLHKY |
| TS_15  | PbTc | 2088 | PTLELPTDIYVRPAVQQFEGDVALLFTLTNSQAEQLQRLAANYGATLYMVLLAAAYTVLLHKY |
| OSY_SE | PbTc | 2087 | PTLELPTDIYVRPAVQQFEGDVALLFTLTNSQAEQLQRLAANYGATLYMVLLAAAYTVLLHKY |

A6 61 pbtC 2148  
TS 15 pbtC 2148  
OSY SE pbtC 2147

TGQDDIIIVCTPIACRNHTTELEPLVCMFVNTLAIRNYPTCEKSPAEELAEVKDTALAAPEM  
TGQDDIIIVCTPIACRNHTTELEPLVCMFVNTLAIRNYPTCEKSPAEELAEVKDTALAAPEM  
TGQDDIIIVCTPIACRNHTTELEPLVCMFVNTLAIRNYPTCEKSPAEELAEVKDTALAAPEM

A6 61 pbtC 2208  
TS 15 pbtC 2208  
OSY SE pbtC 2207

QDIPFETLVEKVHKSQDMGRNPVFDTIPTSVHEHQSSPHIDGLRISPYPHSHSVAKFDLT  
QDIPFETLVEKVHKSQDMGRNPVFDTIPTSVHEHQSSPHIDGLRISPYPHSHSVAKFDLT  
QDIPFETLVEKVHKSQDMGRNPVFDTIPTSVHEHQSSPHIDGLRISPYPHSHSVAKFDLT

A6 61 pbtC 2268  
TS 15 pbtC 2268  
OSY SE pbtC 2267

PHAEQNEEGILCCGLGYATATLYAKETAEEMGEHFVQLIDAIIAEPNAKLSLNMMSLQERE  
PHAEQNEEGILCCGLGYATATLYAKETAEEMGEHFVQLIDAIIAEPNAKLSLNMMSLQERE  
PHAEQNEEGILCCGLGYATATLYAKETAEEMGEHFVQLIDAIIAEPNAKLSLNMMSLQERE

A6 61 pbtC 2328  
TS 15 pbtC 2328  
OSY SE pbtC 2327

QVKLVFNDTIITNYPREKTIQHLFEEQAKSPDAVAIQFGCECLTYRELNERSNRRLARTLR  
QVKLVFNDTIITNYPREKTIQHLFEEQAKSPDAVAIQFGCECLTYRELNERSNRRLARTLR  
QVKLVFNDTIITNYPREKTIQHLFEEQAKSPDAVAIQFGCECLTYRELNERSNRRLARTLR

A6 61 pbtC 2388  
TS 15 pbtC 2388  
OSY SE pbtC 2387

GKGVKAGRCVGLMTDRSLDMIVAIMATLKAGAYVPIIDPDYPEERIHYMIDDSGTSLLVV  
GKGVKAGRCVGLMTDRSLDMIVAIMATLKAGAYVPIIDPDYPEERIHYMIDDSGTSLLVV  
GKGVKAGRCVGLMTDRSLDMIVAIMATLKAGAYVPIIDPDYPEERIHYMIDDSGTSLLVV

A6 61 pbtC 2448  
TS 15 pbtC 2448  
OSY SE pbtC 2447

QRHLQANHIPADCMVVLVDDEECSTYHADGTNLEQHNCAASDLAYVITSGTTCMPKGNLTH  
QRHLQANHIPADCMVVLVDDEECSTYHADGTNLEQHNCAASDLAYVITSGTTCMPKGNLTH  
QRHLQANHIPADCMVVLVDDEECSTYHADGTNLEQHNCAASDLAYVITSGTTCMPKGNLTH

A6 61 pbtC 2508  
TS 15 pbtC 2508  
OSY SE pbtC 2506

RNIVRVVRDAXYIEIDQHDVTVLQSSYAPDGSTFDPFGALLNGAKLVLLTREVVLDAGRL  
RNIVRVVRDAXYIEIDQHDVTVLQSSYAPDGSTFDPFGALLNGAKLVLLTREVVLDAGRL  
RNIVRVVRDAXYIEIDQHDVTVLQSSYAPDGSTFDPFGALLNGAKLVLLTREVVLDAGRL

A6 61 pbtC 2568  
TS 15 pbtC 2568  
OSY SE pbtC 2566

ADTIESKISVMPITTAFFNLLVDLRVDSLRHMRAILFCGERASVSHVRKALRHLOPCKL  
ADTIESKISVMPITTAFFNLLVDLRVDSLRHMRAILFCGERASVSHVRKALRHLOPCKL  
ADTIESKISVMPITTAFFNLLVDLRVDSLRHMRAILFCGERASVSHVRKALRHLOPCKL

