

# **Supporting Information**

## **Structure-activity relationships of daptomycin lipopeptides**

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Contains chemical structures of all analogs synthesized to date,  
with MIC data and also toxicity and hemolytic data where available.

# Table of Contents

- S3 Table S1. Analogs with modifications, by residue (for daptomycin only).
- S4 Analogs **1-4**: Debono, M. et al., *J. Antibiot. (Tokyo)*, **1987**, 40, 6, 761-777.
- S5 Analogs **5-34**: Debono, M. et al., *J. Antibiot. (Tokyo)*, **1988**, 41, 8, 1093-1105.
- S9 Analogs **35-81**: Hill, J. et al., *Bioorg. Med. Chem. Lett.*, 2003, 13, 23, 4187-4191.
- S17 Analogs **82-112**: Siedlecki, J. et al., *Bioorg. & Med. Chem. Lett.*, 2003, 13, 4245-4249.
- S23 Analogs **113-122**: Knight-Connoni, V. et al., *J. Ind. Microbiol. Biotechnol.*, **2016**, 43, 195-204.
- S25 Analogs **123-143**: He, Y. et al., *Bioorg. Med. Chem. Lett.*, **2012**, 22, 19, 6248-6251.
- S29 Analogs **346-348**: Ghosh, M. et al., *J. Med. Chem.*, **2017**, 60, 4577-4583.
- S31 Analogs **144-154**: Grünwald, J. et al., *J. Am. Chem. Soc.*, **2004**, 126, 51, 17025-17031.
- S33 Analogs **155-164**: Kopp, F. et al., *Biochem.*, **2006**, 45, 10474-10481.
- S35 Analogs **165-173**: Chen D. et al., *Org. Lett.*, **2019**, 21, 5639-5644.
- S37 Analogs **174-179**: Nguyen, K. T. et al., *Mol. Microbiol.*, **2006**, 61, 5, 1294-307.
- S38 Analogs **180-191**: Grünwald, J. et al., *Biochem.*, **2004**, 43, 2915-2925.
- S40 Analogs **192-207**: Baltz, R. H., *ACS Synth. Biol.*, **2014**, 3, 10, 738-758.
- S43 Analogs **208-221**: Nguyen, K. T. et al., *PNAS*, **2006**, 103, 46, 17462-17467.
- S46 Analogs **222-239**: Nguyen, K. T., *Antimicrob. Agents Chemother.*, **2010**, 54, 4, 1404-1413.
- S50 Analogs **240-244**: 't Hart P. et al., *Org. Biomol. Chem.*, **2014**, 12, 6, 913-918.
- S51 Analogs **245-248**: Lohani, C. R. et al., *Org. Lett.*, **2015**, 17, 3, 748-751.
- S52 Analogs **249-251**: Lohani, C. R. et al., *Bioorg. Med. Chem. Lett.*, **2015**, 25, 23, 5490-5494.
- S53 Analogs **252-284**: Barwani, G., *Masters Thesis*, **2018**, University of Waterloo, Canada.
- S59 Analogs **285-290**: Xu, B. et al., *Chem. Eur. J.*, **2019**, 25, 14101-14107.
- S60 Analogs **291-294**: Lin, D. et al., *Bioorg. Med. Chem. Lett.*, **2017**, 27, 456-459.
- S61 Analogs **295-298**: Chow, H. Y. et al., *J. Med. Chem.*, **2020**, 63, 3161-3171.
- S62 Analogs **299-345**: Chow, H. W. et al., *ACS Med. Chem. Lett.*, **2020**, 10.1021/acsmedchemlett.0c00175.

**Table S1.** List of daptomycin analogs, grouped by modification at each residue.

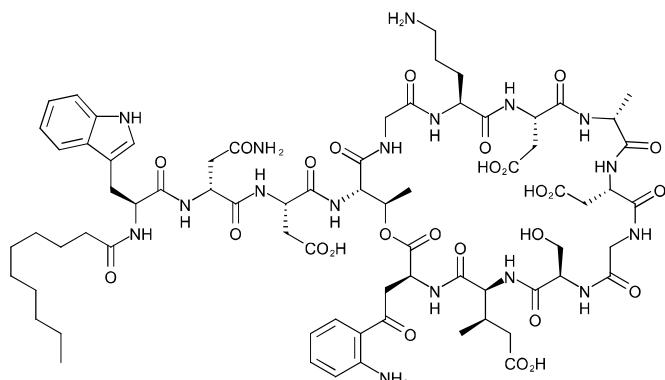
Residue	Analogs with modifications, by residue (for daptomycin only)
N-terminus	2-28, 107-115, 173-178, 192-206, 208-220, 341-344.
L-Trp1	118-139, 253, 288-289, 337-340.
D-Asn2	144-153, 158-159, 242-243, 254, 300.
L-Asp3	146, 158-159, 242-243, 255, 301.
L-Thr4	145, 240-243, 249.
Gly5	159, 256, 297.
L-Orn6	30-75, 77-106, 140-141, 151, 153, 159, 242-243, 257, 265, 267-283, 287, 289, 302, 308-328.
L-Asp7	147, 161, 163, 242-243, 250, 258, 303, 334-335.
D-Ala8	200-201, 204-206, 210, 212, 216, 219-220, 242-243, 259, 304.
L-Asp9	148, 242-243, 260, 305, 329-332, 334-336.
Gly10	261, 333.
D-Ser11	150, 198-199, 202-203, 206, 209, 211-212, 217-218, 242-243, 262, 266-283.
L-3MeGlu12	144-153, 155, 158-159, 176-178, 197, 203, 205, 215, 217, 219, 240-243, 245-247, 249-250, 252-283, 286-289, 291-293, 306, 336.
L-Kyn13	152-153, 193-196, 202, 204, 213, 218, 220, 242-243, 246-247, 249-250, 252-283, 295, 307.

**A21978C, a complex of new acidic peptide antibiotics: isolation, chemistry, and mass spectral structure elucidation**

Debono, M., Barnhart, M., Carrell, C. B., Hoffmann, J. A., Occolowitz, J. L., Abbott, B. J., Fukuda, D. S., Hamill, R. L., Biemann, K., Herlihy, W. C.,  
*J. Antibiot. (Tokyo)*, **1987**, 40, 6, 761-777.

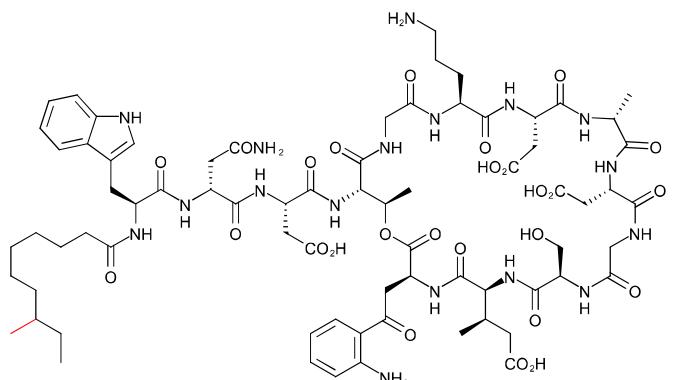
**Note**

Minor components: A21978C<sub>0</sub> contains a C10 fatty acid; A21978C<sub>4</sub> and A21978C<sub>5</sub> contain C12 fatty acids.



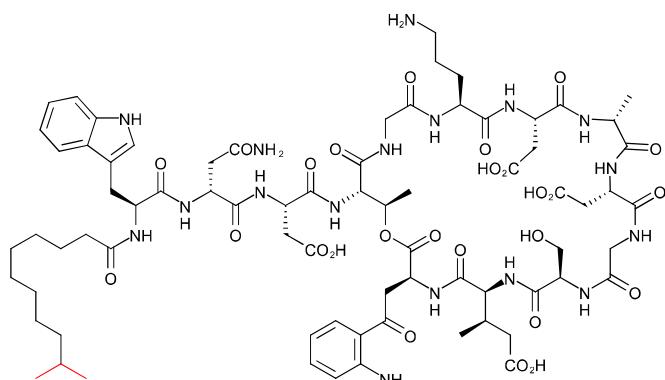
**1. Daptomycin**

LD<sub>50</sub> (mouse, IV) = 600 mg/kg



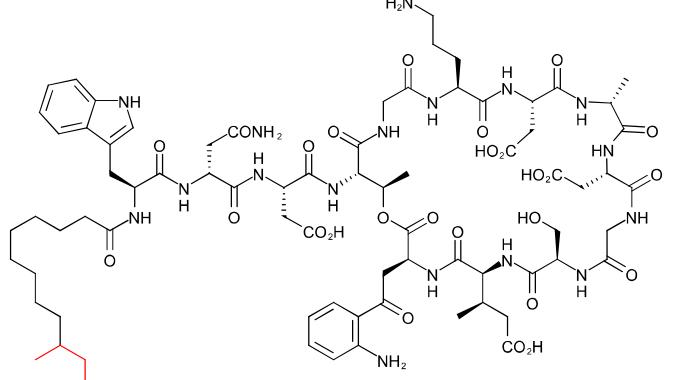
**2. A21978C<sub>1</sub>**

LD<sub>50</sub> (mouse, IV) > 600 mg/kg



**3. A21978C<sub>2</sub>**

LD<sub>50</sub> (mouse, IV) = 175 mg/kg

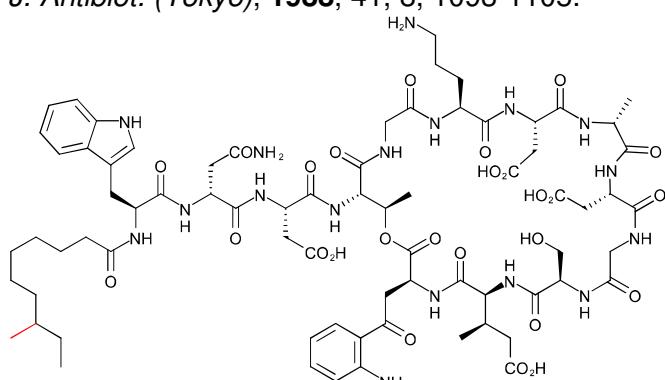


**4. A21978C<sub>3</sub>**

LD<sub>50</sub> (mouse, IV) = 75 mg/kg

**Enzymatic and chemical modifications of lipopeptide antibiotic A21978C: the synthesis and evaluation of daptomycin (LY146032)**

Debono, M., Abbott, B. J., Molloy, R. M., Fukuda, D. S., Hunt, A. H., Daupert, V. M., Counter, F. T., Ott, J. L., Carrell, C. B., Howard, L. C., Boeck, L. D., Hamill, R. L.,  
*J. Antibiot. (Tokyo)*, 1988, 41, 8, 1093-1105.



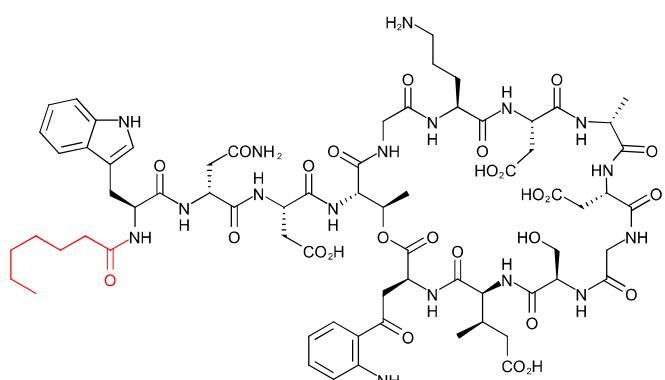
**5. A21978C<sub>1</sub>, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 1

*Staphylococcus epidermidis* = 1

*Streptococcus faecalis* = 8

LD<sub>50</sub> (mouse, IV) > 600 mg/kg



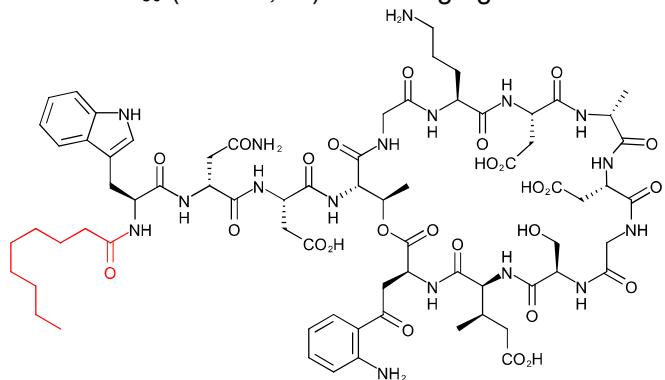
**6. *n*-Heptanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 8

*Staphylococcus epidermidis* = 8

*Streptococcus faecalis* = 128

LD<sub>50</sub> (mouse, IV) > 600 mg/kg



**7. *n*-Octanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 4

*Staphylococcus epidermidis* = 4

*Streptococcus faecalis* = 64

LD<sub>50</sub> (mouse, IV) > 600 mg/kg

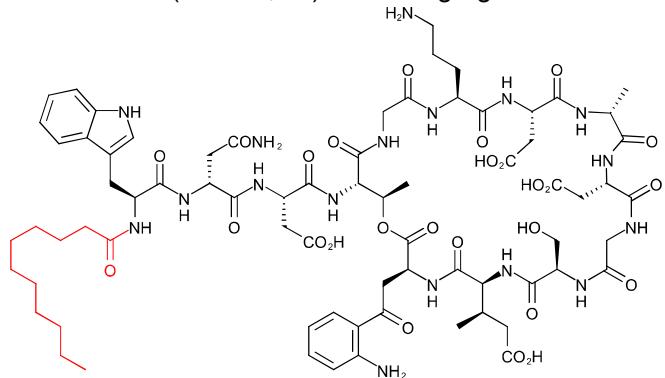
**8. *n*-Nonanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 8

*Staphylococcus epidermidis* = 8

*Streptococcus faecalis* = 128

LD<sub>50</sub> (mouse, IV) > 600 mg/kg



**9. *n*-Decanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5

*Staphylococcus epidermidis* = 0.5

*Streptococcus faecalis* = 16

LD<sub>50</sub> (mouse, IV) = 600 mg/kg

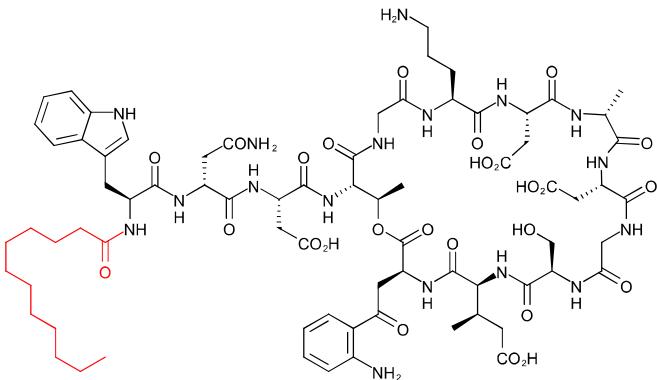
**10. *n*-Undecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.25

*Staphylococcus epidermidis* = 0.5

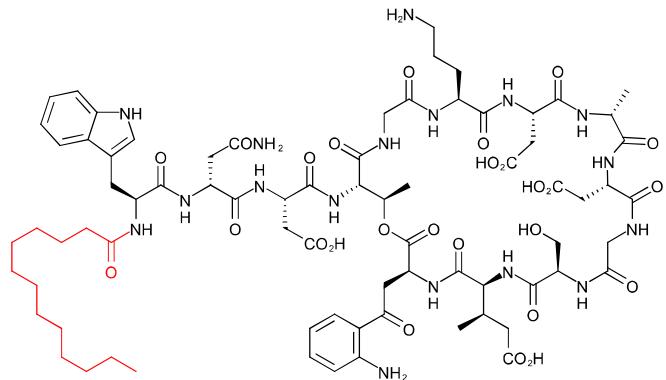
*Streptococcus faecalis* = 2.0

LD<sub>50</sub> (mouse, IV) = 450 mg/kg



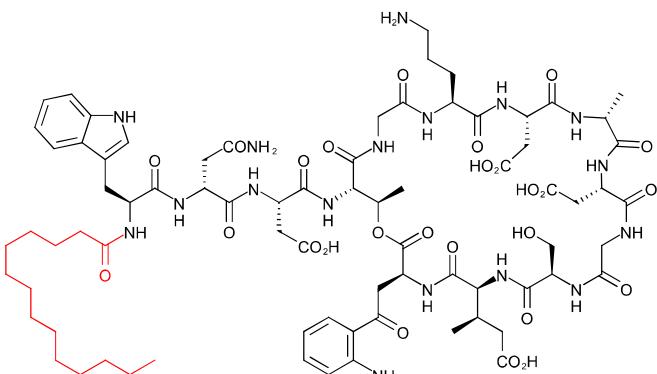
**11. *n*-Dodecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 0.5  
*Streptococcus faecalis* = 4.0  
 $\text{LD}_{50}$  (mouse, IV) = 144 mg/kg



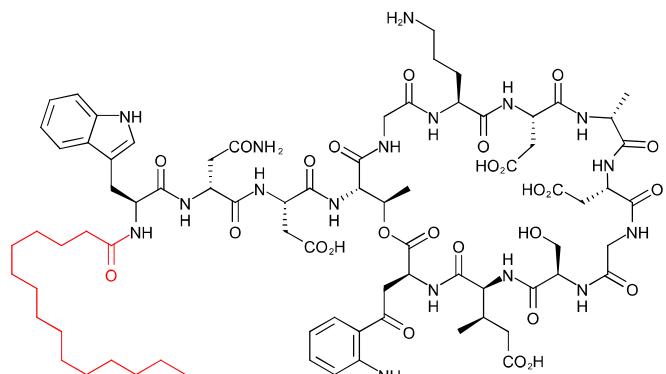
**12. *n*-Tridecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.125  
*Staphylococcus epidermidis* = 0.5  
*Streptococcus faecalis* = 0.03  
 $\text{LD}_{50}$  (mouse, IV) = 112.5 mg/kg



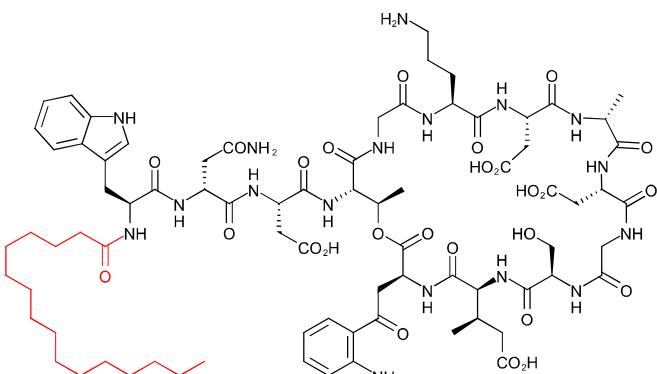
**13. *n*-Tetradecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 2  
*Streptococcus faecalis* = 0.5  
 $\text{LD}_{50}$  (mouse, IV) = 62.5 mg/kg



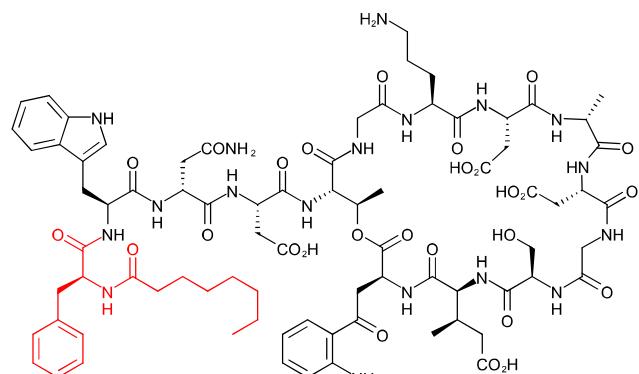
**14. *n*-Pentadecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 1  
*Staphylococcus epidermidis* = 4  
*Streptococcus faecalis* = 2  
 $\text{LD}_{50}$  (mouse, IV) = 56.3 mg/kg



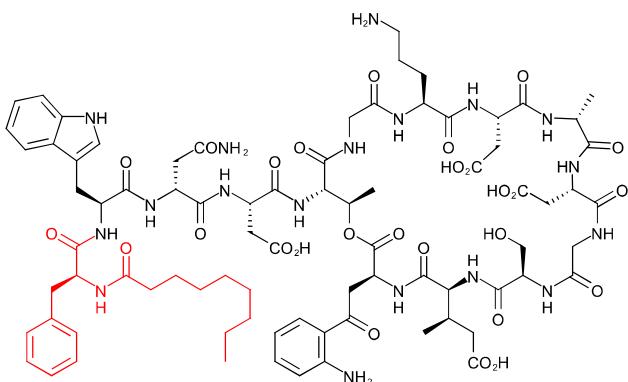
**15. *n*-Hexadecanoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 1  
*Staphylococcus epidermidis* = 2  
*Streptococcus faecalis* = 2  
 $\text{LD}_{50}$  (mouse, IV) = 50 mg/kg



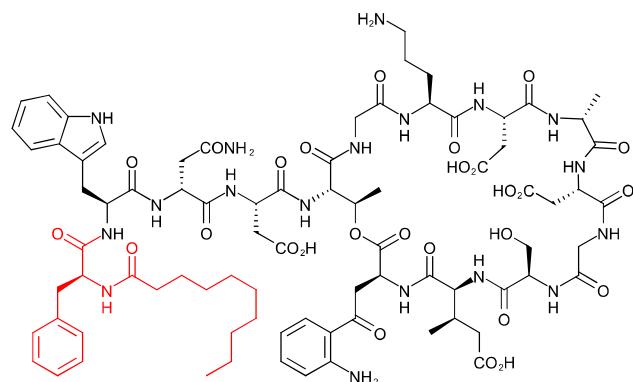
**16. *n*-Octanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 4  
*Staphylococcus epidermidis* = 8  
*Streptococcus faecalis* = 128  
 $\text{LD}_{50}$  (mouse, IV) = 450 mg/kg



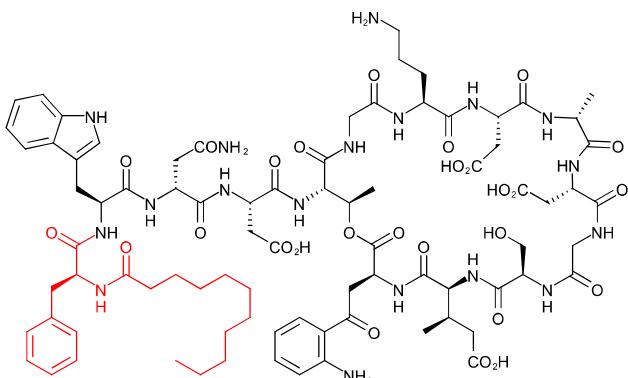
**17. *n*-Nonanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 2  
*Staphylococcus epidermidis* = 2  
*Streptococcus faecalis* = 32  
 LD<sub>50</sub> (mouse, IV) > 600 mg/kg



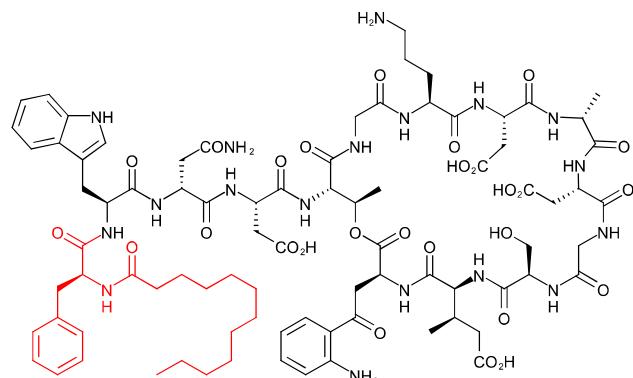
**18. *n*-Decanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 0.5  
*Streptococcus faecalis* = 8  
 LD<sub>50</sub> (mouse, IV) = 600 mg/kg



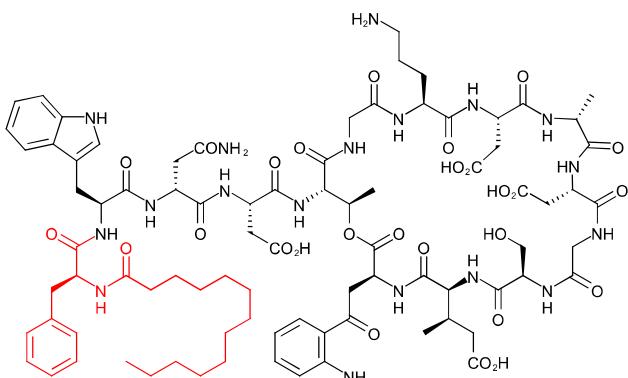
**19. *n*-Undecanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 2  
*Streptococcus faecalis* = 4  
 LD<sub>50</sub> (mouse, IV) = 400 mg/kg



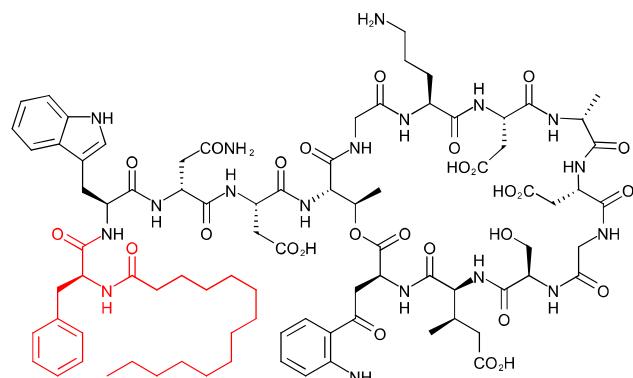
**20. *n*-Dodecanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 1  
*Streptococcus faecalis* = 1  
 LD<sub>50</sub> (mouse, IV) > 250 mg/kg



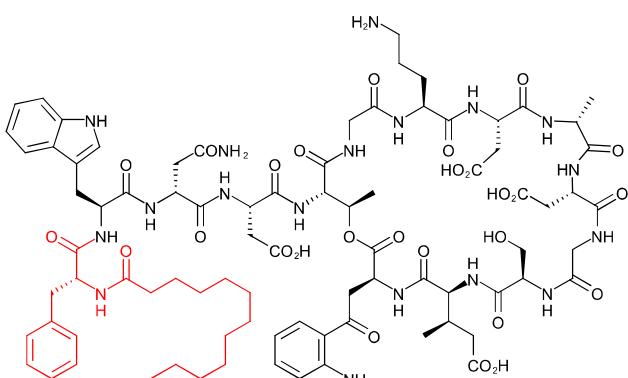
**21. *n*-Tridecanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 2  
*Streptococcus faecalis* = 0.5  
 LD<sub>50</sub> (mouse, IV) = 225 mg/kg



**22. *n*-Tetradecanoyl-L-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5  
*Staphylococcus epidermidis* = 4  
*Streptococcus faecalis* = 1  
 LD<sub>50</sub> (mouse, IV) = 225 mg/kg



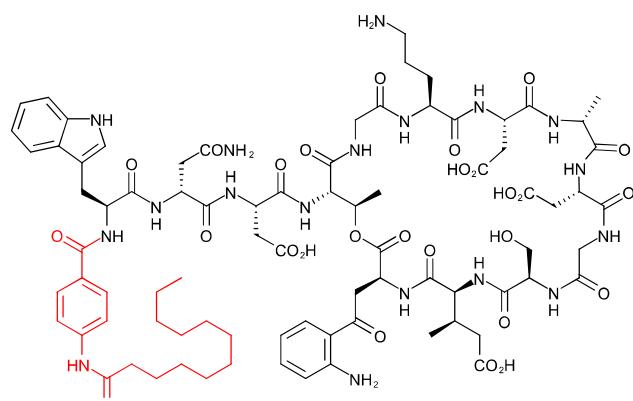
**23. *n*-Dodecanoyl-D-Phe, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5

*Staphylococcus epidermidis* = 4

*Streptococcus faecalis* = 1

LD<sub>50</sub> (mouse, IV) = 250 mg/kg



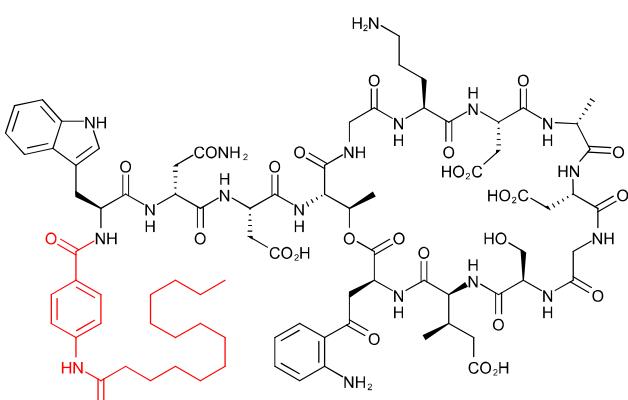
**24. *p*-Dodecanoylamidobenzoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 2

*Staphylococcus epidermidis* = 16

*Streptococcus faecalis* = 32

LD<sub>50</sub> (mouse, IV) < 300 mg/kg



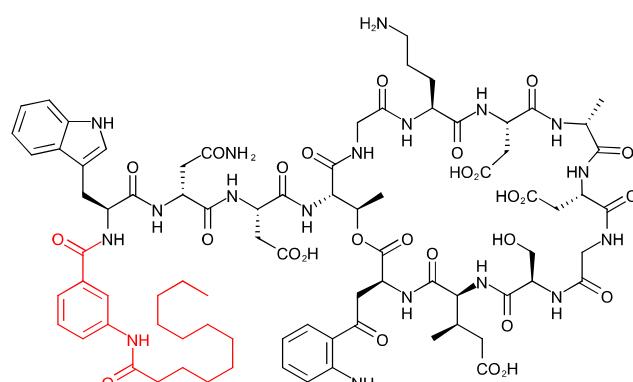
**25. *p*-Tetradecanoylamidobenzoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 1

*Staphylococcus epidermidis* = 4

*Streptococcus faecalis* = 4

LD<sub>50</sub> (mouse, IV) = 250 mg/kg



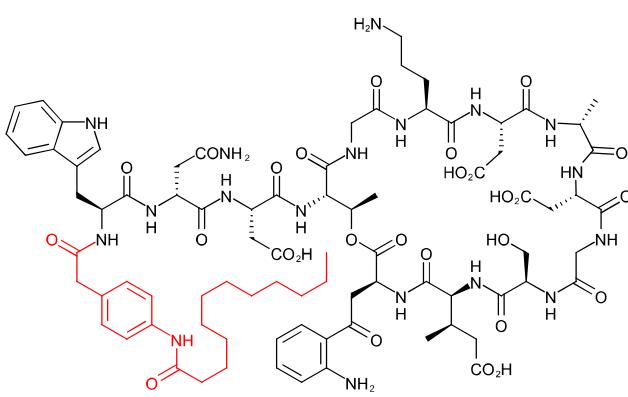
**26. *m*-Dodecanoylamidobenzoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5

*Staphylococcus epidermidis* = 1

*Streptococcus faecalis* = 4

LD<sub>50</sub> (mouse, IV) = 277 mg/kg



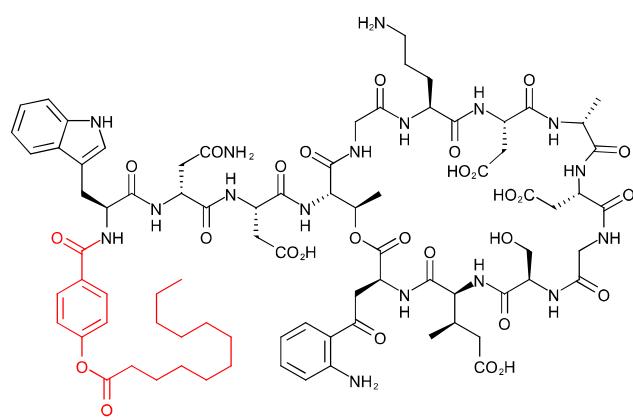
**27. *p*-Dodecanoylamidophenacetyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 0.5

*Staphylococcus epidermidis* = 0.5

*Streptococcus faecalis* = 4

LD<sub>50</sub> (mouse, IV) = 450 mg/kg



**28. *p*-Dodecyloxybenzoyl, MIC ( $\mu\text{g/mL}$ )**

*Staphylococcus aureus* = 1

*Staphylococcus epidermidis* = 2

*Streptococcus faecalis* = 2

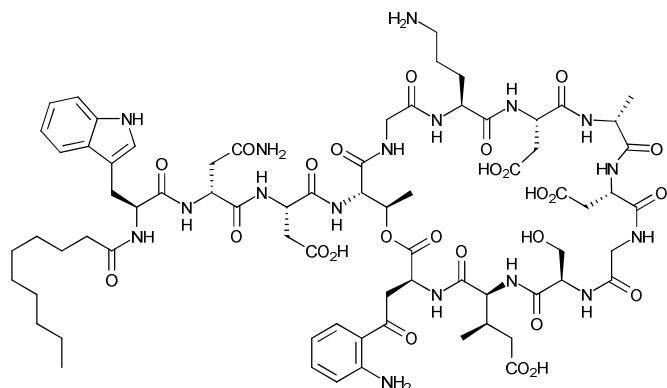
LD<sub>50</sub> (mouse, IV) = 67.5 mg/kg

## Synthesis and biological activity of N-Acylated ornithine analogues of daptomycin

Hill, J., Siedlecki, J., Parr, I., Morytko, M., Yu, X., Zhang, Y., Silverman, J., Controneo, N., Laganas, V., Li, T., Lai, J. J., Keith, D., Shimer, G., Finn, J., *Bioorg. Med. Chem. Lett.*, 2003, 13, 23, 4187-4191.

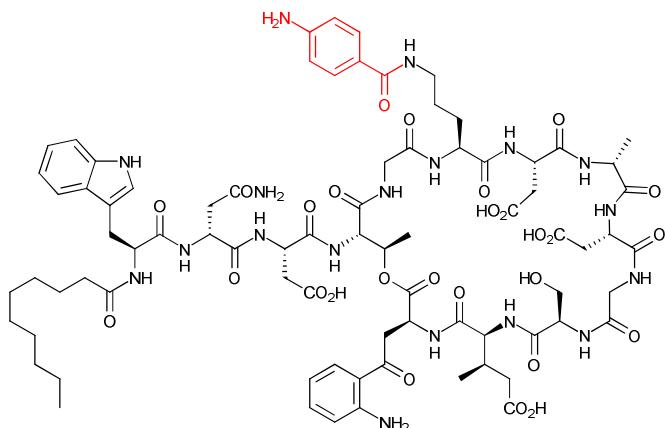
### Notes

1. Bacterial strains used for MIC determinations. MSSA: *S. aureus* ATCC 29213; MRSA: *S. aureus* ATCC 43300; *Enterococcus faecium* ATCC 6569; *Enterococcus faecalis* ATCC 49452.
2. The  $\alpha$ -carbon stereochemistry of the bicyclic substituent in Compound 23 is unspecified.



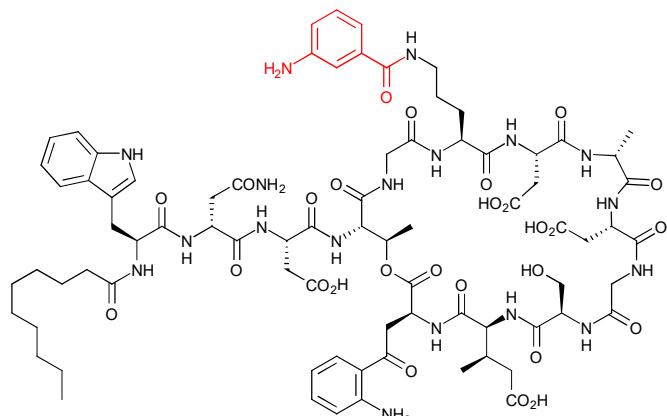
**29. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78      *E. faecium* = 1.56  
MRSA = 0.39      *E. faecalis* = 1.56



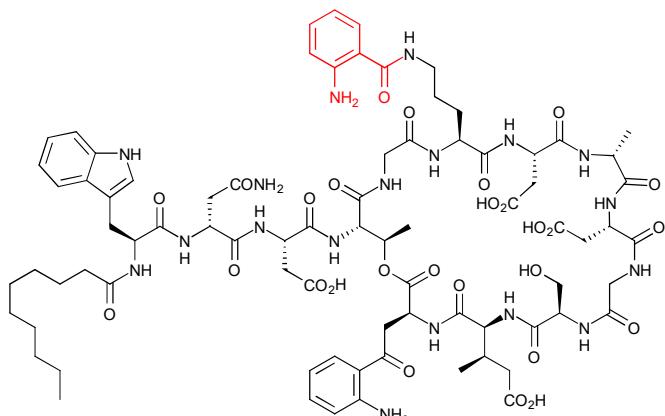
**30. Compound 1, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1      *E. faecium* = 25  
MRSA = 3.1      *E. faecalis* = 25



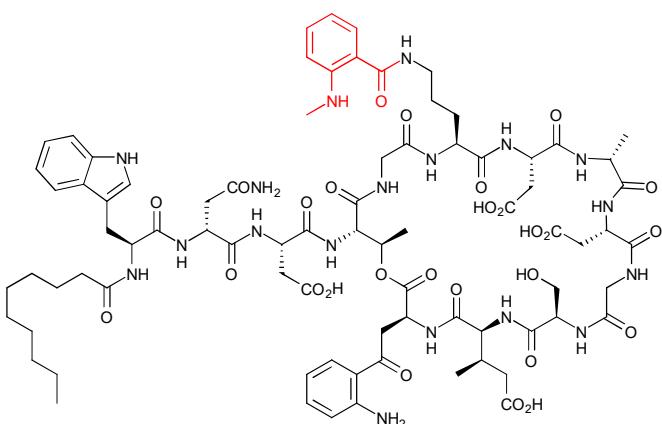
**31. Compound 2, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1      *E. faecium* = 12.5  
MRSA = 1.56      *E. faecalis* = 25



**32. Compound 3, MIC ( $\mu\text{g/mL}$ )**

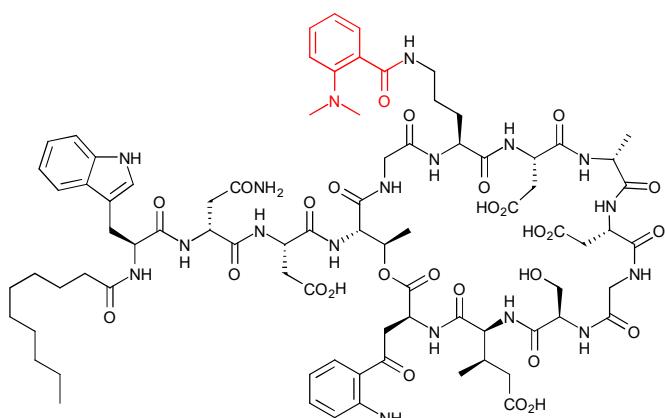
MSSA = 0.78      *E. faecium* = 6.25  
MRSA = 1.56      *E. faecalis* = 12.5



**33. Compound 4, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 0.39

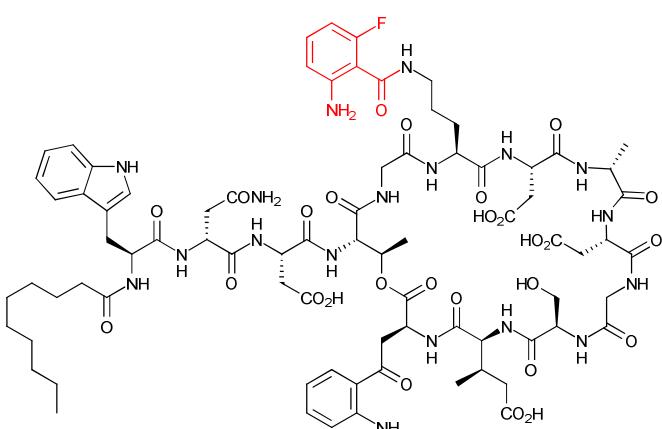
*E. faecium* = 6.25  
*E. faecalis* = 6.25



**34. Compound 5, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 3.1

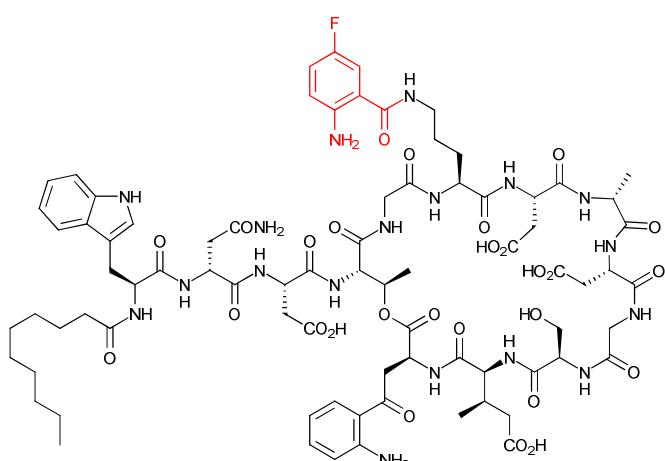
*E. faecium* = 12.5  
*E. faecalis* = 50



**35. Compound 6, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 0.78

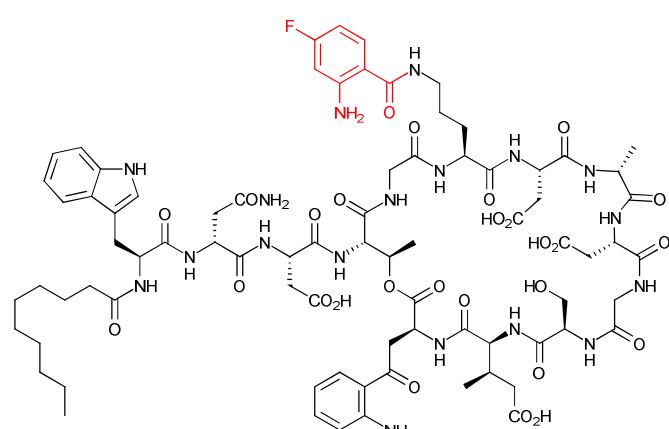
*E. faecium* = 3.1  
*E. faecalis* = 3.1



**36. Compound 7, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 1.56

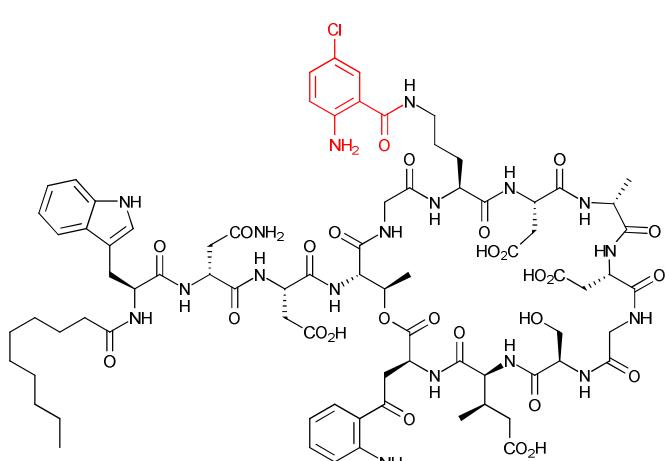
*E. faecium* = 6.25  
*E. faecalis* = 6.25



**37. Compound 8, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56

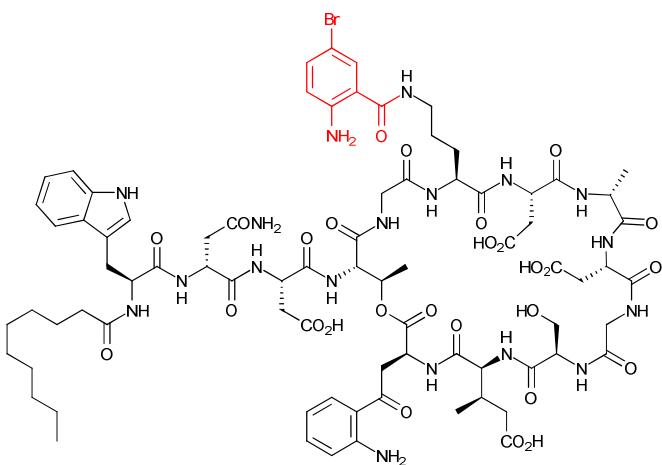
*E. faecium* = 12.5  
*E. faecalis* = 12.5



**38. Compound 9, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = ND

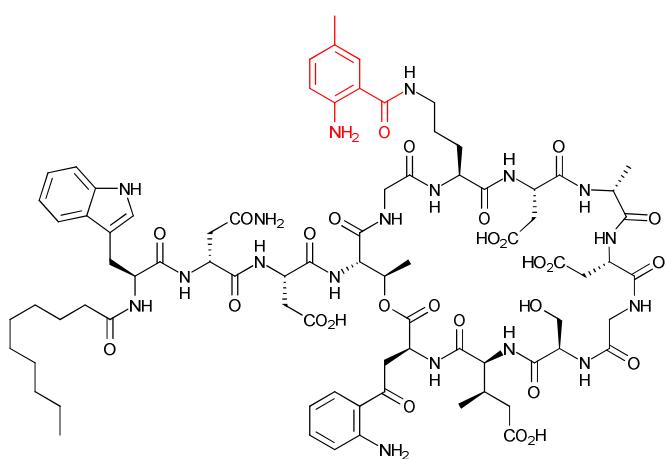
*E. faecium* = 10  
*E. faecalis* = 10



**39. Compound 10, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 0.78

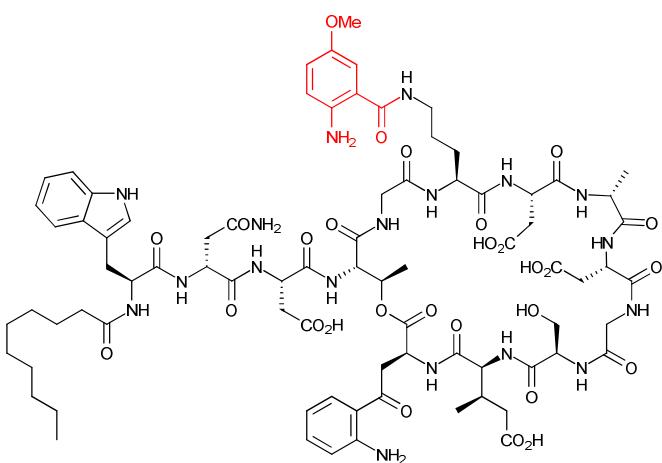
*E. faecium* = 3.1  
*E. faecalis* = 6.25



**40. Compound 11, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.25  
MRSA = ND

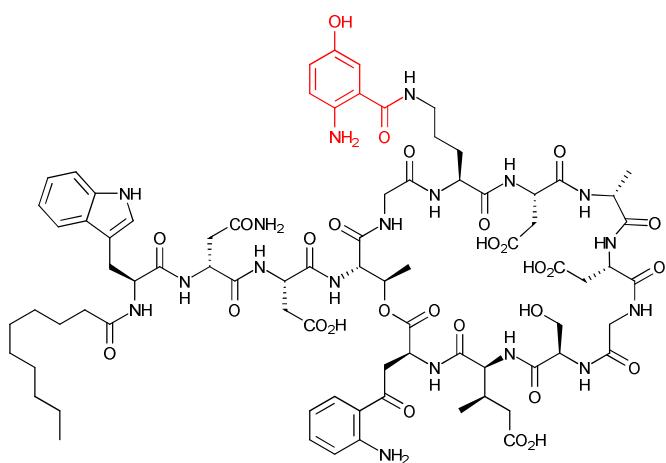
*E. faecium* = 10  
*E. faecalis* = 10



**41. Compound 12, MIC ( $\mu\text{g/mL}$ )**

MSSA = 2.5  
MRSA = ND

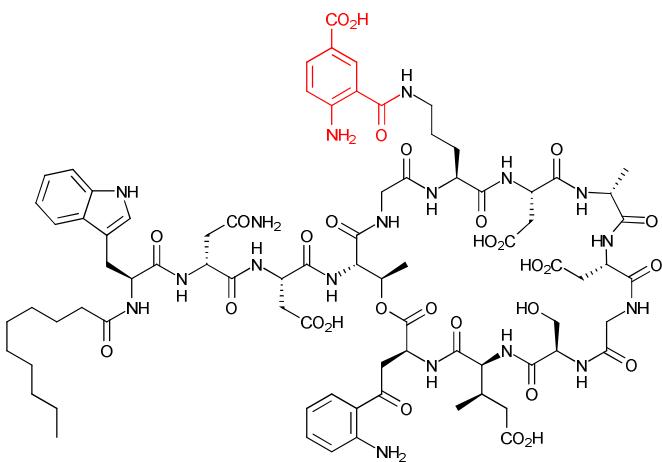
*E. faecium* = 10  
*E. faecalis* = 10



**42. Compound 13, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.25  
MRSA = ND

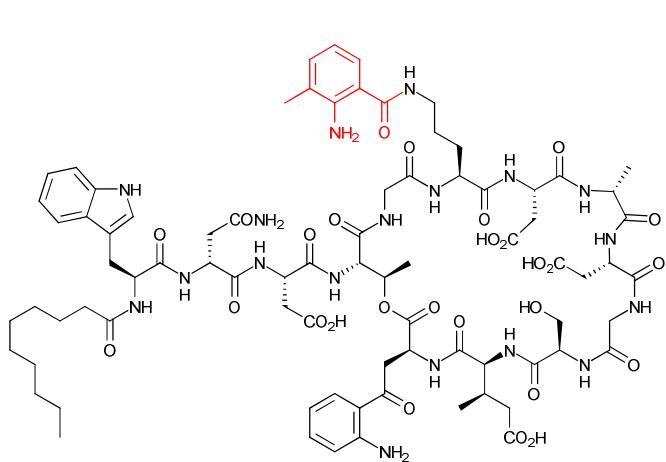
*E. faecium* = 10  
*E. faecalis* = 10



**43. Compound 14, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.25  
MRSA = 3.1

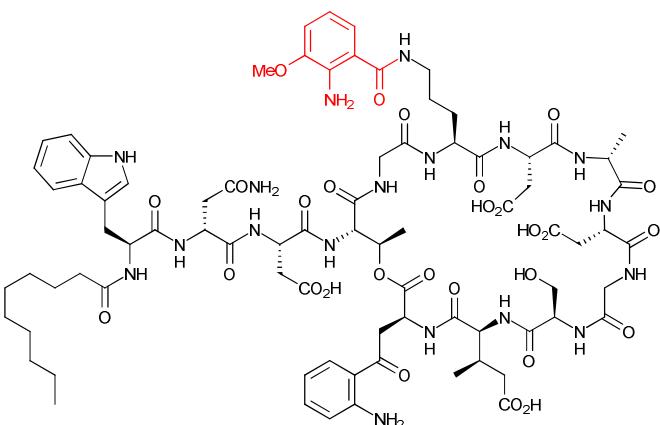
*E. faecium* = 10  
*E. faecalis* = 12.5