FIG. 18F

|             |      |                                                                 |
|-------------|------|-----------------------------------------------------------------|
| AS_61_pbtC  | 2628 | KHVIQPTSTVFATSHNVDEVADSAVTIPICRPIONTAVYIVGEGDVLOPIGVAGELCVA     |
| TS_15_pbtC  | 2628 | KHVIQPTSTVFATSHNVDEVADSAVTIPICRPIONTAVYIVGEGDVLOPIGVAGELCVA     |
| OSY_SE_pbtC | 2626 | KHVIQPTSTVFATSHNVDEVADSAVTIPICRPIONTAVYIVNAQNDLOPIGVAGELCVA     |
| AS_61_pbtC  | 2688 | GDGVAEGYLNRRPELSCAKFVNNPFVPGDRMYRTGDLARNLSDCITIEYVGRKDDQVKIRGY  |
| TS_15_pbtC  | 2688 | GDGVAEGYLNRRPELSCAKFVNNPFVPGDRMYRTGDLARNLSDCITIEYVGRKDDQVKIRGY  |
| OSY_SE_pbtC | 2686 | GDGVAEGYLNRRPELSCAKFVNNPFVPGDRMYRTGDLARNLSDCITIEYVGRKDDQVKIRGY  |
| AS_61_pbtC  | 2748 | RIELGEVEAHLLEDLEAIQEAVVIVREESDQQRRLCAYYVVAERLITAGEMRIALAOCLPGY  |
| TS_15_pbtC  | 2748 | RIELGEVEAHLLEDLEAIQEAVVIVREESDQQRRLCAYYVVAERLITAGEMRIALAOCLPGY  |
| OSY_SE_pbtC | 2746 | RIELGEVEAHLLEDLEAIQEAVVIVREESDQQRRLCAYYVVAERLITAGEMRIALAOCLPGY  |
| AS_61_pbtC  | 2808 | MLPSYFVQDKLPSPNGKVNRRKALPAPELHVQAASEYVAPRTPOEVLLAHINREVLGLG     |
| TS_15_pbtC  | 2808 | MLPSYFVQDKLPSPNGKVNRRKALPAPELHVQAASEYVAPRTPOEVLLAHINREVLGLG     |
| OSY_SE_pbtC | 2806 | MLPSYFVQDKLPSPNGKVNRRKALPAPELHVQAASEYVAPRTPOEVLLAHINREVLGLG     |
| AS_61_pbtC  | 2868 | QVGVKDNPFELGCHSLSLMGLVERVYTTETEVEIPIHSEVFPREPTIEAMAYEMLYSELACKA |
| TS_15_pbtC  | 2868 | QVGVKDNPFELGCHSLSLMGLVERVYTTETEVEIPIHSEVFPREPTIEAMAYEMLYSELACKA |
| OSY_SE_pbtC | 2866 | QVGVKDNPFELGCHSLSLMGLVERVYTTETEVEIPIHSEVFPREPTIEAMAYEMLYSELACKA |
| AS_61_pbtC  | 2928 | GNHFMKLNENGHI PVFCFPPGCGYGLSYLELAKQLDHHCILHGIDFIDDAKTRRELLERY   |
| TS_15_pbtC  | 2928 | GNHFMKLNENGHI PVFCFPPGCGYGLSYLELAKQLDHHCILHGIDFIDDAKTRRELLERY   |
| OSY_SE_pbtC | 2926 | SSQPTKLNENGHI PVFCFPPGCGYGLSYLELAKQLDHHCILHGIDFIDDAKTRRELLERY   |
| AS_61_pbtC  | 2988 | VDAIILAVQPPQPPFLLGYSLOGCNLTFEVAKALEC                            |
| TS_15_pbtC  | 2988 | VDAIILAVQPPQPPFLLGYSLOGCNLTFEVAKALEC                            |
| OSY_SE_pbtC | 2986 | VDAIILAVQPPQPPFLLGYSLOGCNLTFEVAKALEC                            |

FIG.18G

|             |      |                                                              |
|-------------|------|--------------------------------------------------------------|
| A6 6i PtbC  | 3048 | EDIDQMGVGEELKEMLVHHPLLRDOVKNKMRAYMSYATELVNSDIIDANIKHALMAEPSE |
| TS 15 PtbC  | 3048 | EDIDQMGVGEELKEMLVHHPLLRDOVKNKMRAYMSYATELVNSDIIDANIKHALMAEPSE |
| OSY SE PtbC | 3046 | SPIDQMGVGEELKEMLVHHPLLRDOVKNKMRAYMSYATELVNSDIIDANIKHALMAEPSE |
| A6 6i PtbC  | 3108 | VNODGCGAARDMAEGYERQVCGVQPTRCARRSASTPFGSSER                   |
| TS 15 PtbC  | 3108 | VNODGCGAARDMAEGYERQVCGVQPTRCARRSASTPFGSSER                   |
| OSY SE PtbC | 3106 | AVRPPNVTSLDDEATROAVCEHRLICVHEDVLLPFGSSER                     |
| A6 6i PtbC  | 3168 | -----                                                        |
| TS 15 PtbC  | 3168 | -----                                                        |
| OSY SE PtbC | 3166 | EVLSE                                                        |

A6 6i PtbC is SEQ ID NO. 13  
TS-15 PtbC is SEQ ID NO. 16  
OSY SE PtbC is SEQ ID NO. 19

# FIG. 8B

Compound of the present invention SEQ ID NO. 4

Compounds Identified in this Work