**44. Compound 15, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.63  
MRSA = ND

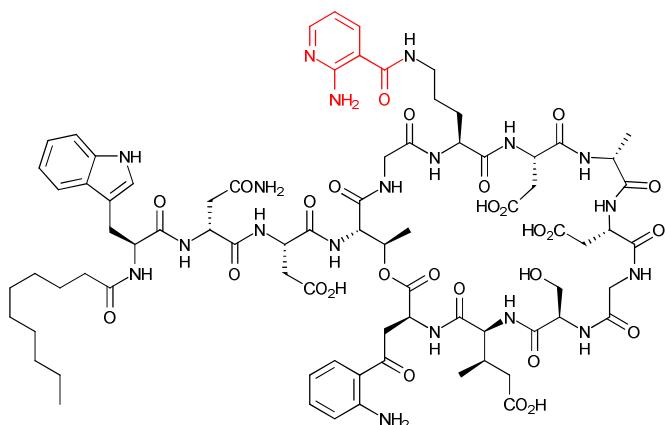
*E. faecium* = 10  
*E. faecalis* = 10



**45. Compound 16, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.63  
MRSA = ND

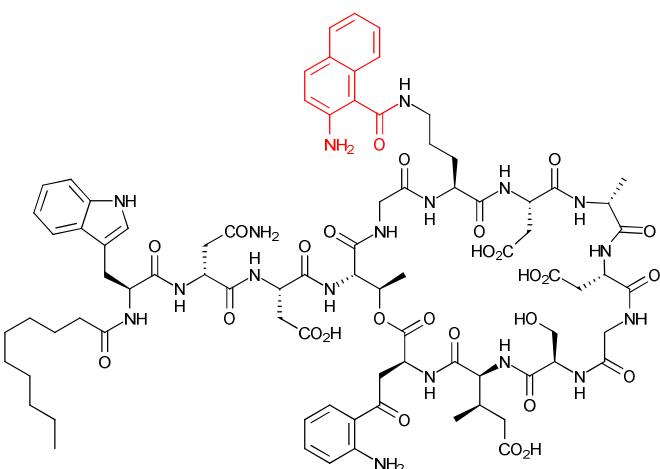
*E. faecium* = 10  
*E. faecalis* = 10



**46. Compound 17, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.63  
MRSA = ND

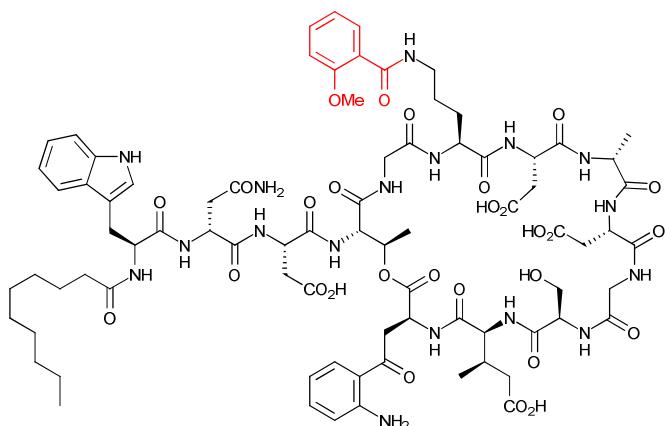
*E. faecium* = 10  
*E. faecalis* = 10



**47. Compound 18, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 0.78

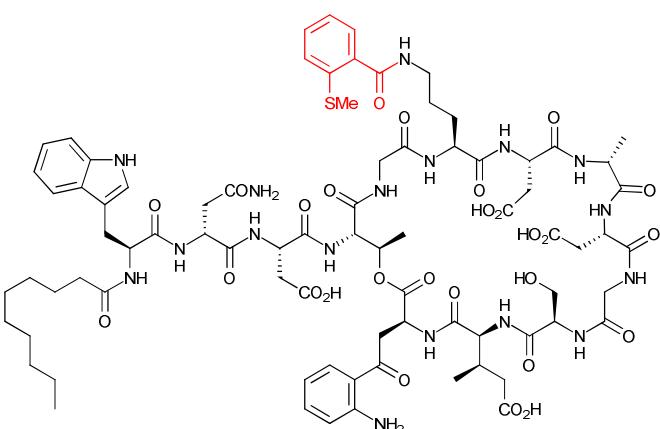
*E. faecium* = 6.25  
*E. faecalis* = 6.25



**48. Compound 19, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.25  
MRSA = 3.1

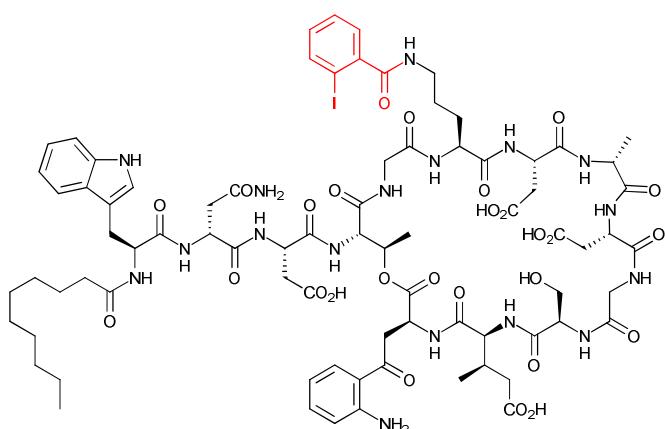
*E. faecium* = 6.25  
*E. faecalis* = 25



**49. Compound 20, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1  
MRSA = 1.56

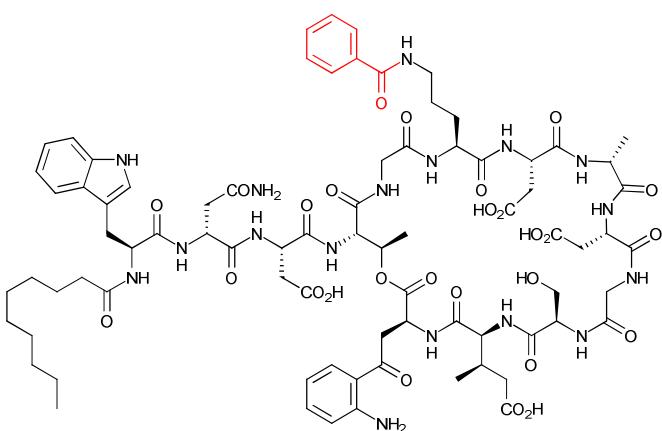
*E. faecium* = 6.25  
*E. faecalis* = 25



**50. Compound 21, MIC ( $\mu\text{g/mL}$ )**

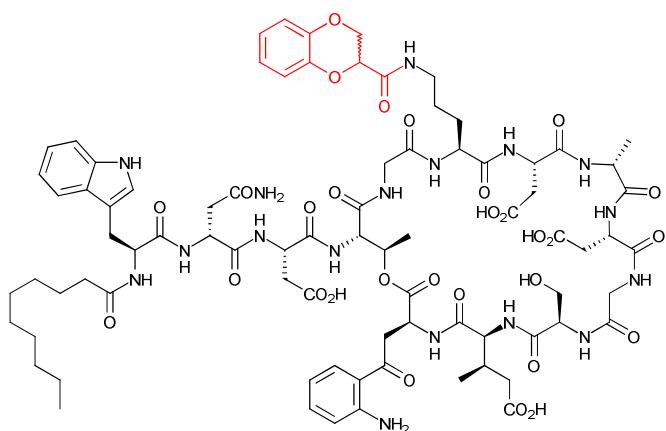
MSSA = 1.56  
MRSA = 1.56

*E. faecium* = 3.1  
*E. faecalis* = 12.5



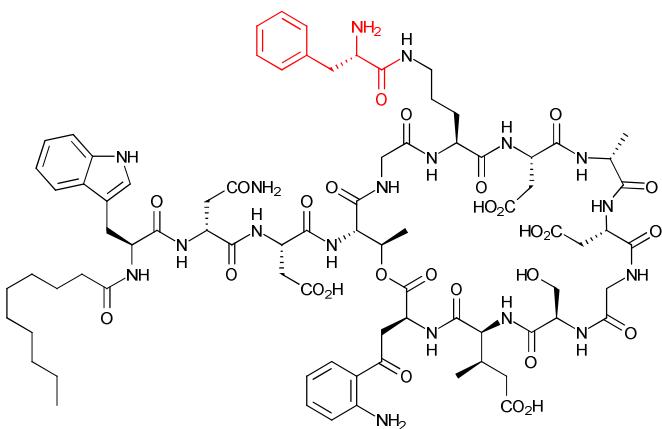
**51. Compound 22, MIC ( $\mu\text{g/mL}$ )**

MSSA = 6.25      *E. faecium* = 25  
MRSA = 12.5      *E. faecalis* = 25



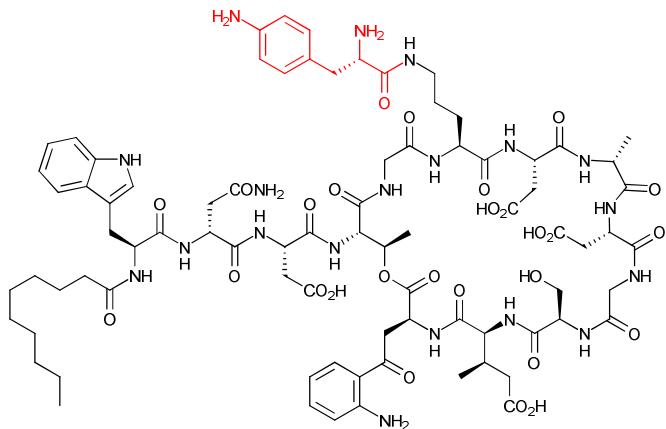
**52. Compound 23, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56      *E. faecium* = 25  
MRSA = 1.56      *E. faecalis* = 25



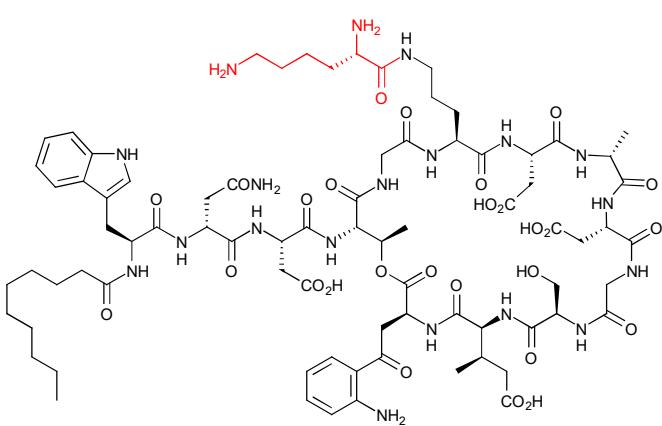
**53. Compound 24, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1      *E. faecium* = 6.25  
MRSA = 3.1      *E. faecalis* = 25



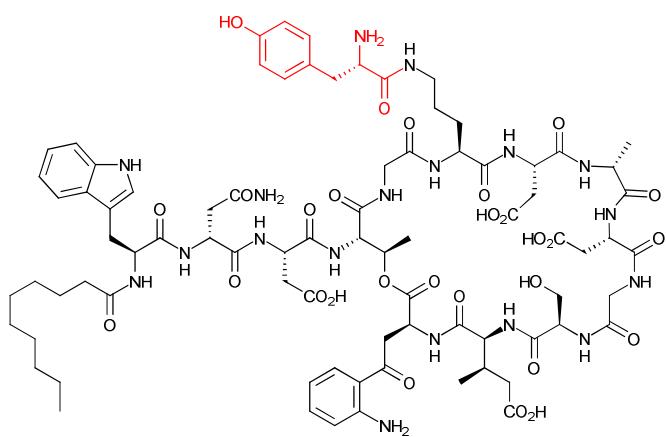
**54. Compound 25, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1      *E. faecium* = 25  
MRSA = 1.56      *E. faecalis* = 12.5



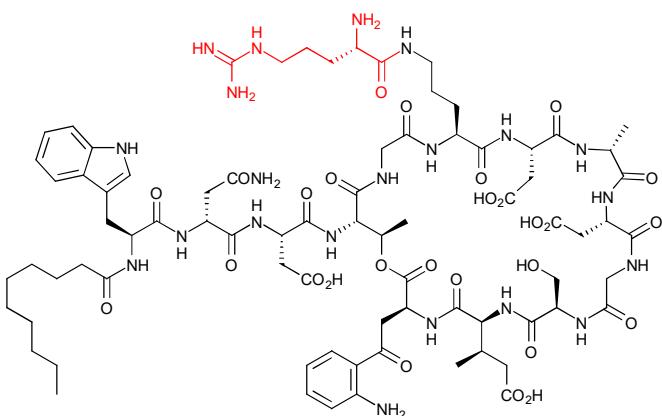
**55. Compound 26, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56      *E. faecium* = ND  
MRSA = 0.78      *E. faecalis* = 6.25



**56. Compound 27, MIC ( $\mu\text{g/mL}$ )**

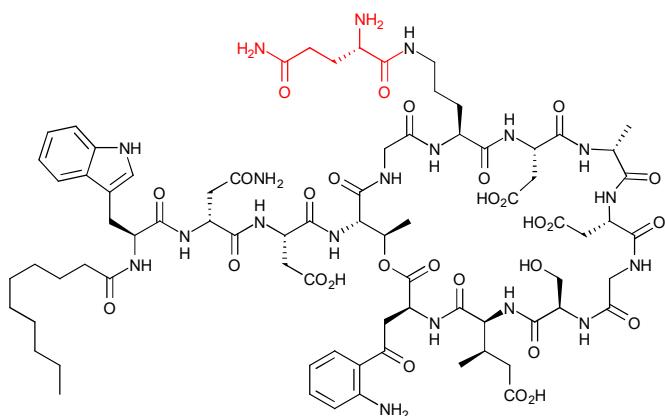
MSSA = 0.78      *E. faecium* = 3.1  
MRSA = 1.56      *E. faecalis* = 6.25



**57. Compound 28, MIC ( $\mu\text{g/mL}$ )**

MSSA = 6.25  
MRSA = 6.25

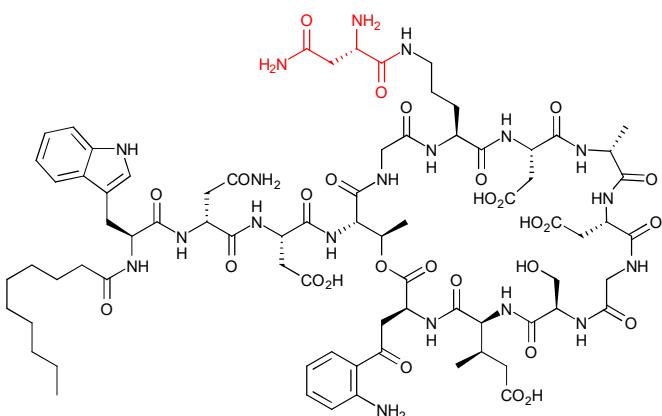
*E. faecium* = 25  
*E. faecalis* = 50



**58. Compound 29, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.25  
MRSA = ND

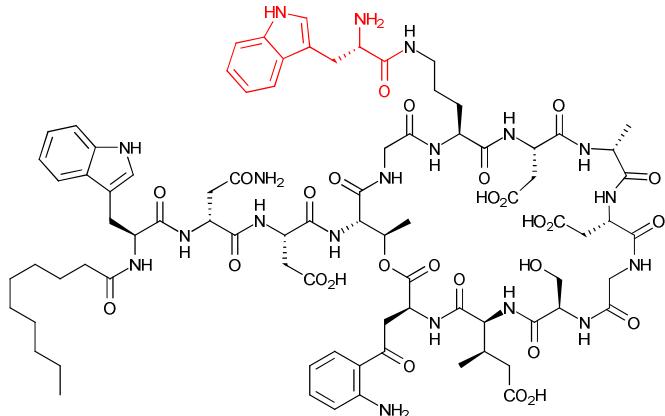
*E. faecium* = 5  
*E. faecalis* = 10



**59. Compound 30, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.63  
MRSA = ND

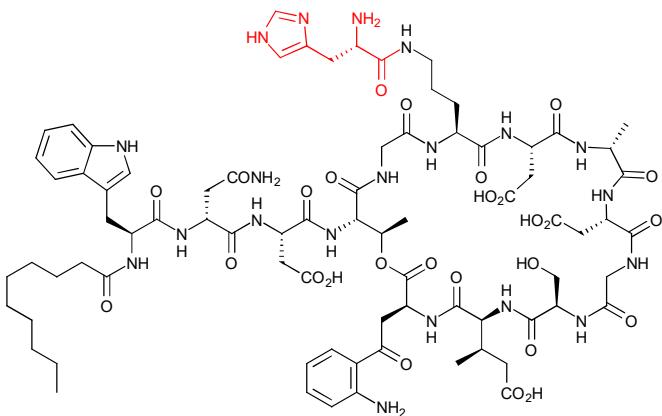
*E. faecium* = 5  
*E. faecalis* = 10



**60. Compound 31, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78  
MRSA = 0.78

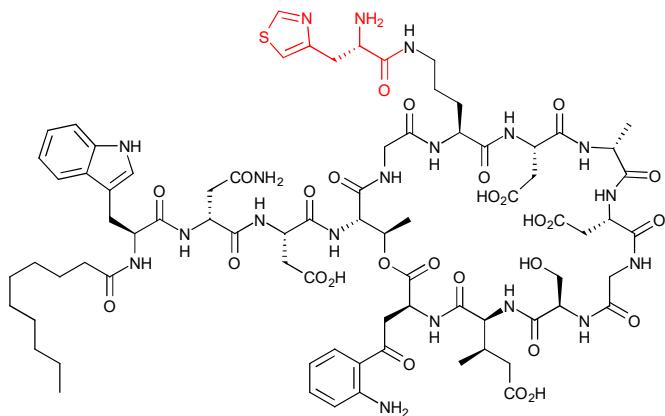
*E. faecium* = 1.56  
*E. faecalis* = 3.1



**61. Compound 32, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56

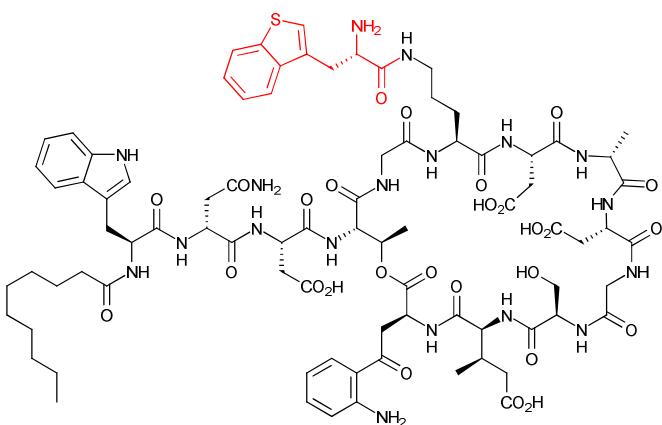
*E. faecium* = 12.5  
*E. faecalis* = 50



**62. Compound 33, MIC ( $\mu\text{g/mL}$ )**

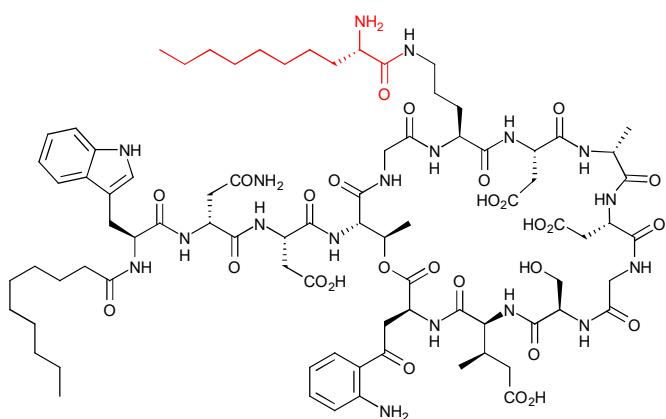
MSSA = 1.56  
MRSA = 0.78

*E. faecium* = 6.25  
*E. faecalis* = 25



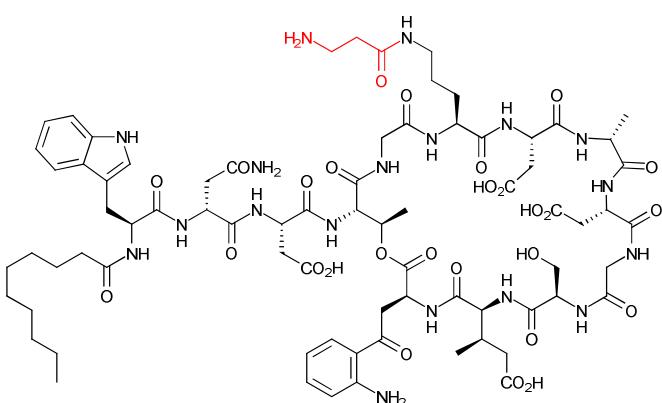
**63. Compound 34, MIC ( $\mu\text{g/mL}$ )**

MSSA = 12.5      *E. faecium* = 50  
 MRSA = 6.25      *E. faecalis* = 100



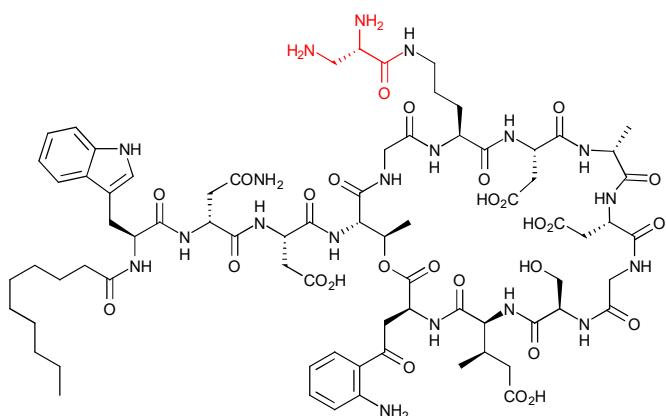
**64. Compound 35, MIC ( $\mu\text{g/mL}$ )**

MSSA > 100      *E. faecium* > 100  
 MRSA > 100      *E. faecalis* > 100



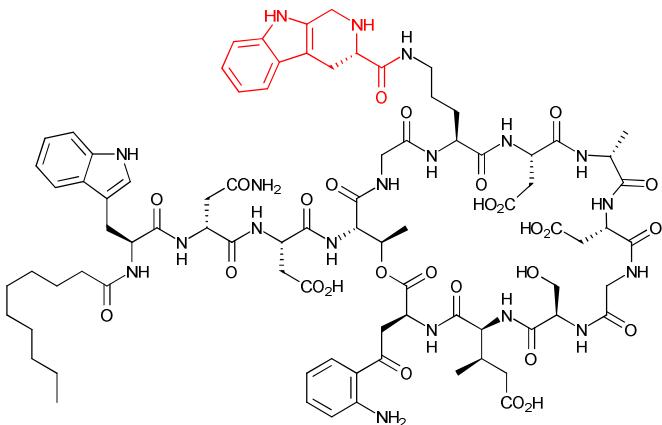
**65. Compound 36, MIC ( $\mu\text{g/mL}$ )**

MSSA = 6.25      *E. faecium* = 25  
 MRSA = 6.25      *E. faecalis* = 100



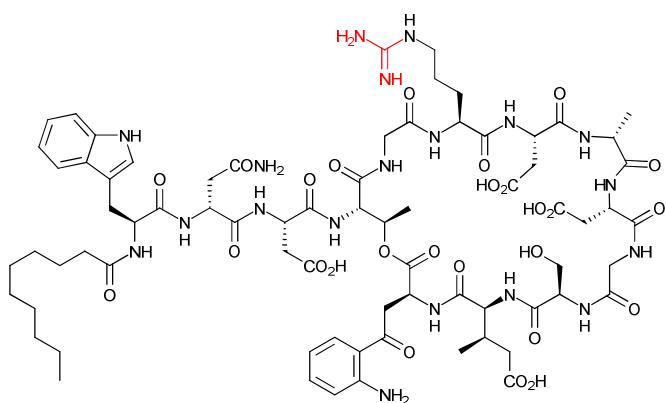
**66. Compound 37, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1      *E. faecium* = 25  
 MRSA = 3.1      *E. faecalis* = 50



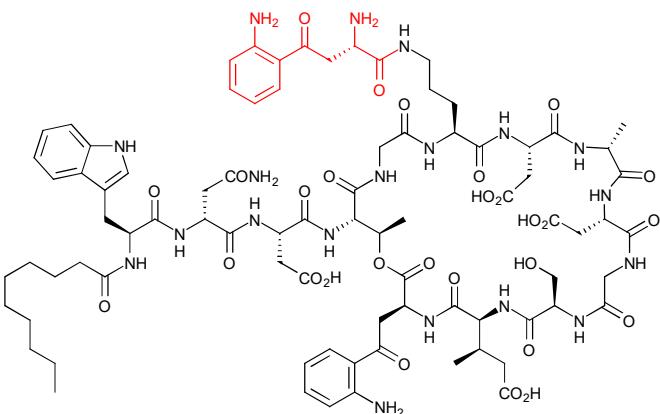
**67. Compound 38, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78      *E. faecium* = 3.1  
 MRSA = 0.78      *E. faecalis* = 12.5



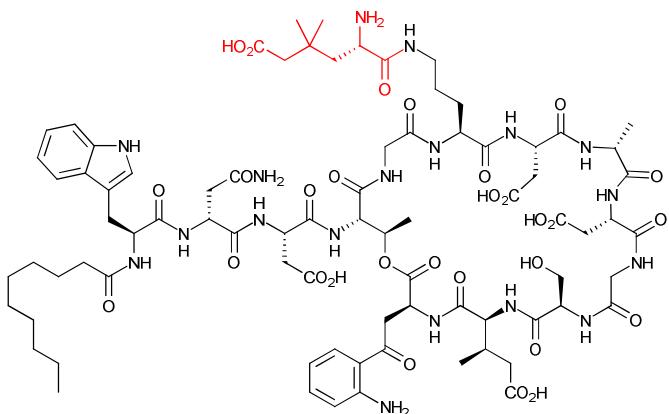
**68. Compound 39, MIC ( $\mu\text{g/mL}$ )**

MSSA = 0.78      *E. faecium* = 6.25  
 MRSA = 0.78      *E. faecalis* = 12.5



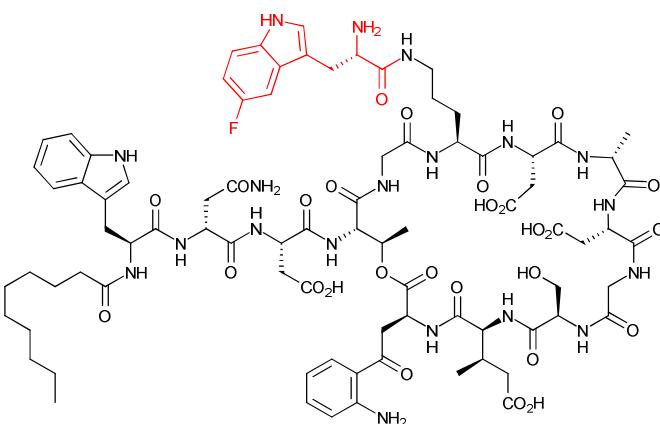
**69. Compound 40, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56



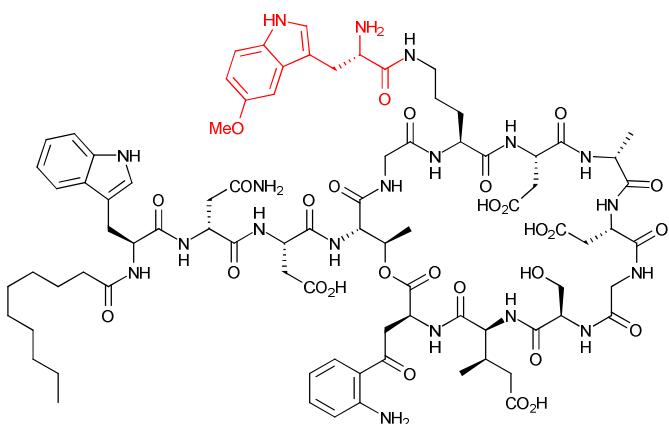
**70. Compound 41, MIC ( $\mu\text{g/mL}$ )**

MSSA = 12.5  
MRSA = 12.5



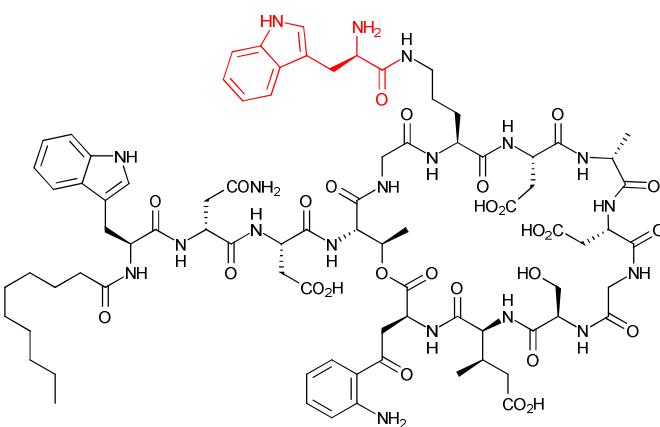
**71. Compound 42, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56



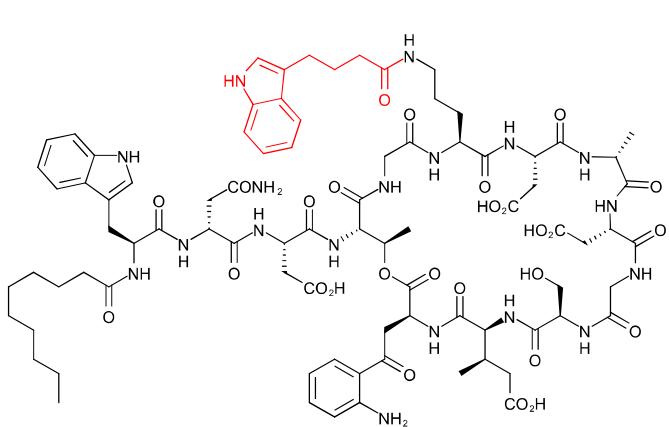
**72. Compound 43, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56



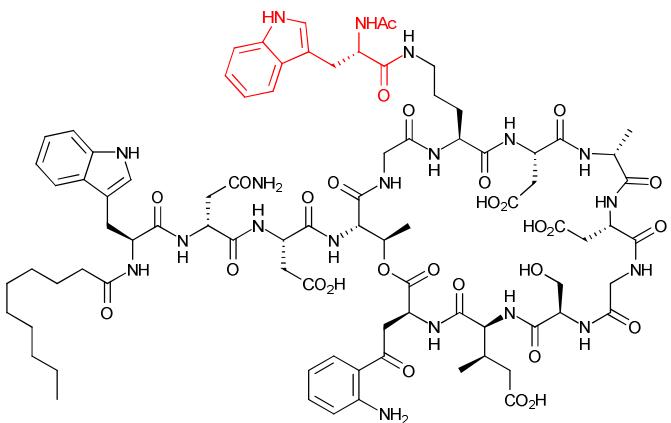
**73. Compound 44, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56



**74. Compound 45, MIC ( $\mu\text{g/mL}$ )**

MSSA = 1.56  
MRSA = 1.56



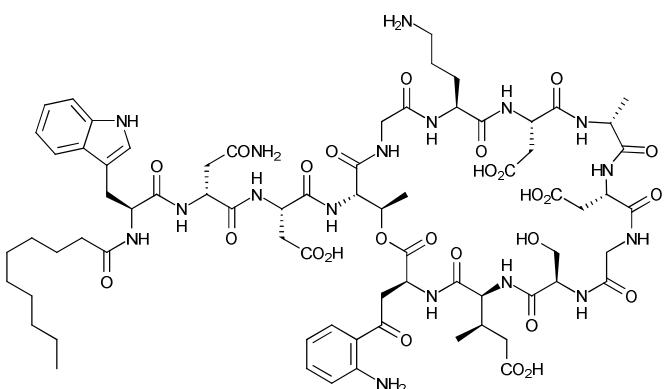
**75. Compound 46, MIC ( $\mu\text{g/mL}$ )**

MSSA = 3.1  
MRSA = 3.1

*E. faecium* = 12.5  
*E. faecalis* = 25

### Array Synthesis of Novel Lipodepsipeptide

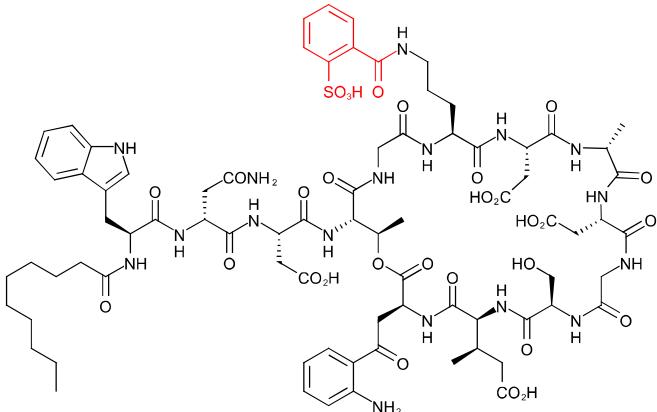
Siedlecki, J., Hill, J., Parr, I., Yu, X., Morytko, M., Zhang, Y., Silverman, J., Controneo, N., Laganas, V., Li, T., Li, J., Keith, D., Shimer, G., Finn, J.,  
*Bioorg. & Med. Chem. Lett.*, **2003**, 13, 4245–4249.



**76. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

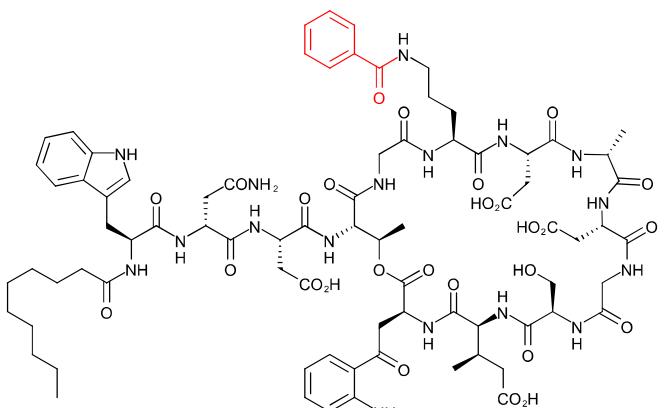
*E. faecalis* = 1.56  
*E. faecium* = 1.56



**77. Compound 1, MIC ( $\mu\text{g/mL}$ )**

MRSA = 100  
MSSA = 100

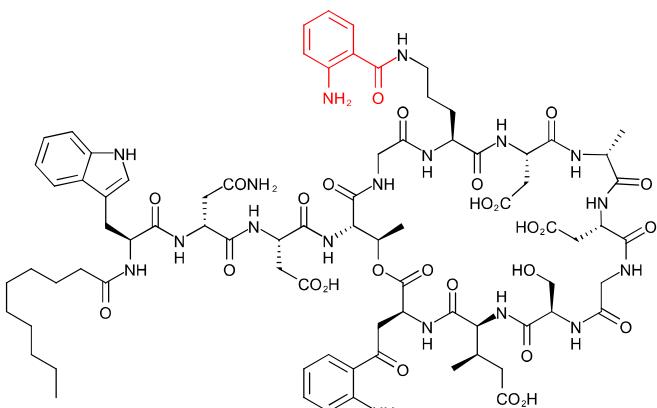
*E. faecalis* = 100  
*E. faecium* = 100



**78. Compound 2, MIC ( $\mu\text{g/mL}$ )**

MRSA = 6.25  
MSSA = 12.5

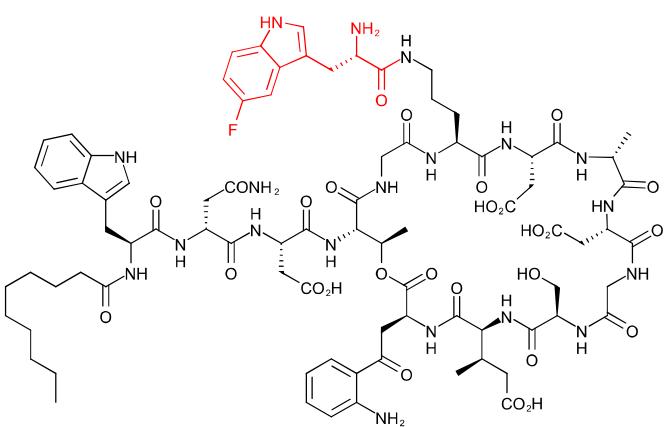
*E. faecalis* = 25  
*E. faecium* = 25



**79. Compound 3, MIC ( $\mu\text{g/mL}$ )**

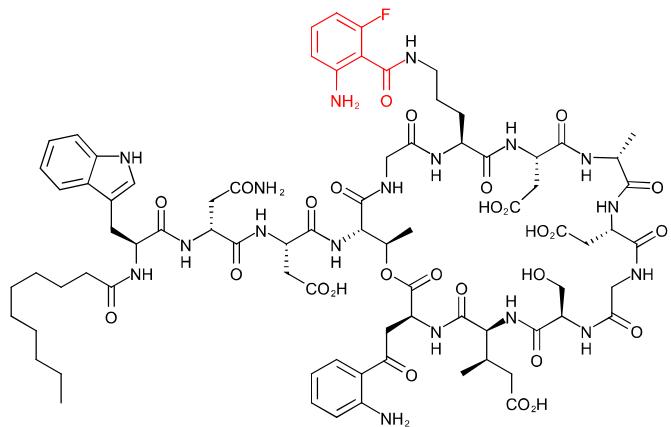
MRSA = 0.78  
MSSA = 1.56

*E. faecalis* = 3.1  
*E. faecium* = 12.5



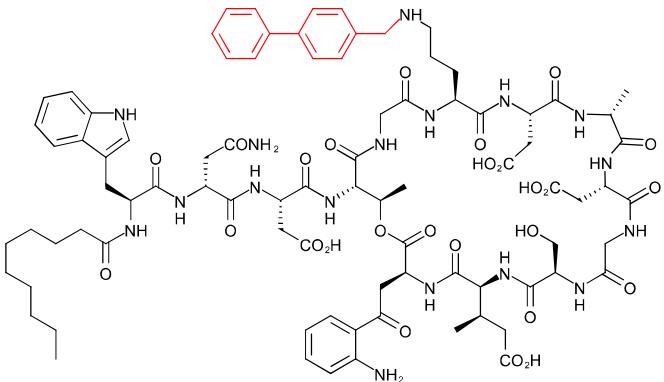
**80. Compound 4, MIC ( $\mu\text{g/mL}$ )**

MRSA = 1.56      *E. faecalis* = 3.1  
MSSA = 1.56      *E. faecium* = 12.5



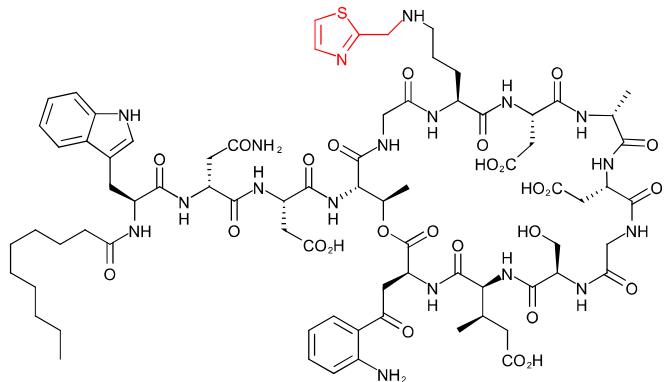
**81. Compound 5, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 3.1  
MSSA = 0.78      *E. faecium* = 3.1



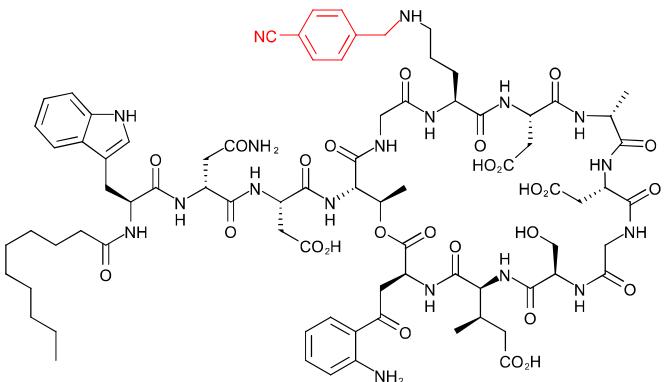
**82. Compound 6, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.20      *E. faecalis* = 1.56  
MSSA = 0.39      *E. faecium* = 1.56



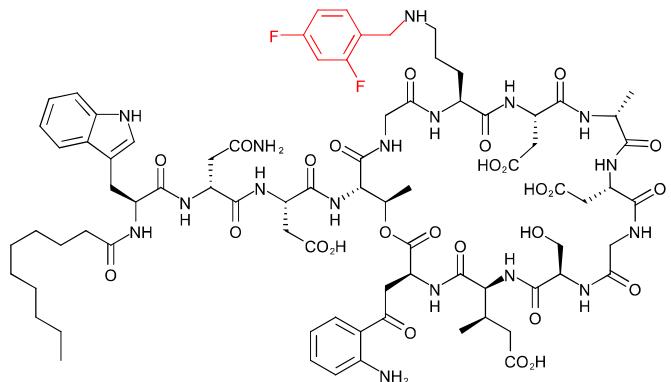
**83. Compound 9, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 6.25  
MSSA = 0.78      *E. faecium* = 6.25



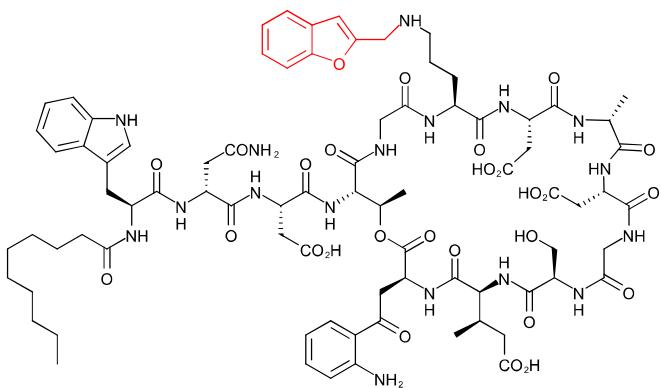
**84. Compound 10, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 6.25  
MSSA = 0.78      *E. faecium* = 6.25



**85. Compound 17, MIC ( $\mu\text{g/mL}$ )**

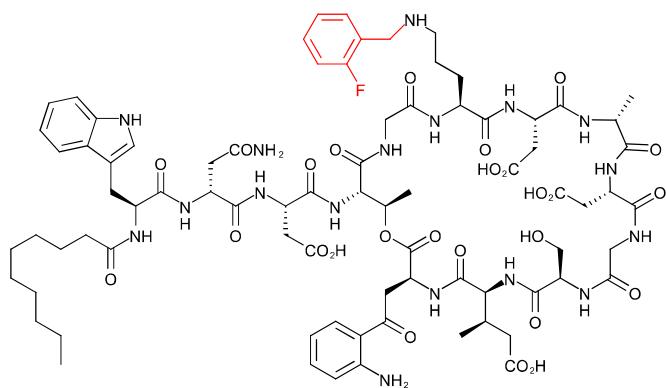
MRSA = 0.78      *E. faecalis* = 6.25  
MSSA = 1.56      *E. faecium* = 6.25



**86. Compound 45, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

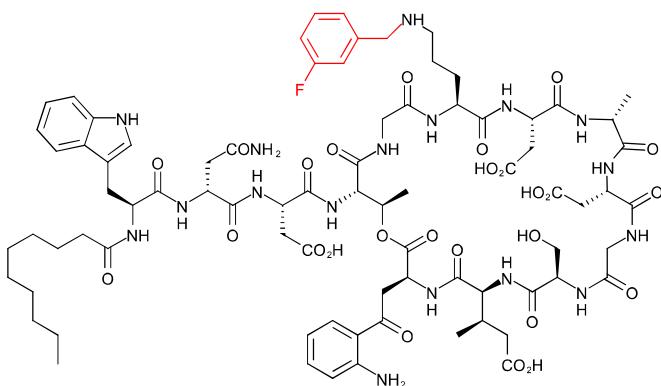
*E. faecalis* = 3.13  
*E. faecium* = 3.13



**87. Compound 48, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

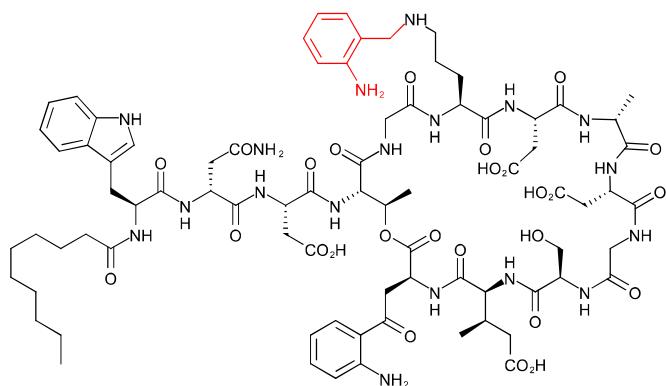
*E. faecalis* = 6.25  
*E. faecium* = 6.25



**88. Compound 49, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

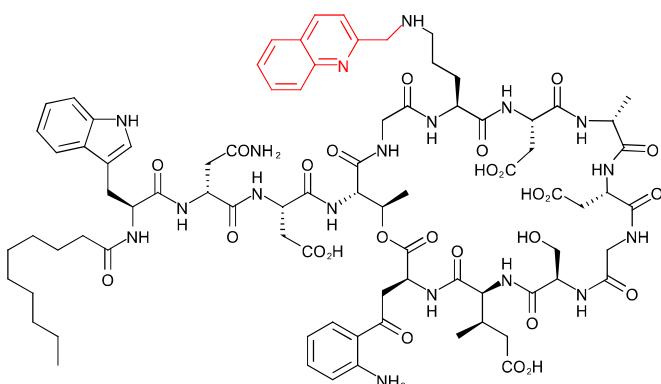
*E. faecalis* = 6.25  
*E. faecium* = 12.5



**89. Compound 51, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

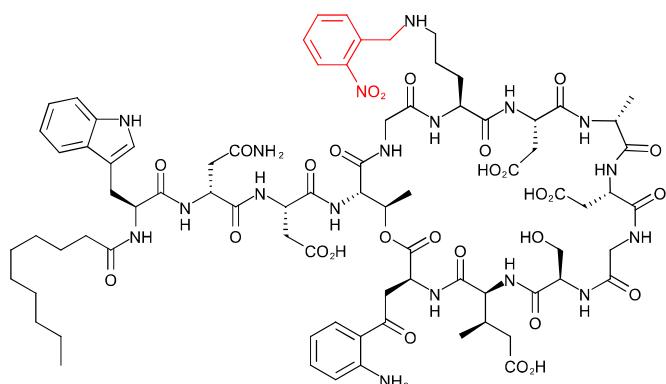
*E. faecalis* = 6.25  
*E. faecium* = 6.25



**90. Compound 54, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

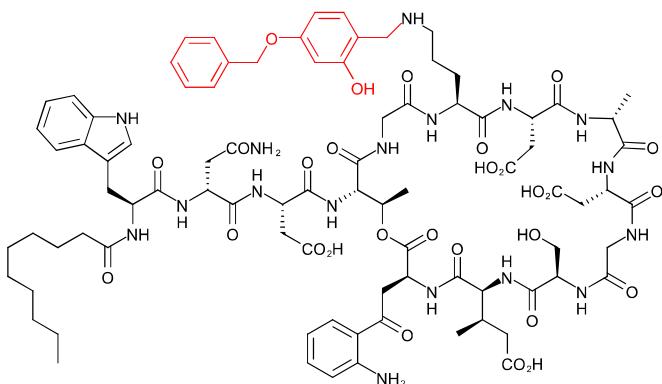
*E. faecalis* = 6.25  
*E. faecium* = 6.25



**91. Compound 55, MIC ( $\mu\text{g/mL}$ )**

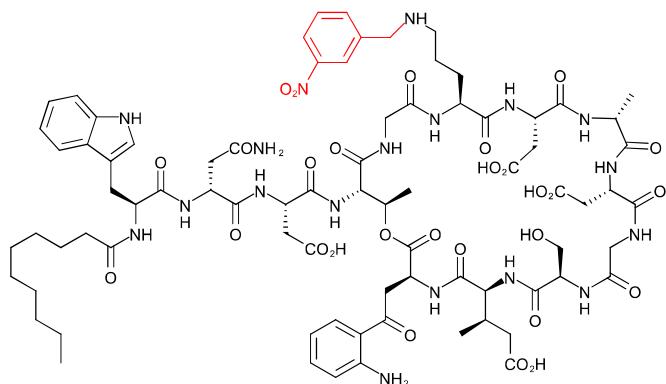
MRSA = 0.78  
MSSA = 0.78

*E. faecalis* = 12.5  
*E. faecium* = 12.5



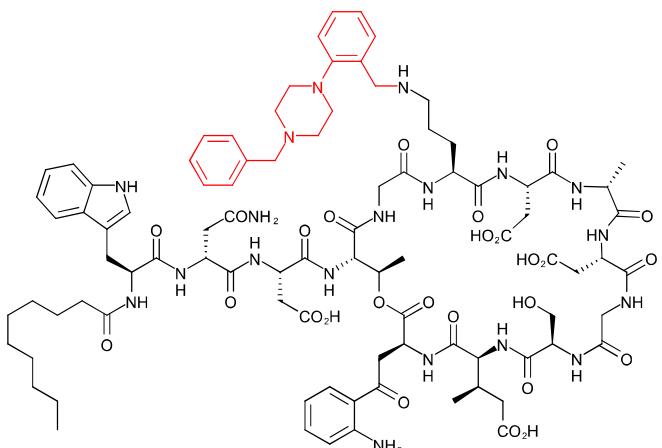
**92. Compound 78, MIC ( $\mu\text{g/mL}$ )**

MRSA = 1.56      *E. faecalis* = 1.56  
MSSA = 3.13      *E. faecium* = 6.25



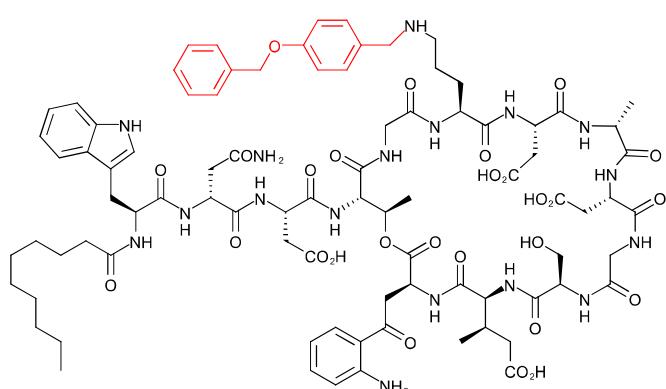
**93. Compound 79, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 6.25  
MSSA = 0.78      *E. faecium* = 6.25



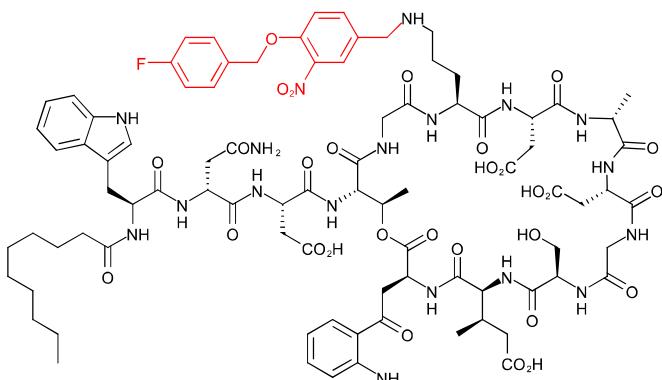
**94. Compound 81, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 6.25  
MSSA = 0.78      *E. faecium* = 12.5



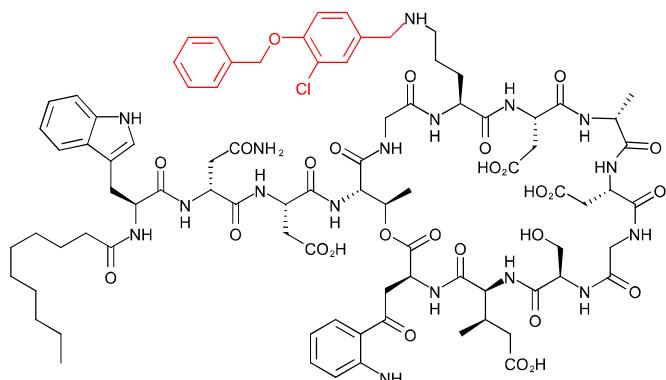
**95. Compound 82, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78      *E. faecalis* = 1.56  
MSSA = 0.78      *E. faecium* = 3.13



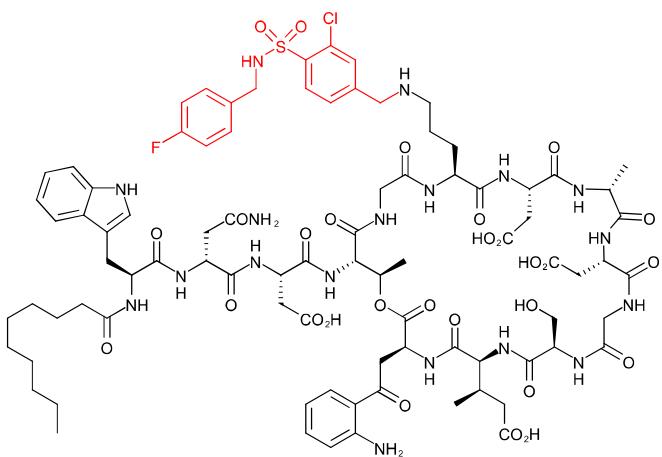
**96. Compound 97, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.39      *E. faecalis* = 0.78  
MSSA = 0.78      *E. faecium* = 1.56



**97. Compound 98, MIC ( $\mu\text{g/mL}$ )**

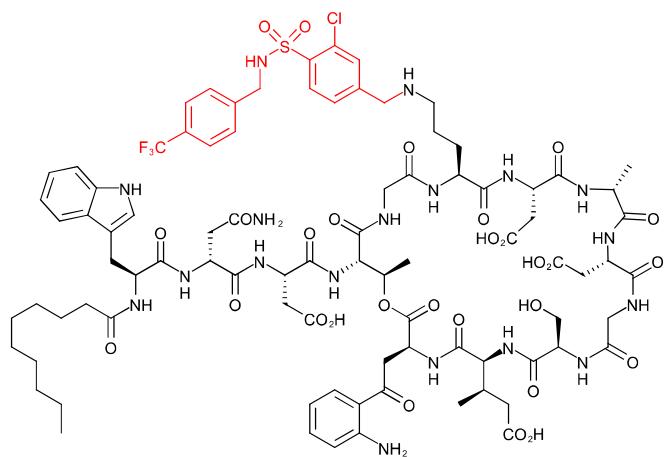
MRSA = 0.78      *E. faecalis* = 0.78  
MSSA = 0.78      *E. faecium* = 0.39



**98. Compound 99, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.39  
MSSA = 0.39

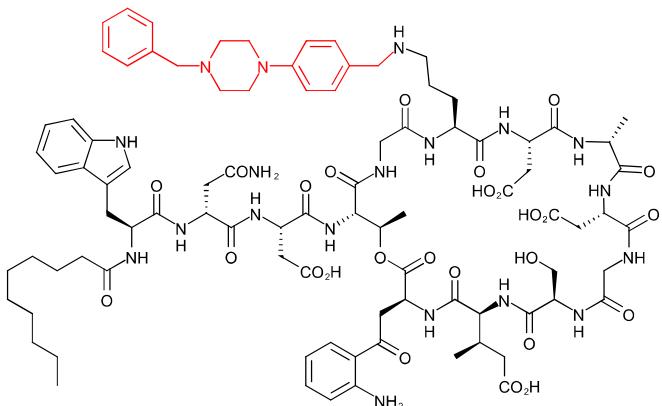
*E. faecalis* = 1.56  
*E. faecium* = 1.56



**99. Compound 100, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.39  
MSSA = 0.78

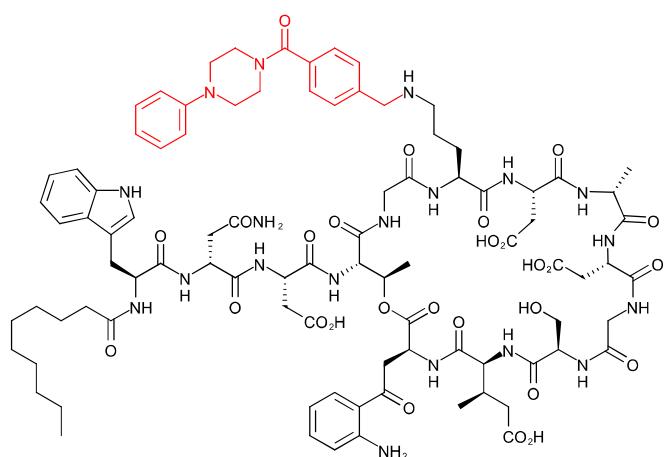
*E. faecalis* = 0.78  
*E. faecium* = 0.39



**100. Compound 101, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.39  
MSSA = 0.78

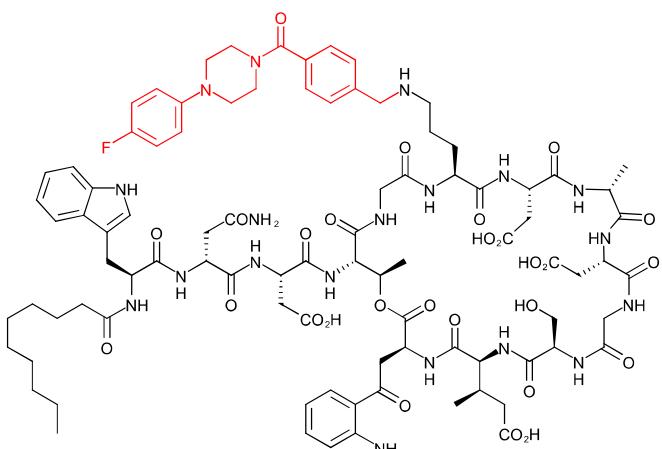
*E. faecalis* = 6.25  
*E. faecium* = 3.13



**101. Compound 102, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

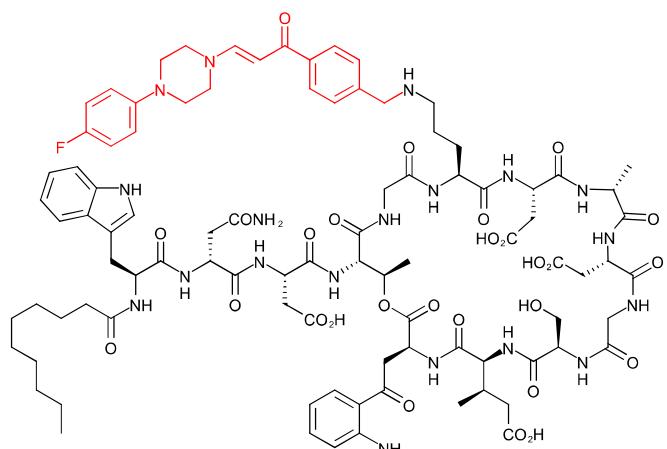
*E. faecalis* = 3.13  
*E. faecium* = 6.25



**102. Compound 103, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

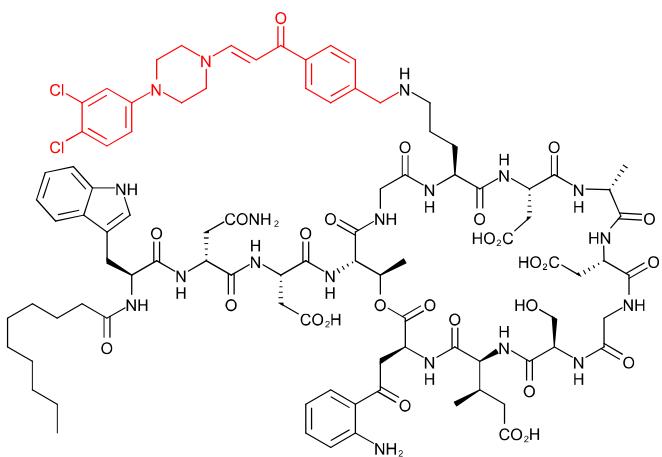
*E. faecalis* = 3.13  
*E. faecium* = 6.25



**103. Compound 104, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.39

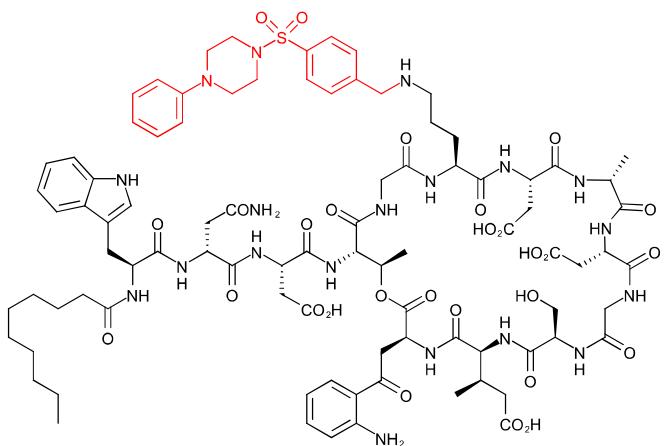
*E. faecalis* = 1.56  
*E. faecium* = 3.13



**104. Compound 105, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.78

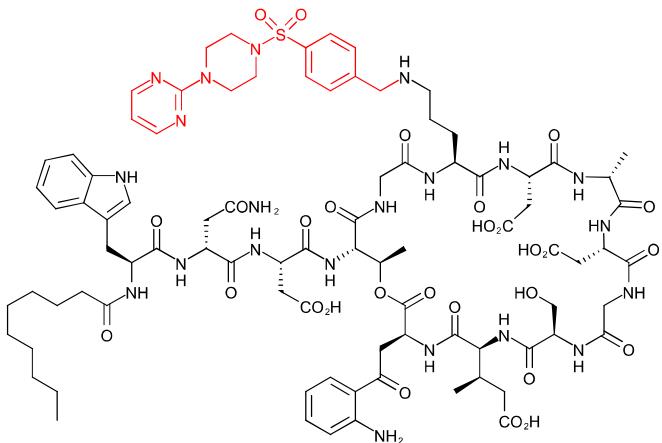
*E. faecalis* = 1.56  
*E. faecium* = 1.56



**105. Compound 106, MIC ( $\mu\text{g/mL}$ )**

MRSA = 0.78  
MSSA = 0.39

*E. faecalis* = 0.78  
*E. faecium* = 1.56



**106. Compound 107, MIC ( $\mu\text{g/mL}$ )**

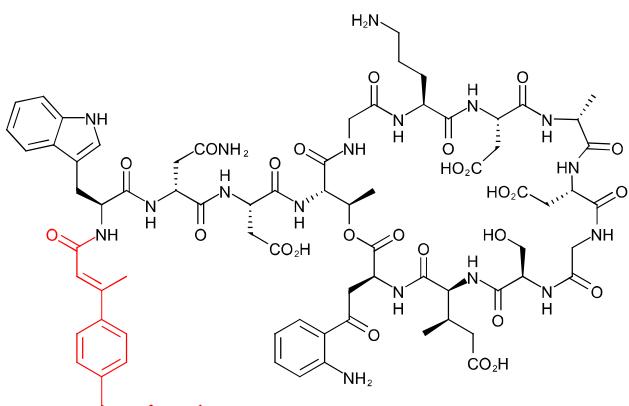
MRSA = 0.39  
MSSA = 0.78

*E. faecalis* = 3.13  
*E. faecium* = 3.13

## Discovery and development of surotomycin for the treatment of *Clostridium difficile*

Knight-Connoni, V., Mascio, C., Chesnel, L., Silverman, J.,

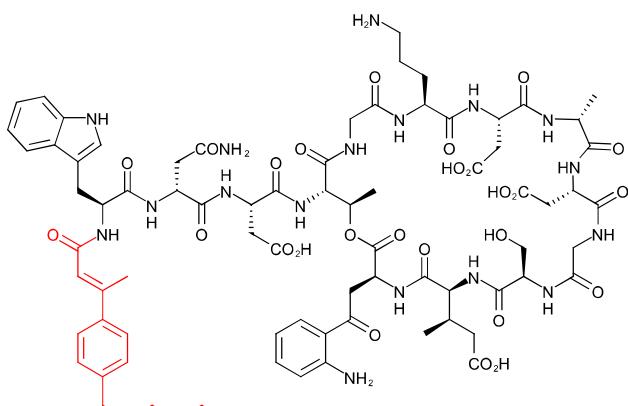
*J. Ind. Microbiol. Biotechnol.*, 2016, 43, 195–204.



107. CB-183,315 (surotomycin), MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 0.5

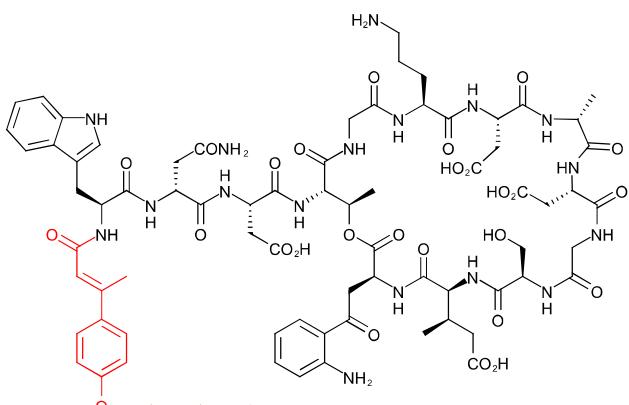
DapR *Enterococcus faecium* = 4



108. CB-183,314, MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 0.5

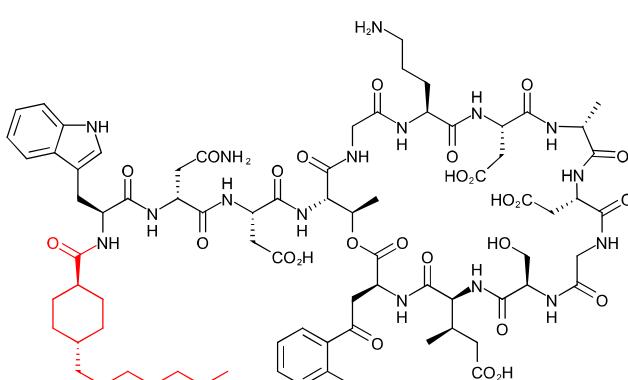
DapR *Enterococcus faecium* = 4



109. CB-183,468, MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 0.5

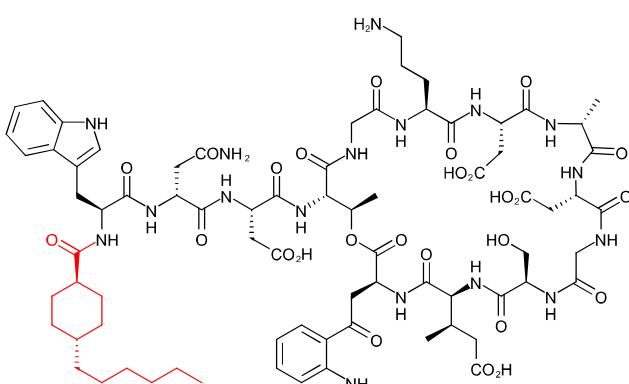
*E. faecium* = 8



110. CB-183,252, MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 1

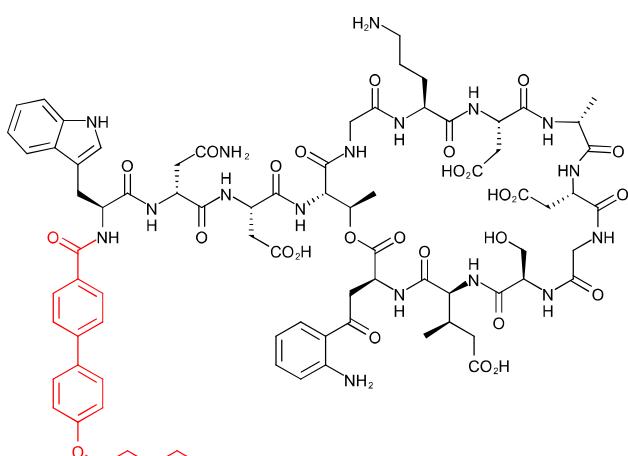
DapR *Enterococcus faecium* = 8



111. CB-183,251, MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 1

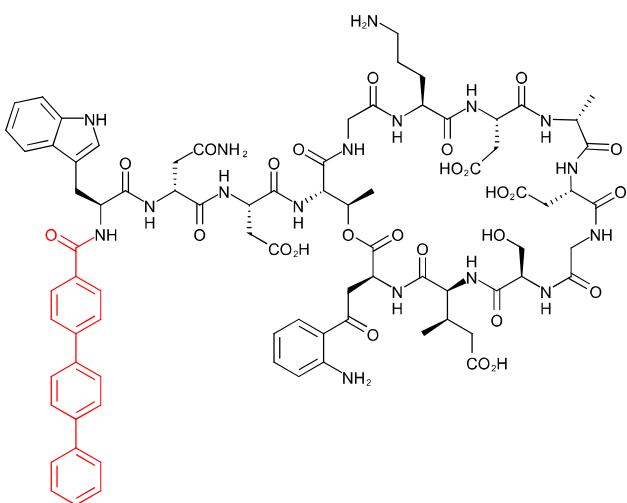
DapR *Enterococcus faecium* = 8



112. CB-183,367, MIC ( $\mu\text{g/mL}$ )

*Clostridium difficile* = 2

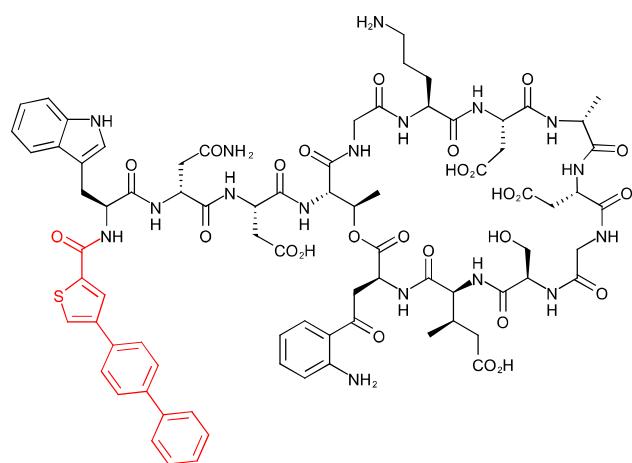
DapR *Enterococcus faecium* = 2



**113. CB-183,511, MIC ( $\mu\text{g/mL}$ )**

*Clostridium difficile* = 2

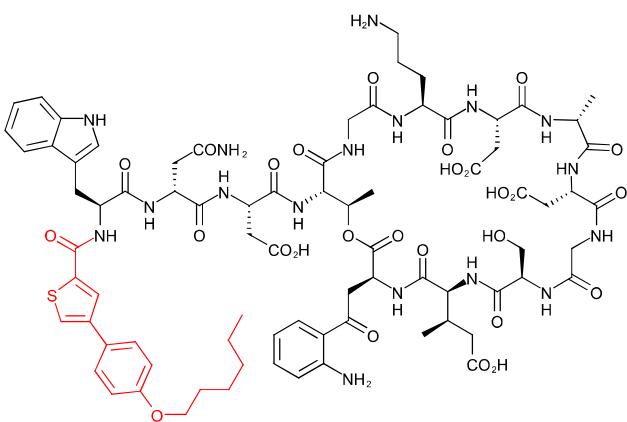
DapR *Enterococcus faecium* = 4



**114. CB-183,368, MIC ( $\mu\text{g/mL}$ )**

*Clostridium difficile* = 2

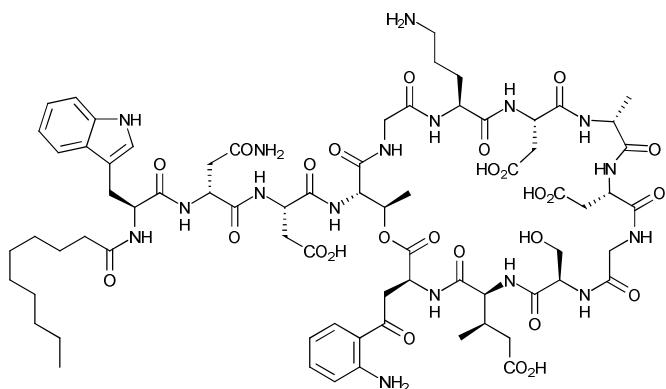
DapR *Enterococcus faecium* = 4



**115. CB-183,277, MIC ( $\mu\text{g/mL}$ )**

*Clostridium difficile* = 4

DapR *Enterococcus faecium* = 1



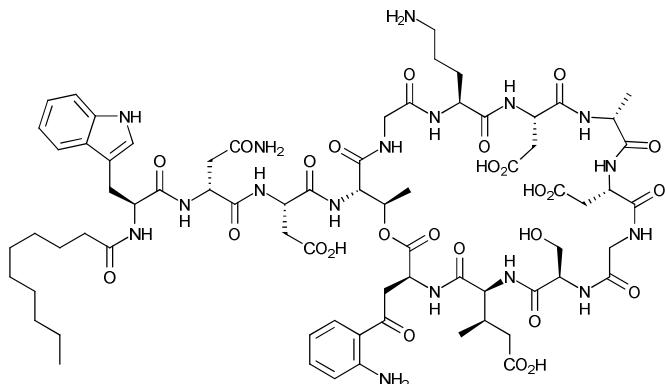
**116. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*Clostridium difficile* = 2

DapR *Enterococcus faecium* > 32

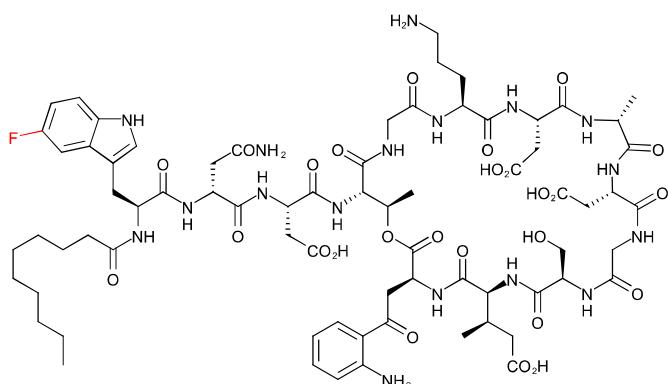
**Reduced pulmonary surfactant interaction of daptomycin analogs via tryptophan replacement with alternative amino acids**

He, Y., Li, J., Yin, N., Herradura, P. S., Martel, L., Zhang, Y., Pearson, A. L., Kulkarni, V., Mascio, C., Howland, K., Silverman, J. A., Keith, D. D., Metcalf, C. A.,  
*Bioorg. Med. Chem. Lett.*, **2012**, 22, 19, 6248-6251.



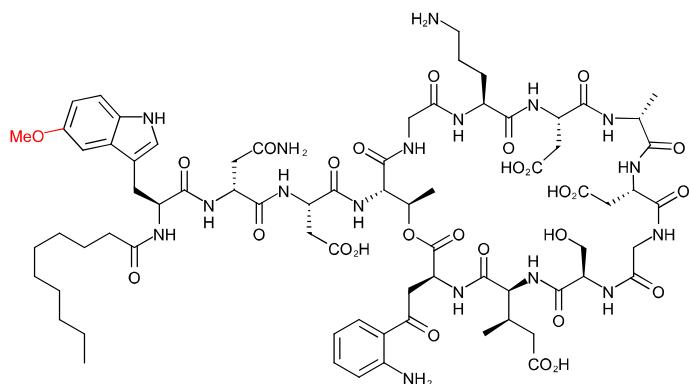
**117. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*S. Aureus* ATCC 29213 = 1



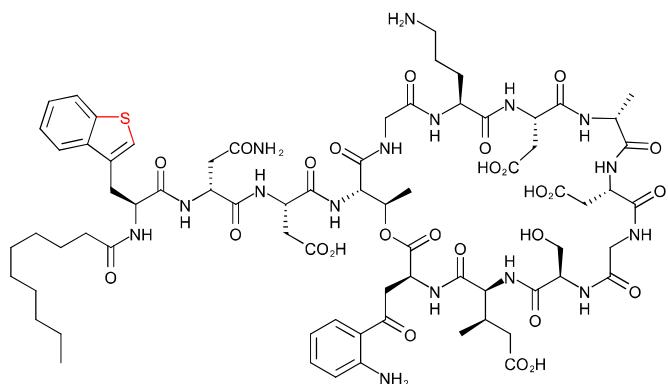
**118. Compound 4a, MIC ( $\mu\text{g/mL}$ )**

*S. Aureus* ATCC 29213 = 0.25



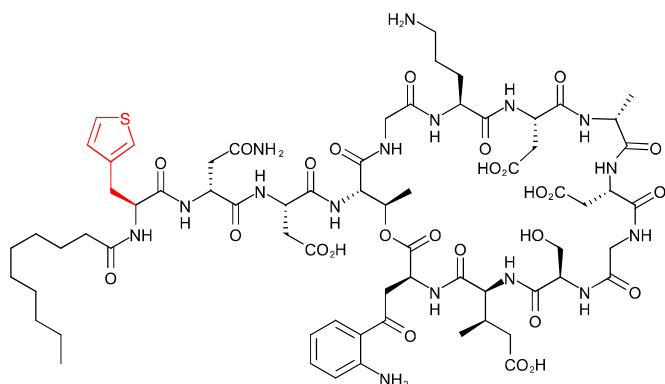
**119. Compound 4b, MIC ( $\mu\text{g/mL}$ )**

*S. Aureus* ATCC 29213 = 4



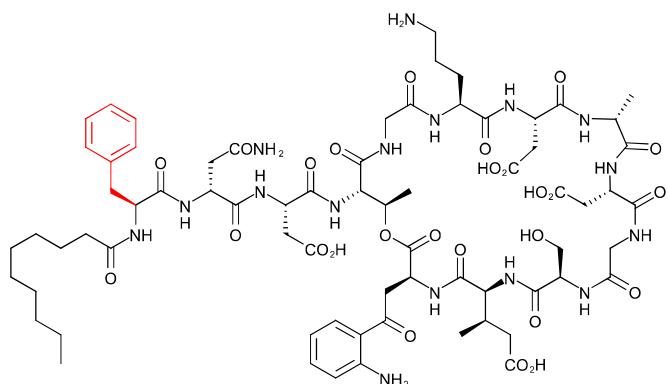
**120. Compound 4c, MIC ( $\mu\text{g/mL}$ )**

*S. Aureus* ATCC 29213 = 2



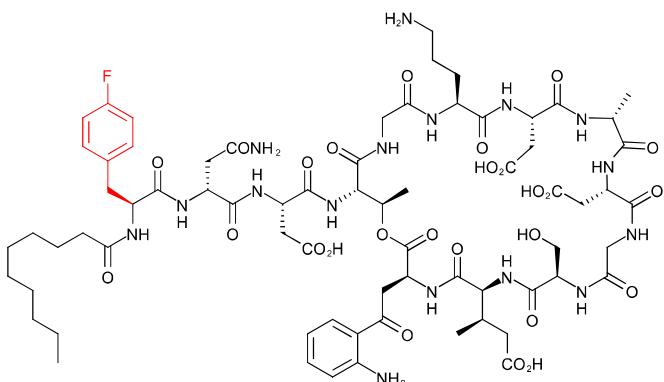
**121. Compound 4d, MIC ( $\mu\text{g/mL}$ )**

*S. Aureus* ATCC 29213 = 4

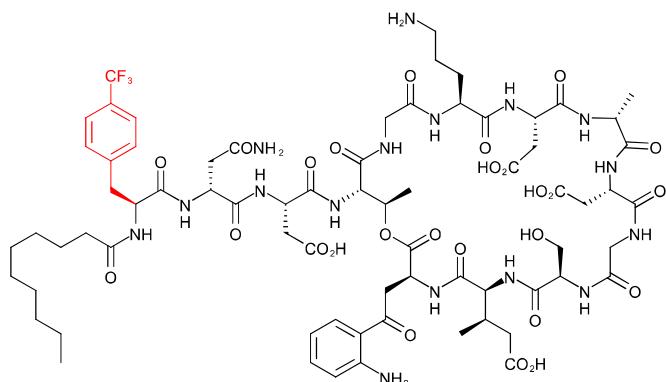


**122. Compound 4e, MIC ( $\mu\text{g/mL}$ )**

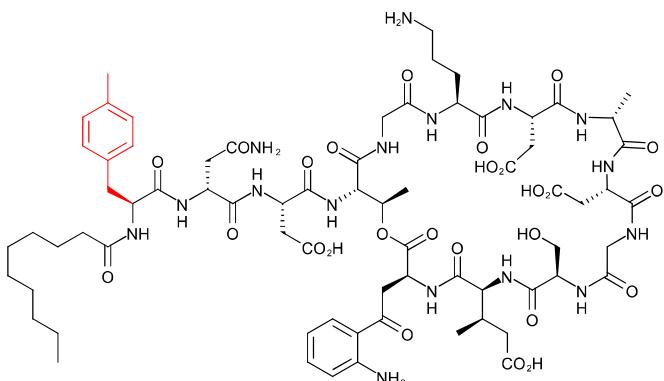
*S. Aureus* ATCC 29213 = 2



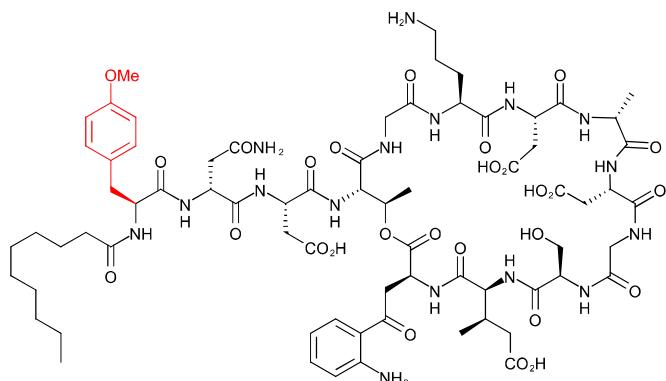
**123. Compound 4f, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



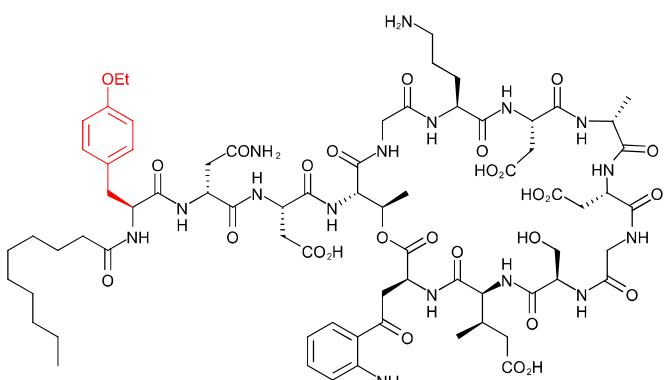
**124. Compound 4g, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



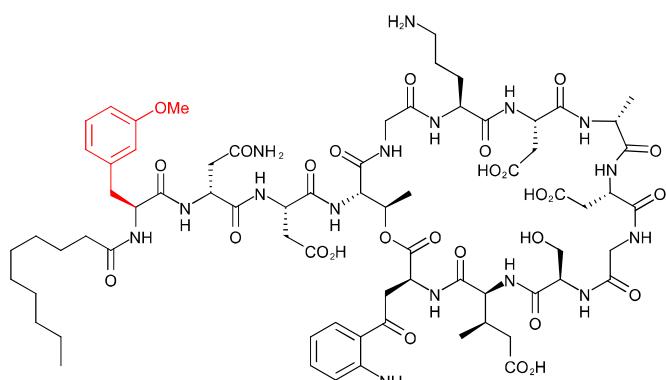
**125. Compound 4h, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 1



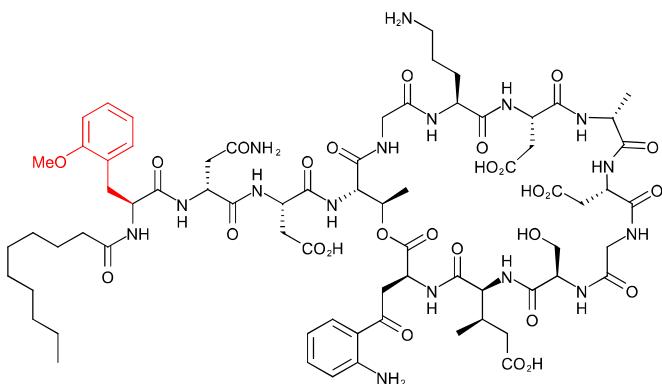
**126. Compound 4i, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



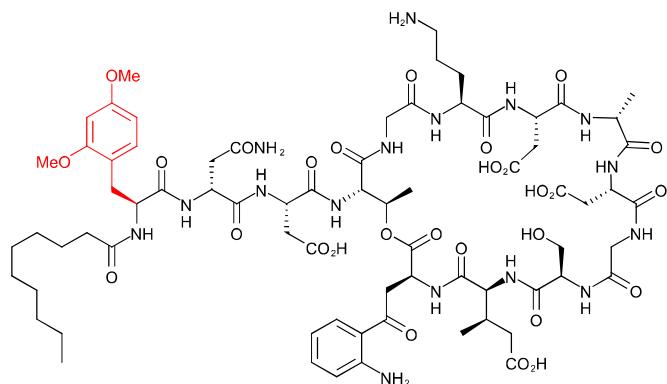
**127. Compound 4j, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 4



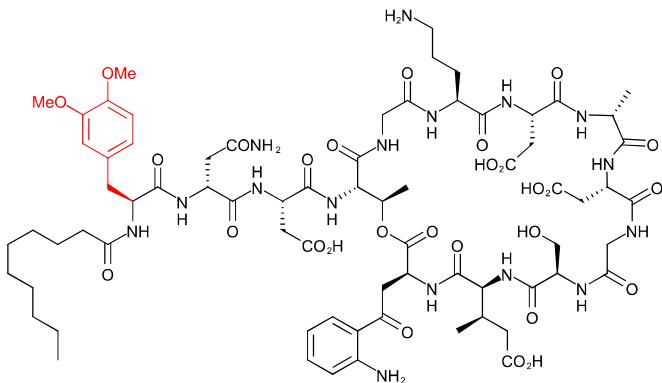
**128. Compound 4k, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



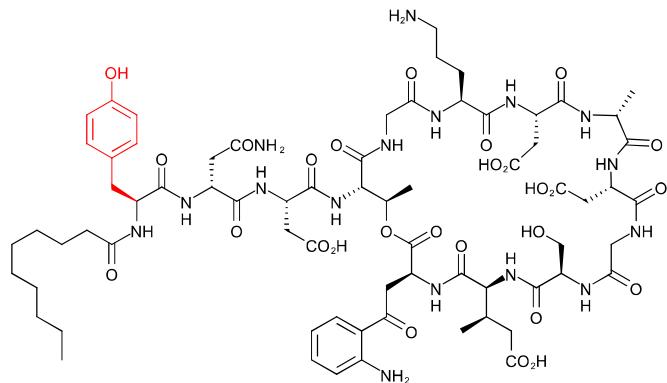
**129. Compound 4l, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



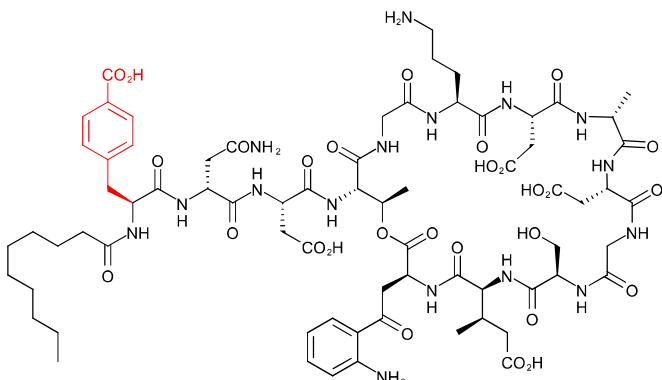
**130. Compound 4m, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 8



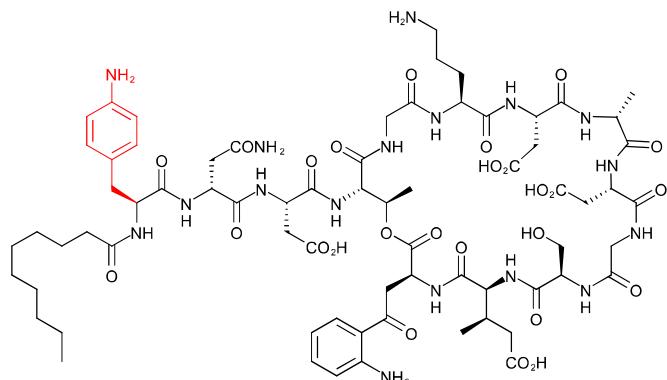
**131. Compound 4n, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 16



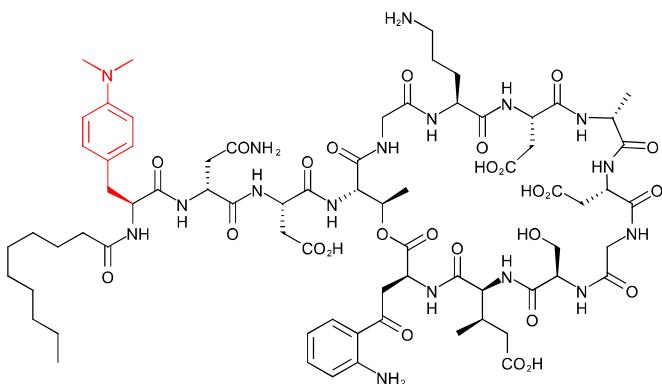
**132. Compound 4o, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 > 32



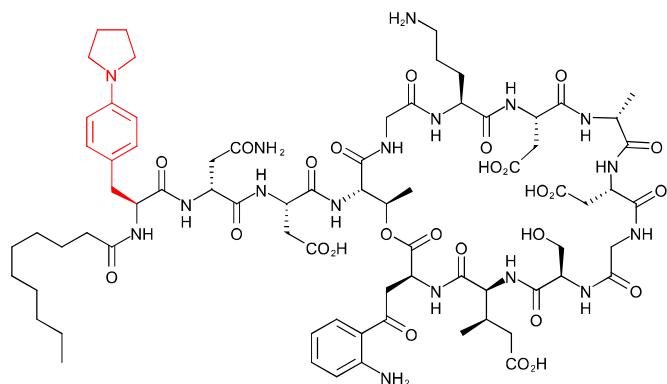
**133. Compound 4p, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 > 32



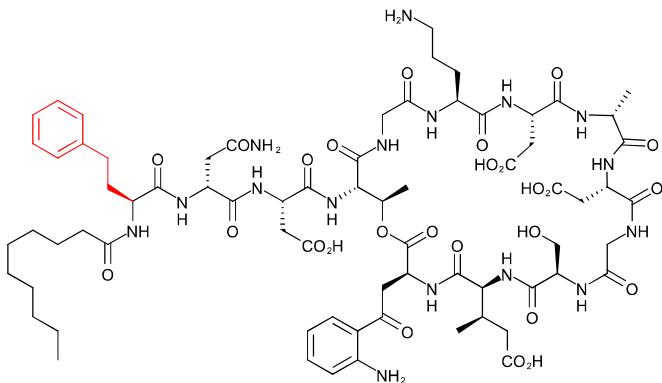
**134. Compound 4q, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 16



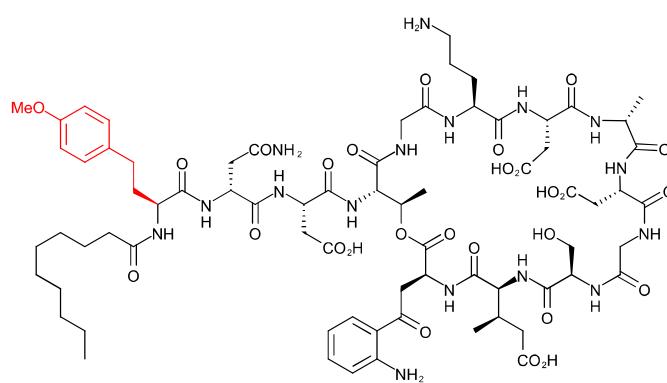
**135. Compound 4r, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



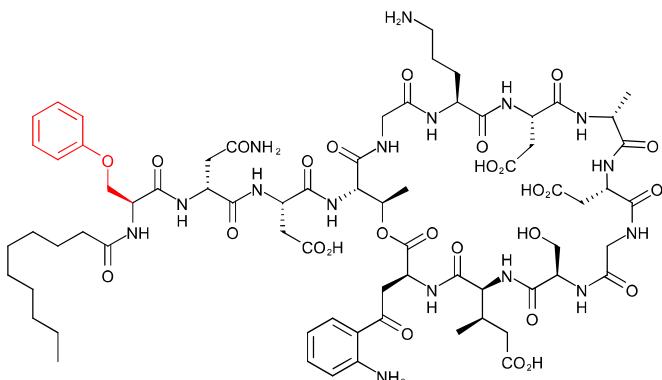
**136. Compound 4s, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 1



**137. Compound 4t, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 1



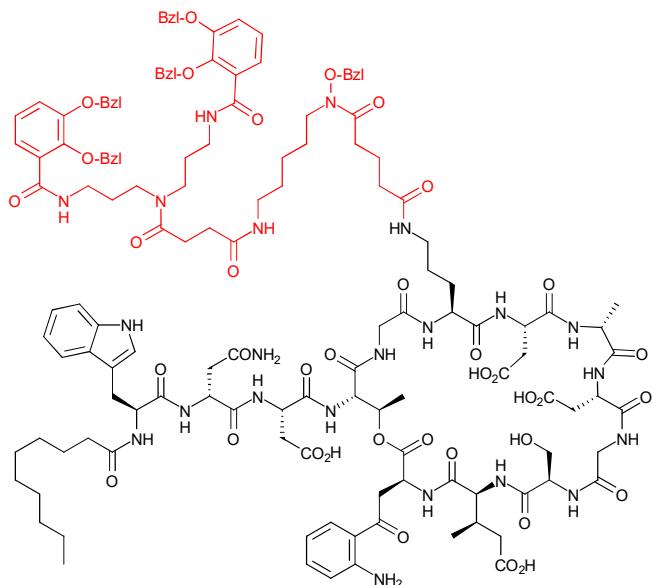
**138. Compound 4u, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 2



**139. Compound 4v, MIC ( $\mu\text{g/mL}$ )**  
*S. Aureus* ATCC 29213 = 4

**Targeted Antibiotic Delivery: Selective Siderophore Conjugation with Daptomycin Confers Potent Activity against Multidrug Resistant *Acinetobacter baumannii* Both in Vitro and in Vivo**

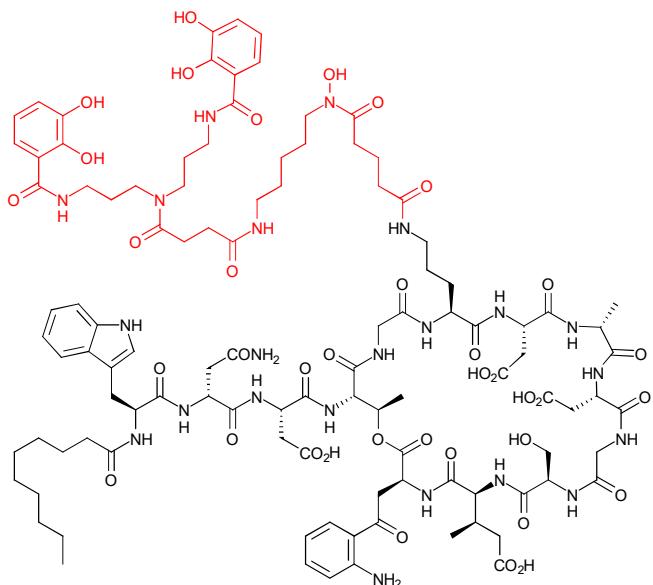
Ghosh, M., Miller, P. A., Möllmann, U., Claypool, W. D., Schroeder, V. A., Wolter, W. R., Suckow, M., Yu, H., Li, S., Huang, W., Zajicek, J., Miller, M. J.  
*J. Med. Chem.*, **2017**, 60, 4577-4583.



**140. Sideromycin-(Bzl)<sub>5</sub>, MIC (μM)**

*A. baumanii*:

ATCC 17961 > 50	ATCC BAA 1710 > 50
ATCC 1793 > 50	ATCC BAA 1797 > 50
ATCC 1800 > 50	ARC 3484 > 50
ARC 3486 > 50	ARC 5079 > 50
ARC 5081 > 50	ATCC 19606 > 50



**141. Sideromycin, MIC ( $\mu\text{M}$ )**

*A. baumanii* ATCC 17961 = 0.4

*A. baumanii* ARC 3486 = 0.4

*P. aeruginosa* PAO1 > 100

*B. multivorans* AU0100 > 100

*S. aureus* SG511 = 6

*S. aureus* ATCC 11632 = 12.5

*E. coli* DCO > 100

*A. baumanii*:

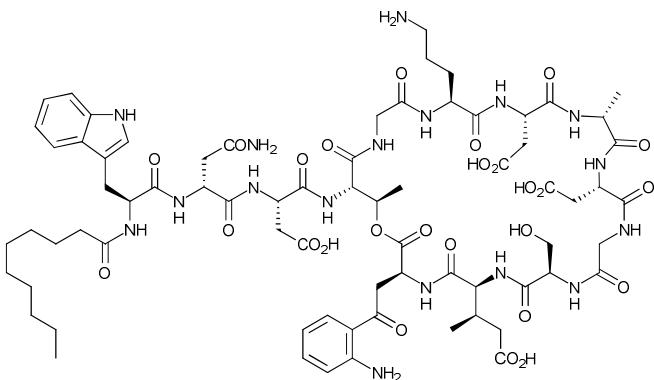
ATCC 17961 = 0.4	ATCC BAA 1710 = 0.8
------------------	---------------------

ATCC 1793 = 0.8	ATCC BAA 1797 = 0.8
-----------------	---------------------

ATCC 1800 = 0.8	ARC 3484 = 0.4
-----------------	----------------

ARC 3486 = 0.4	ARC 5079 = 0.8
----------------	----------------

ARC 5081 = 0.4	ATCC 19606 = 0.8
----------------	------------------



**142. Daptomycin, MIC ( $\mu\text{M}$ )**

*A. baumanii* ATCC 17961 > 100

*A. baumanii* ARC 3486 > 100

*P. aeruginosa* PAO1 > 100

*B. multivorans* AU0100 > 100

*S. aureus* SG511 = 0.05

*S. aureus* ATCC 11632 = 0.4

*E. coli* DCO > 100

*A. baumanii*:

ATCC 17961 > 100	ATCC BAA 1710 > 100
------------------	---------------------

ATCC 1793 > 100	ATCC BAA 1797 > 100
-----------------	---------------------

ATCC 1800 > 100	ARC 3484 > 100
-----------------	----------------

ARC 3486 > 100	ARC 5079 > 100
----------------	----------------

ARC 5081 > 100	ATCC 19606 = NT
----------------	-----------------

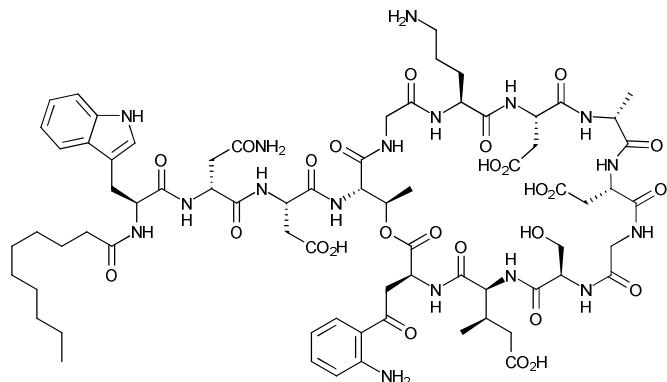
## Synthesis and derivatization of daptomycin: a chemoenzymatic route to acidic lipopeptide antibiotics

Grünewald, J., Sieber, S. A., Mahlert, C., Linne, U., Marahiel, M. A.,

*J. Am. Chem. Soc.*, 2004, 126, 51, 17025-17031.

### Note

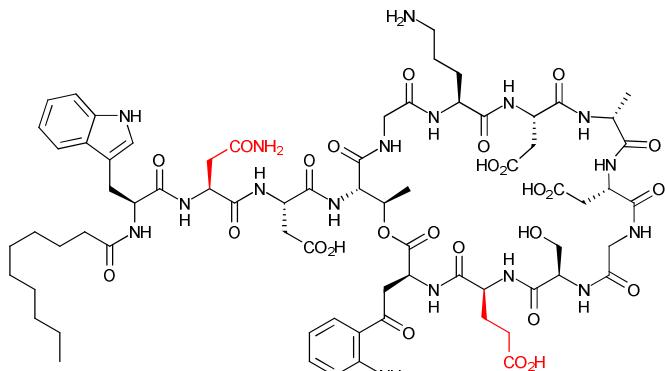
All analogues were synthesized with L-Asn at position 2, which was mis-assigned at the time of publication.



**143. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 3

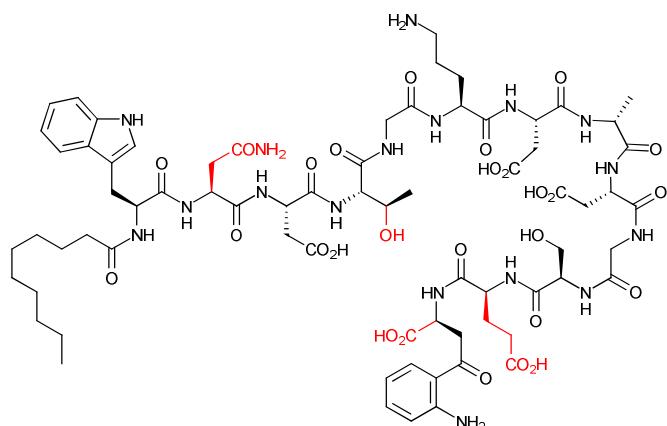
*B. subtilis* PY79, 23.6 mg/L  $\text{Ca}^{2+}$  = 20



**144. Dap, MIC ( $\mu\text{g/mL}$ )**

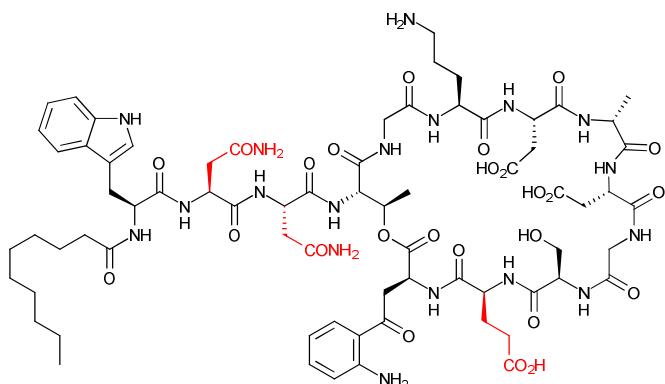
*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 20

*B. subtilis* PY79, 23.6 mg/L  $\text{Ca}^{2+}$  > 240



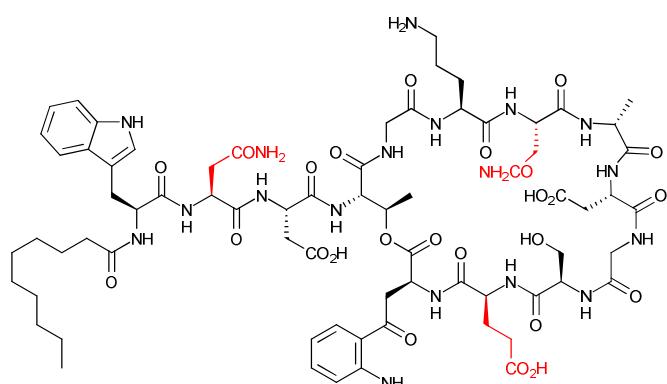
**145. Dap-Hyd, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  > 960



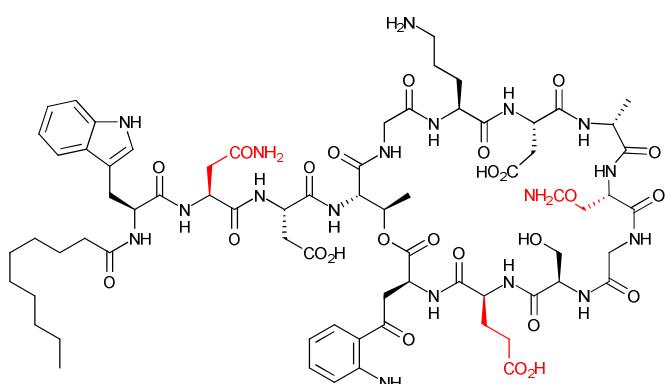
**146. Dap-N3, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 80



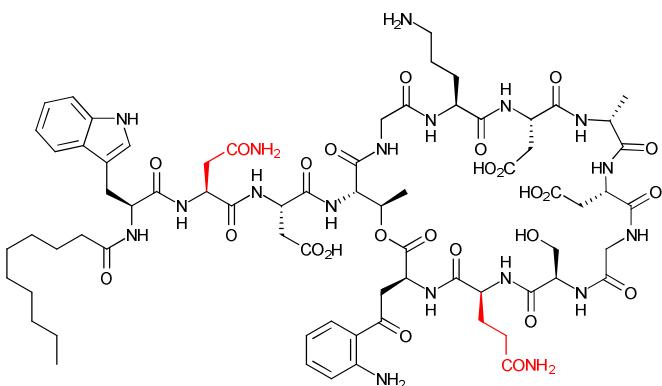
**147. Dap-N7, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  > 960



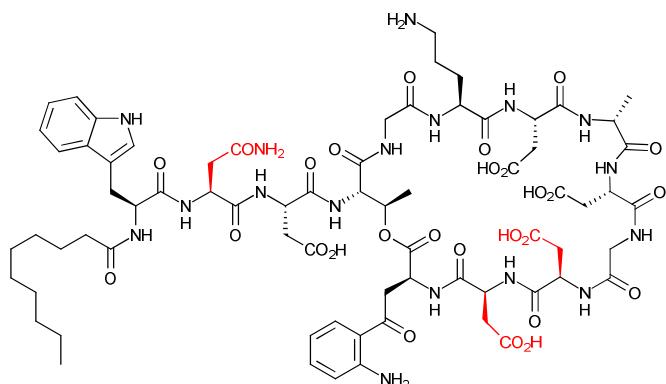
**148. Dap-N9, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  > 960



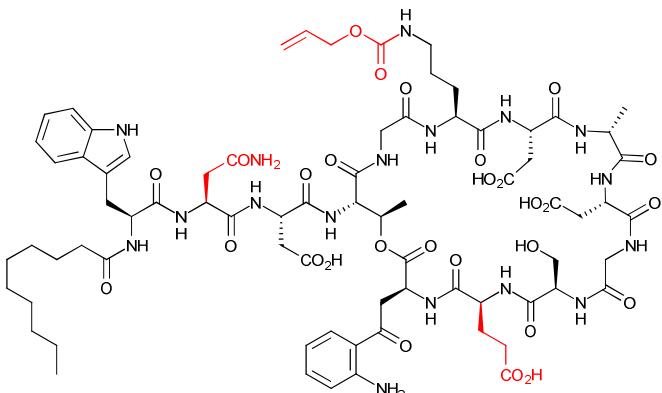
**149. Dap-Q12, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> = 30



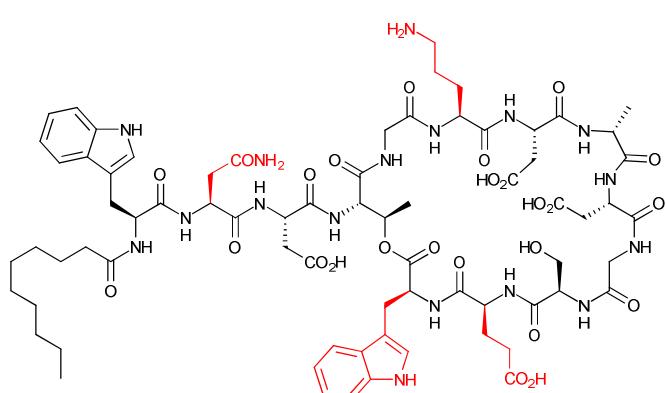
**150. Dap-D11, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> > 320



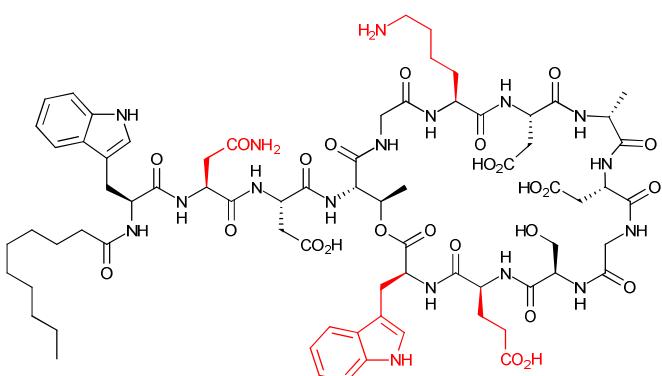
**151. Dap-Aloc, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> = 80



**152. Dap-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> = 100



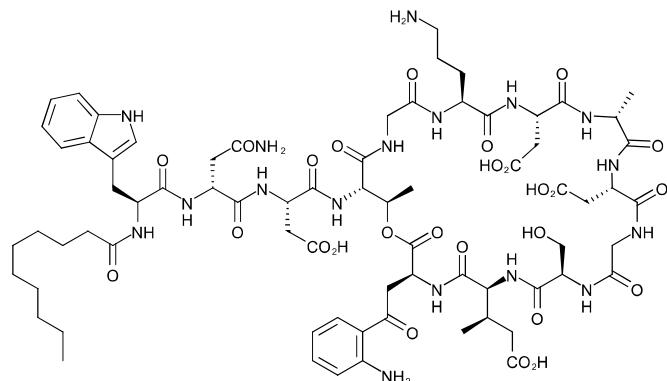
**153. Dap-W13K6, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> = 100

# Chemoenzymatic Design of Acidic Lipopeptide Hybrids: New Insights into the Structure-Activity Relationship of Daptomycin and A54145

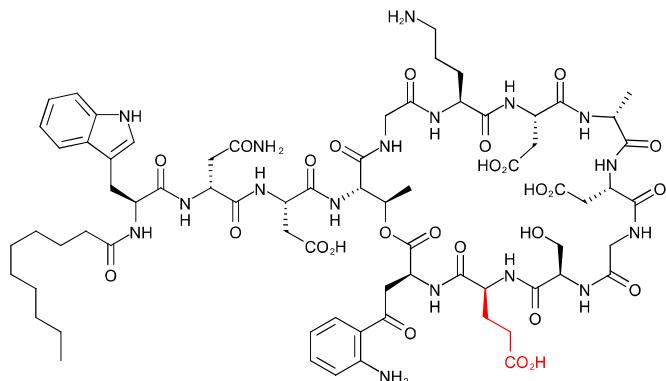
Kopp, F., Grünwald, J., Mahlert, C., Marahiel, M. A.,  
*Biochem.*, 2006, 45, 10474-10481.

Note: compounds **157-158** and **161-164** are based on A54145, not daptomycin.



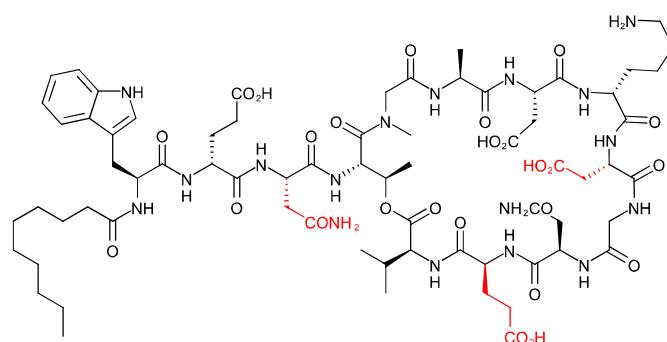
**154. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 2



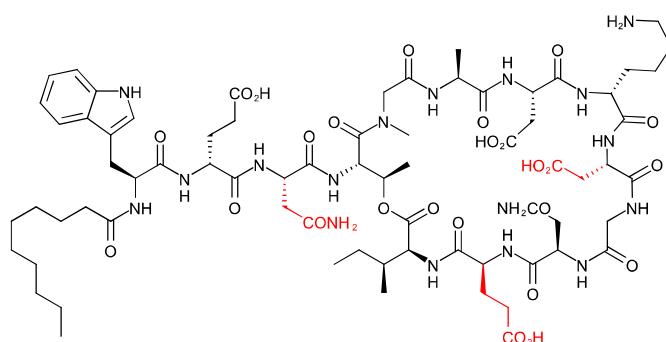
**155. Dap, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 11



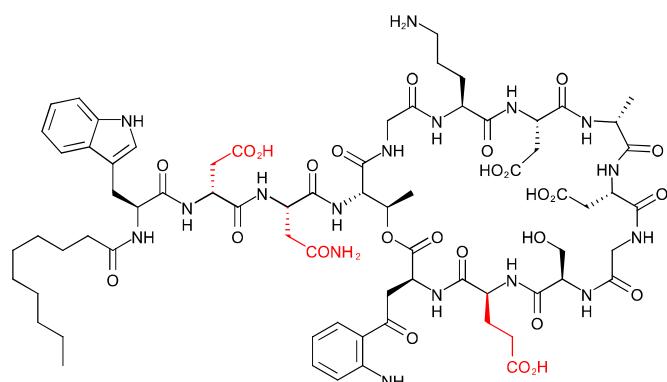
**156. A54145(Val), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 200



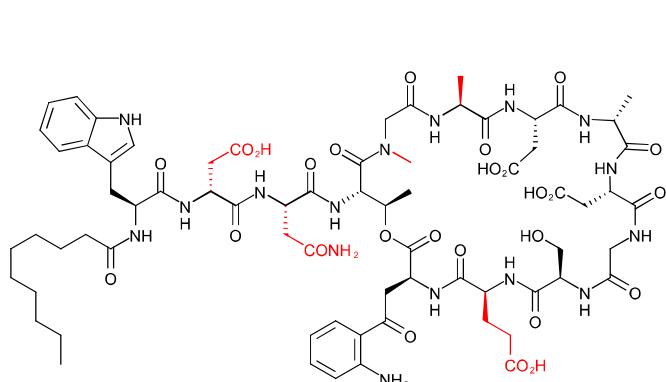
**157. A54145(Ile), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 25



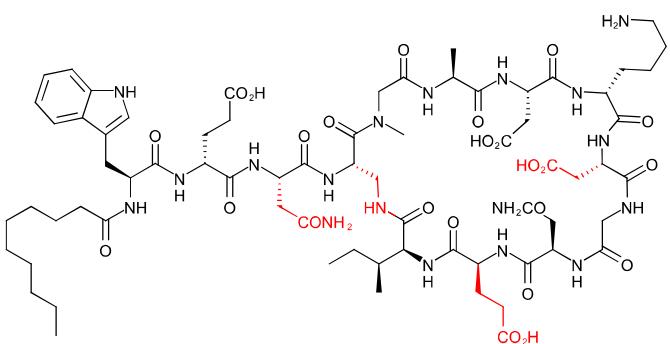
**158. Dap(A541-3), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 20



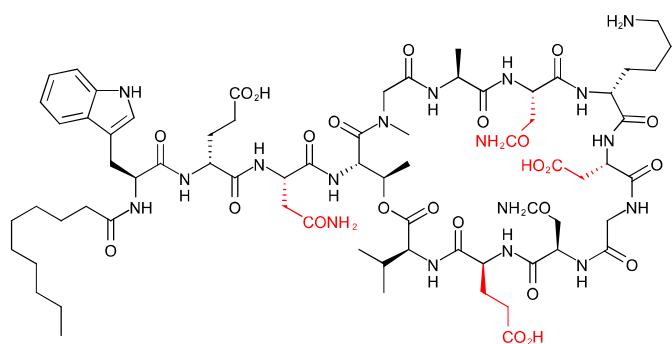
**159. Dap(A541-6), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L  $\text{Ca}^{2+}$  = 20



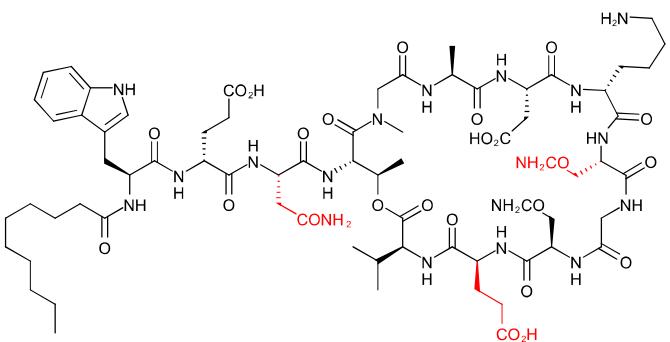
**160. A54145(DAP), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> = 25



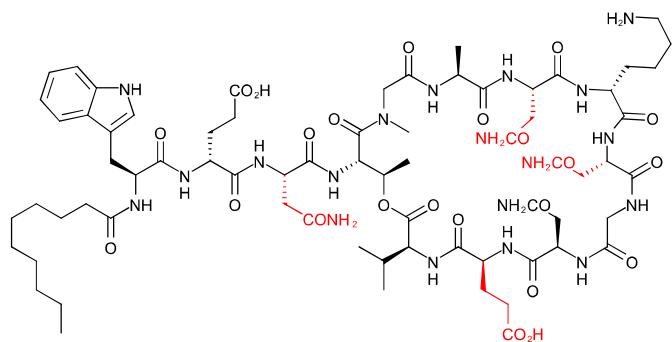
**161. A54145(NXDG), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> > 900



**162. A54145(DXNG), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> > 900



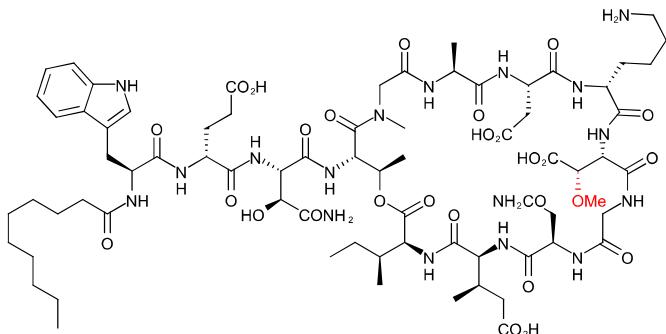
**163. A54145(NXNG), MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* PY79, 73.6 mg/L Ca<sup>2+</sup> > 900

**Total Synthesis and Structural Establishment/Revision of Antibiotics A54145**

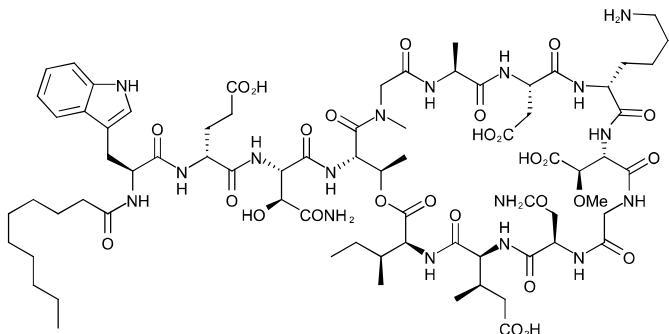
Chen, D., Chow, H. Y., Po, K. H. L., Ma, W., Leung, E. L. Y., Sun, Z., Liu, M., Chen, S., Li X.,  
*Org. Lett.*, **2019**, 21, 5639-5644.

Note: structural isomer of the iso-decanoyl moiety in **169**, **171** and **172** is not specified.



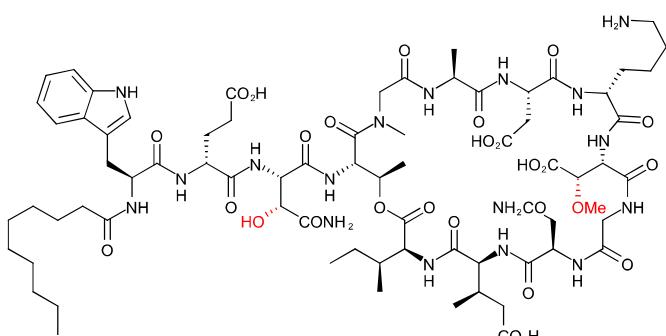
**164. Compound 24a, MIC ( $\mu\text{g/mL}$ )**

MRSA 86  $\geq$  32      MRSA 88  $\geq$  32  
 SA ATCC29213  $\geq$  32



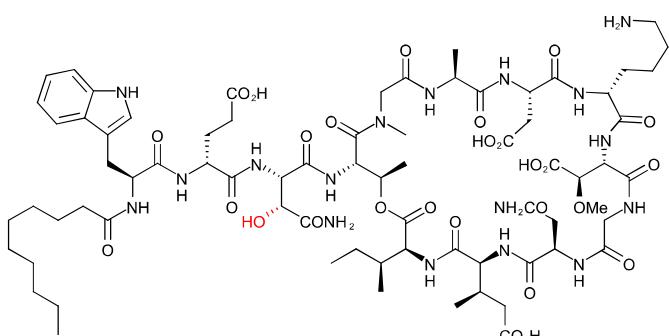
**165. Compound 24b, MIC ( $\mu\text{g/mL}$ )**

MRSA 86 = 1      MRSA 88 = 0.5  
 SA ATCC29213  $\geq$  32



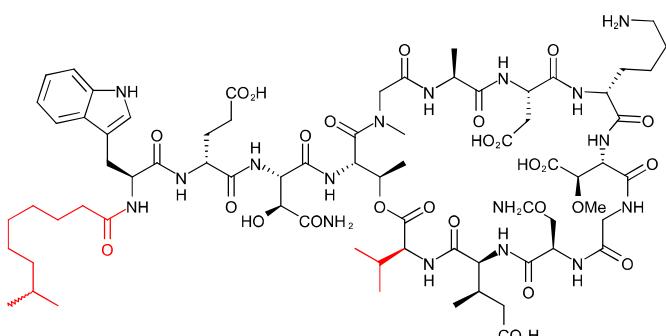
**166. Compound 24c, MIC ( $\mu\text{g/mL}$ )**

MRSA 86  $\geq$  32      MRSA 88  $\geq$  32  
 SA ATCC29213  $\geq$  32



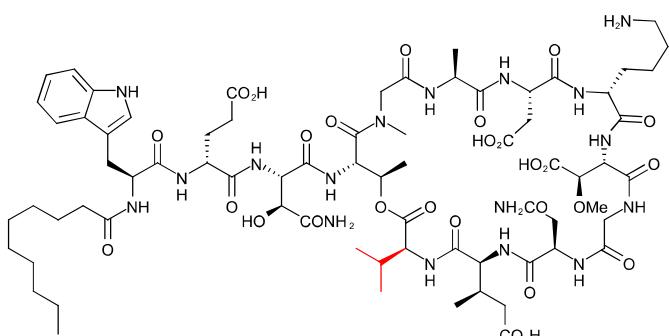
**167. Compound 24d, MIC ( $\mu\text{g/mL}$ )**

MRSA 86  $\geq$  32      MRSA 88  $\geq$  32  
 SA ATCC29213  $\geq$  32



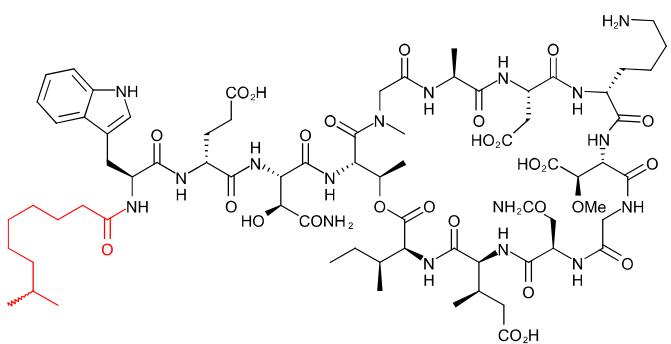
**168. Compound 25a, MIC ( $\mu\text{g/mL}$ )**

MRSA 86 = 16      MRSA 88 = 8  
 SA ATCC29213 = 8



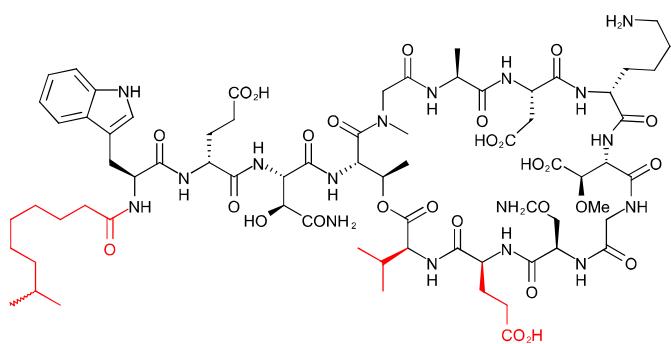
**169. Compound 25b, MIC ( $\mu\text{g/mL}$ )**

MRSA 86 = 8      MRSA 88 = 8  
 SA ATCC29213 = 8



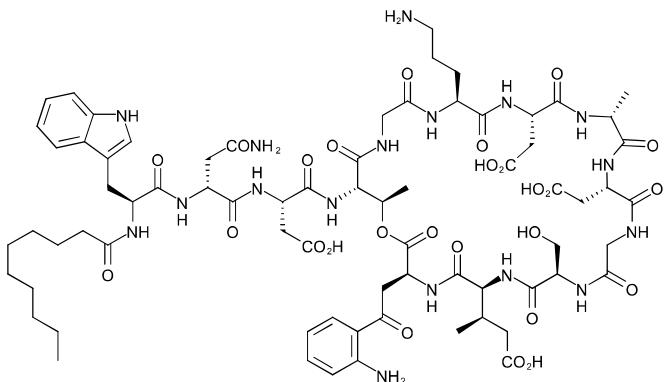
**170. Compound 25c, MIC ( $\mu\text{g/mL}$ )**

MRSA 86 = 2      MRSA 88 = 2  
SA ATCC29213 = 2



**171. Compound 25d, MIC ( $\mu\text{g/mL}$ )**

MRSA 86  $\geq$  32      MRSA 88 = 16  
SA ATCC29213 = 16

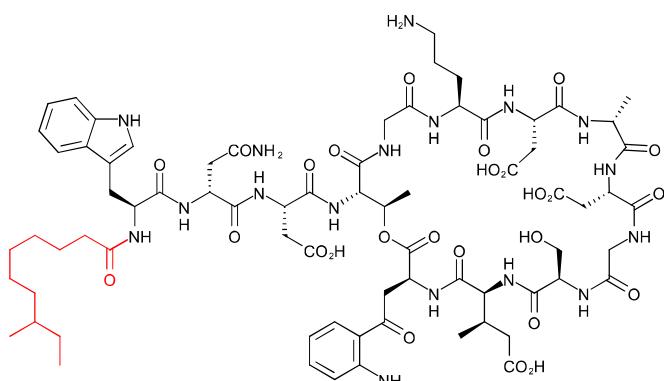


**172. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

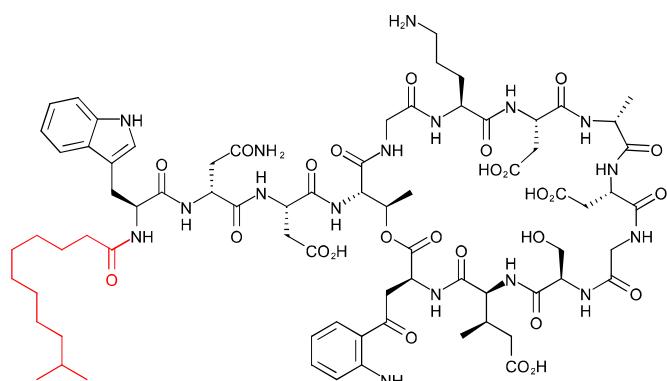
MRSA 86 = 0.5      MRSA 88 = 0.5  
SA ATCC29213 = 0.5

**A glutamic acid 3-methyltransferase encoded by an accessory gene locus important for daptomycin biosynthesis in *Streptomyces roseosporus***

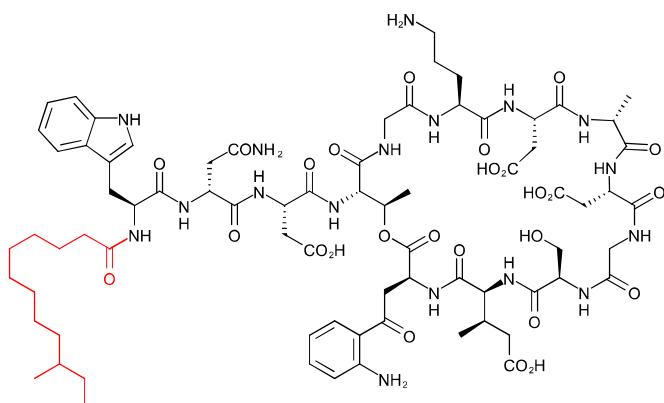
Nguyen, K. T., Kau, D., Gu, J. Q., Brian, P., Wrigley, S.K., Baltz, R. H., Miao, V.,  
*Mol. Microbiol.*, **2006**, 61, 5, 1294-307.



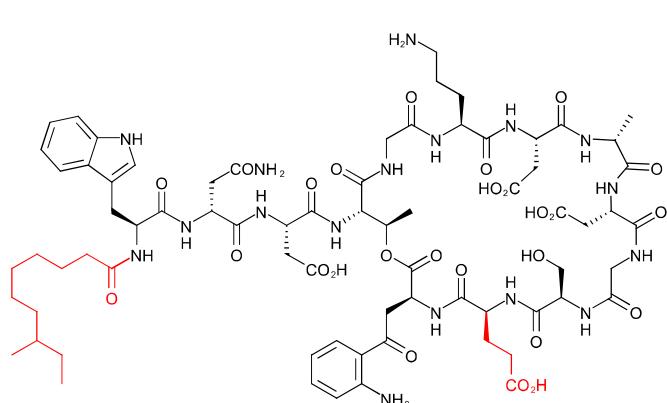
**173. A21978C<sub>1</sub>, MIC (μg/mL)**  
*Staphylococcus Aureus* = 0.5



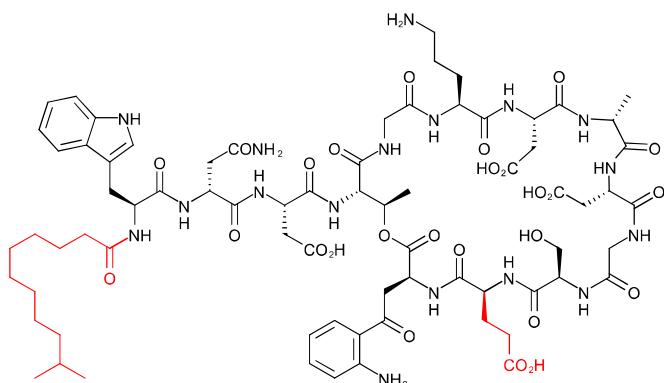
**174. A21978C<sub>2</sub>, MIC (μg/mL)**  
*Staphylococcus Aureus* = 0.25



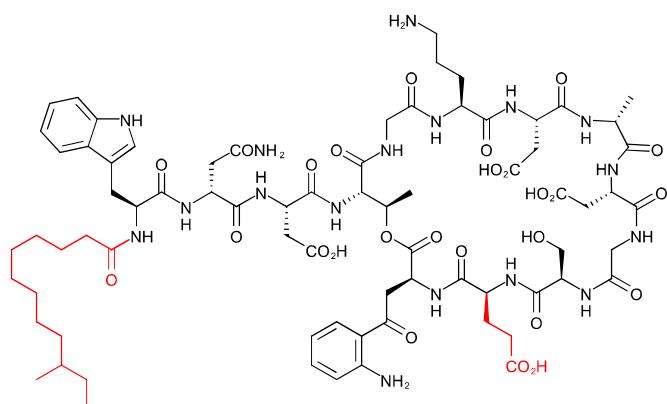
**175. A21978C<sub>3</sub>, MIC (μg/mL)**  
*Staphylococcus Aureus* = 0.5



**176. A21978C<sub>1</sub>(Glu12), MIC (μg/mL)**  
*Staphylococcus Aureus* = 4.0



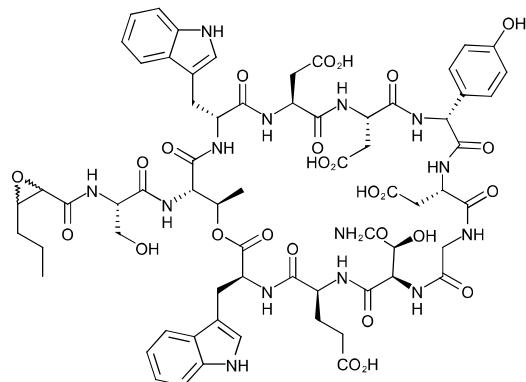
**177. A21978C<sub>2</sub>(Glu12), MIC (μg/mL)**  
*Staphylococcus Aureus* = 2.0



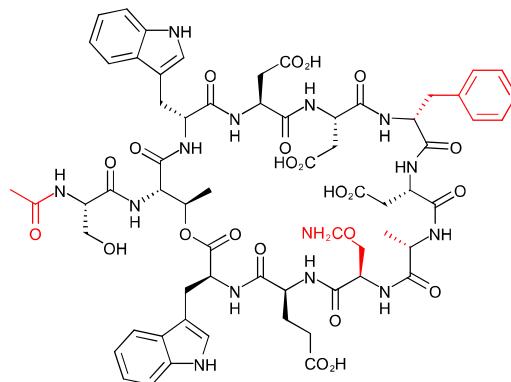
**178. A21978C<sub>3</sub>(Glu12), MIC (μg/mL)**  
*Staphylococcus Aureus* = 2.0

# Chemo- and Regioselective Peptide Cyclization Triggered by the N-Terminal Fatty Acid Chain Length: The Recombinant Cyclase of the Calcium-Dependent Antibiotic from *Streptomyces coelicolor*

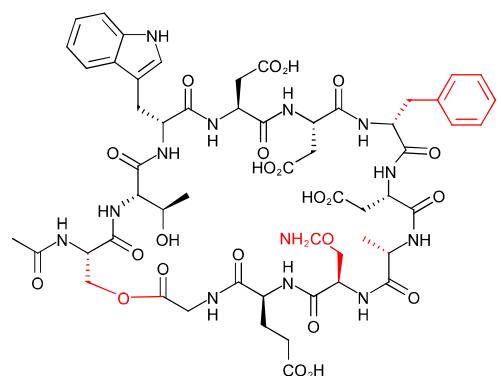
Grünewald, J., Stephan A. Sieber, S. A., Marahiel, M. A.,  
*Biochem.*, 2004, 43, 2915-2925.



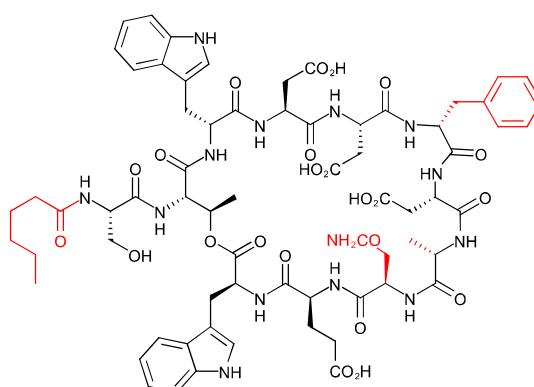
**179. CDA3b**  
Native structure



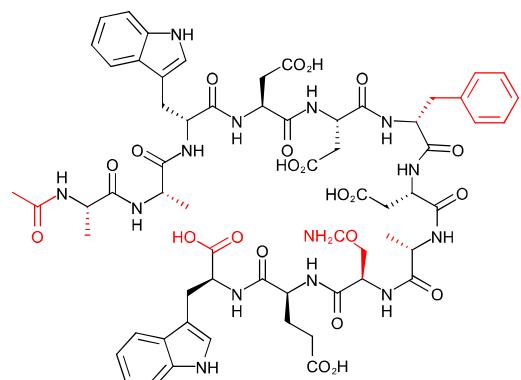
**180. Compound 1**  
10-mer ring (major product)



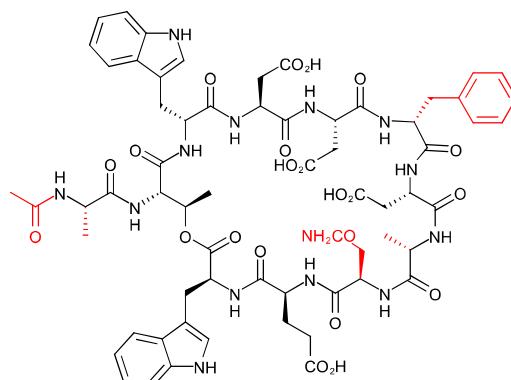
**181. Compound 1\***  
11-mer ring (minor product)



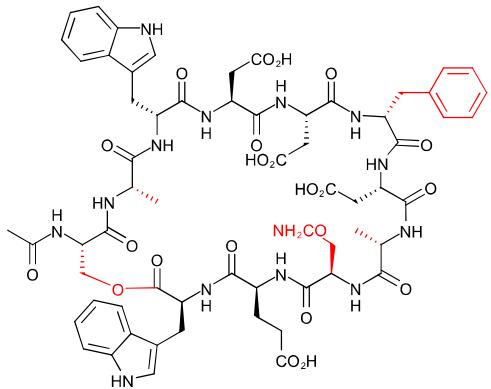
**182. Compound 2**  
10-mer ring (forms exclusively with hexanoic tail)



**183. Compound 3**  
No cyclization (*L*-Ala1  
and *L*-Ala2 substitutions)

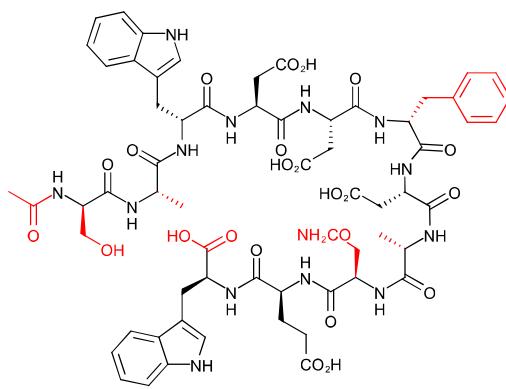


**184. Compound 4**  
10-mer ring (*L*-Ala1  
substitution)



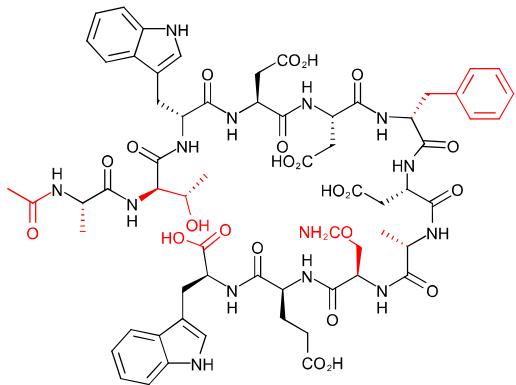
**185. Compound 5**

11-mer ring (*L*-Ala2 substitution,  
significant hydrolysis observed)



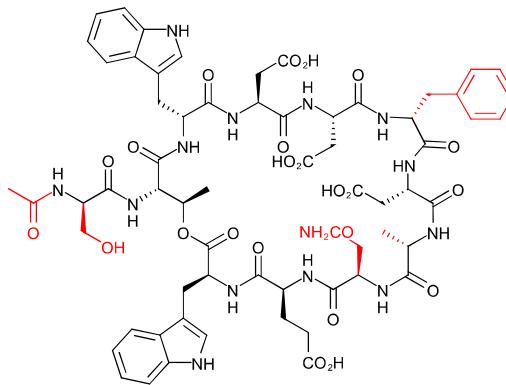
**186. Compound 6**

Hydrolysis product (*D*-Ser1  
and *L*-Ala2 substitutions)



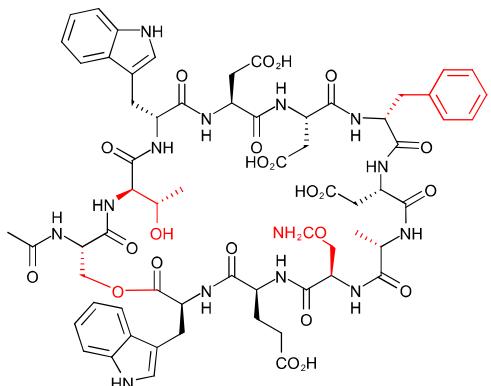
**187. Compound 7**

Hydrolysis product (*L*-Ala1  
and *D*-Thr2 substitutions)



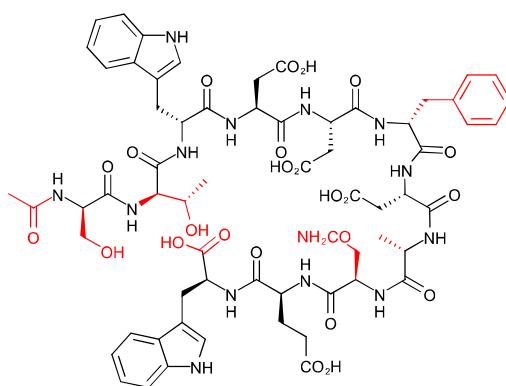
**188. Compound 8**

10-mer ring (*D*-Ser1  
substitution)



**189. Compound 9**

11-mer ring (*D*-Thr2 substitution,  
significant hydrolysis observed)



**190. Compound 10**

Hydrolysis product (*D*-Ser1  
and *D*-Ile2 substitutions)

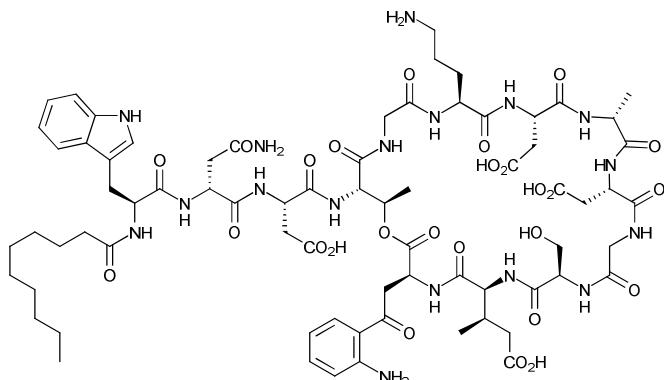
# Combinatorial biosynthesis of cyclic lipopeptide antibiotics: a model for synthetic biology to accelerate the evolution of secondary metabolite biosynthetic pathways

Baltz, R. H.,

ACS Synth. Biol., 2014, 3, 10, 738-758.

## Notes

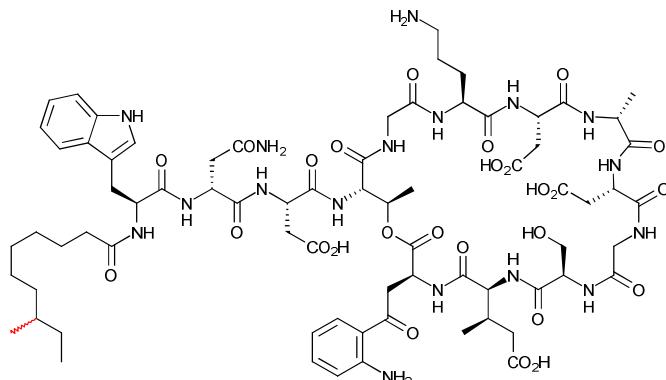
1. The C8 stereochemistry of the *anteiso*-undecanoyl fatty acid is unspecified.
2. MICs were determined in the presence and absence of 1% bovine surfactant, denoted +surf. And -surf.



**191. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 0.5

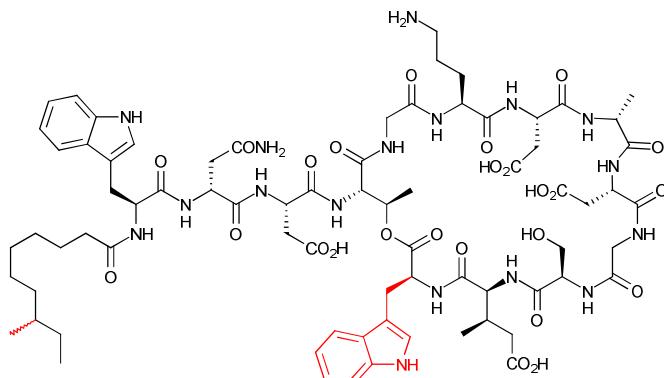
*S. aureus* 42, +surf. = 64



**192. CB-181,220, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 0.5

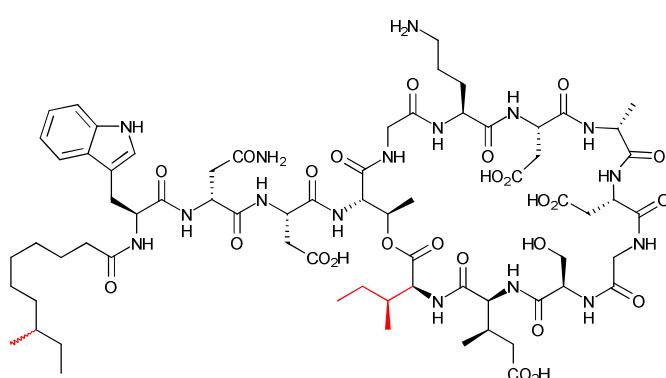
*S. aureus* 42, +surf. = 64



**193. CB-182,098, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 1

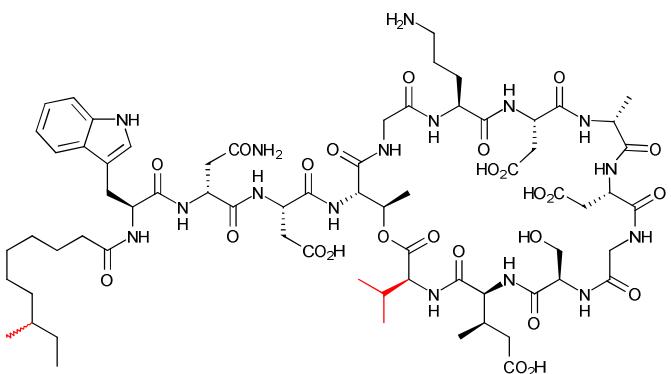
*S. aureus* 42, +surf. = 32



**194. CB-182,107, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 2

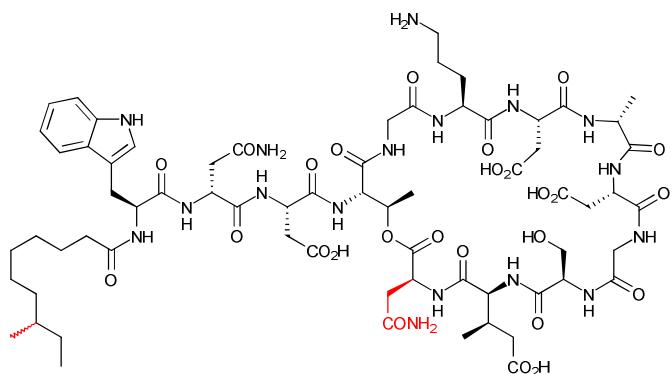
*S. aureus* 42, +surf. = 8



**195. CB-182,106, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 4

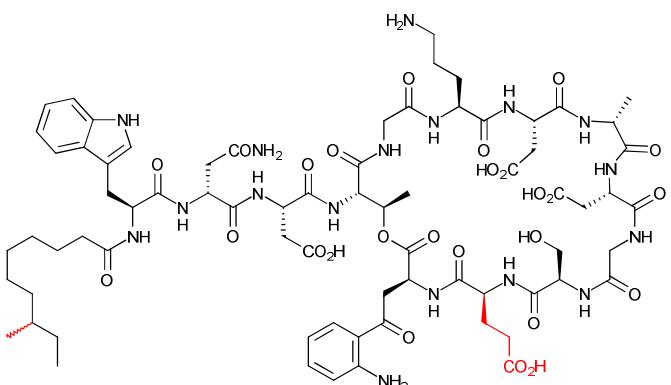
*S. aureus* 42, +surf. = 8



**196. A21978C1(Asn13), MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 128

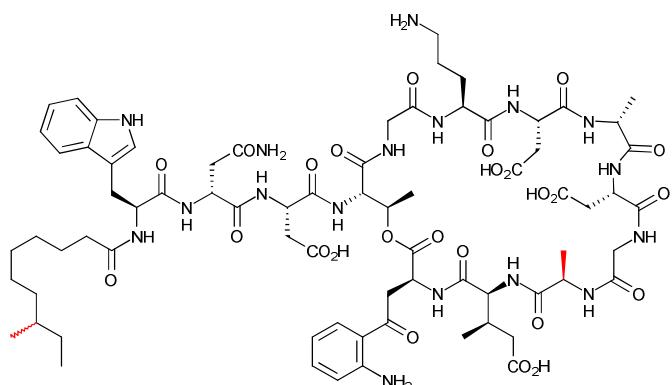
*S. aureus* 42, +surf. = ND



**197. CB-182,130, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8

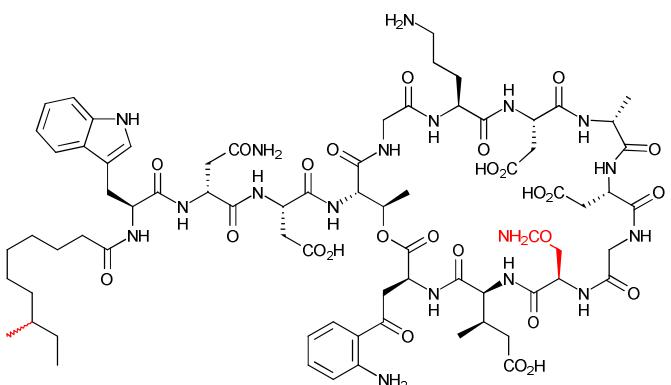
*S. aureus* 42, +surf. = 16



**198. CB-182,166, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 1

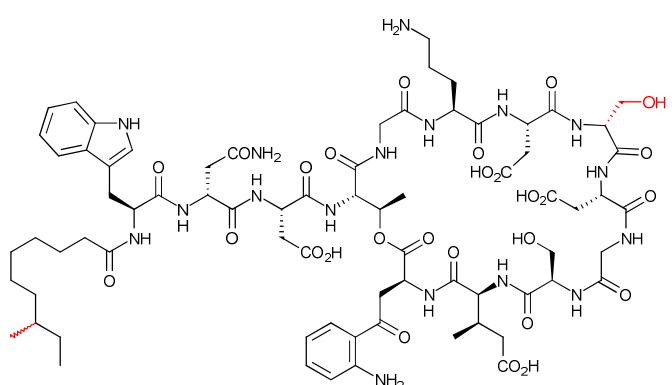
*S. aureus* 42, +surf. = 16



**199. CB-182,290, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 1

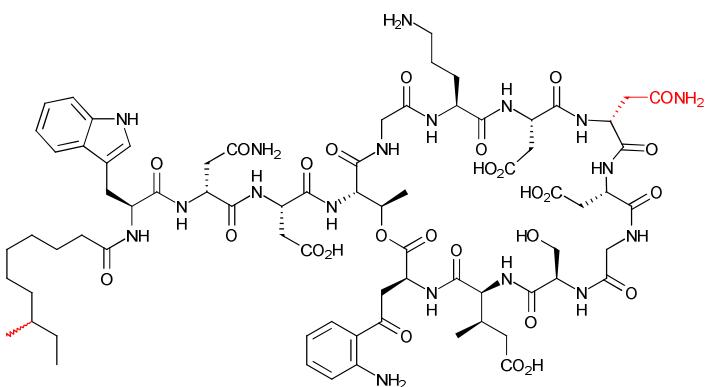
*S. aureus* 42, +surf. = 16



**200. CB-182,123, MIC ( $\mu\text{g/mL}$ )**

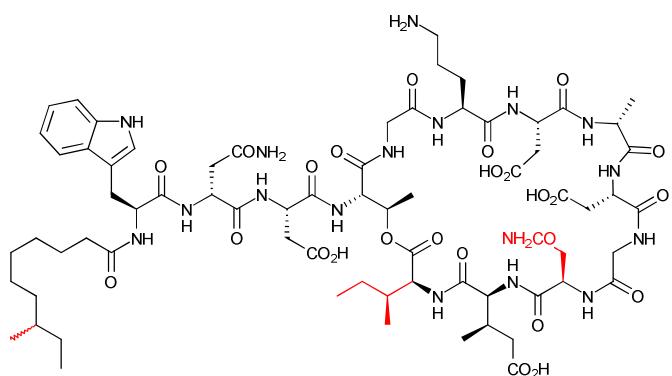
*S. aureus* 42, -surf. = 1

*S. aureus* 42, +surf. = 32



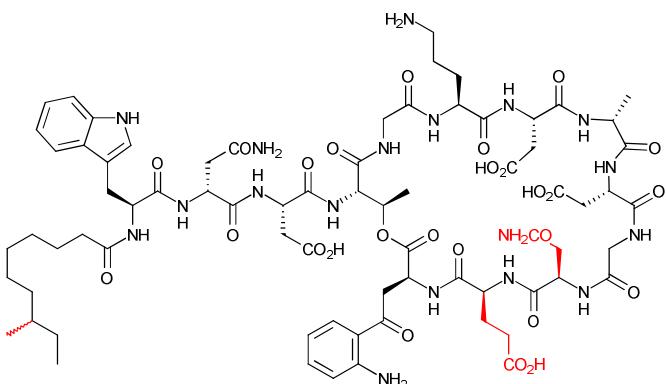
**201. CB-182,257, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8  
*S. aureus* 42, +surf. = ND



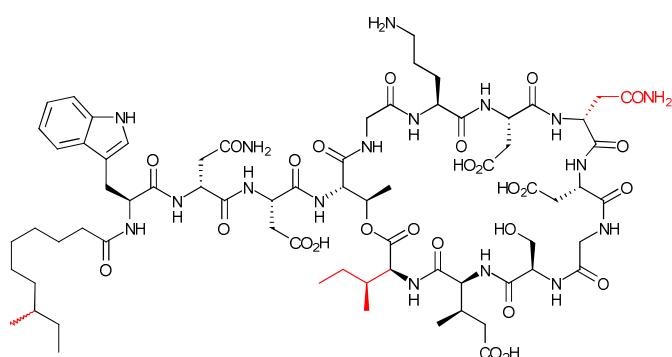
**202. CB-182,286, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 4  
*S. aureus* 42, +surf. = ND



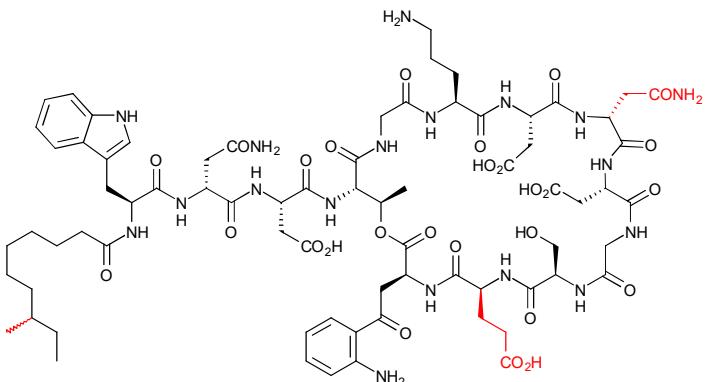
**203. CB-182,251, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 32  
*S. aureus* 42, +surf. = ND



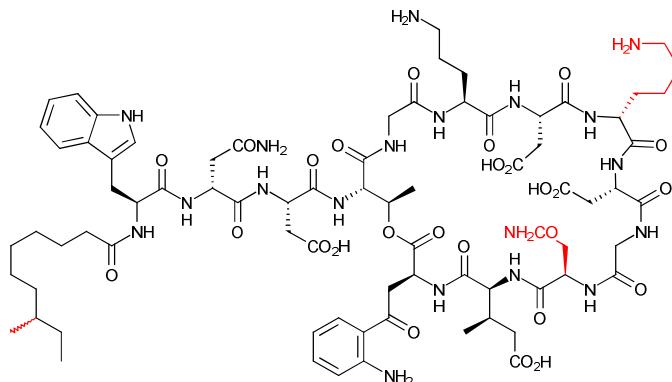
**204. CB-182,263, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 16  
*S. aureus* 42, +surf. = ND



**205. CB-182,269, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 128  
*S. aureus* 42, +surf. = ND



**206. CB-182,296, MIC ( $\mu\text{g/mL}$ )**

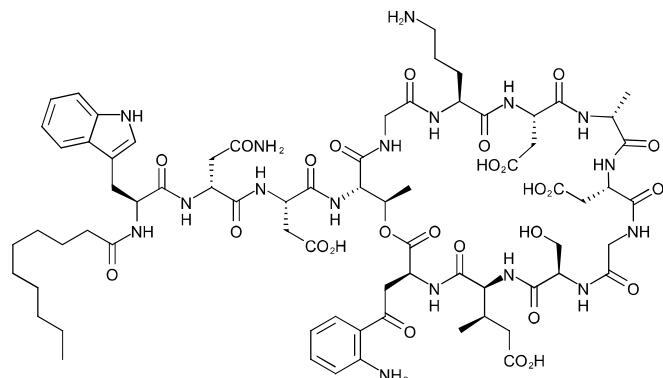
*S. aureus* 42, -surf. = 1  
*S. aureus* 42, +surf. = 32

## Combinatorial biosynthesis of novel antibiotics related to daptomycin

Nguyen, K. T., Ritz, D., Gu, J.-Q., Alexander, D., Chu, M., Miao, V., Brian, P., Baltz, R. H.,  
*PNAS*, 2006, 103, 46, 17462-17467.

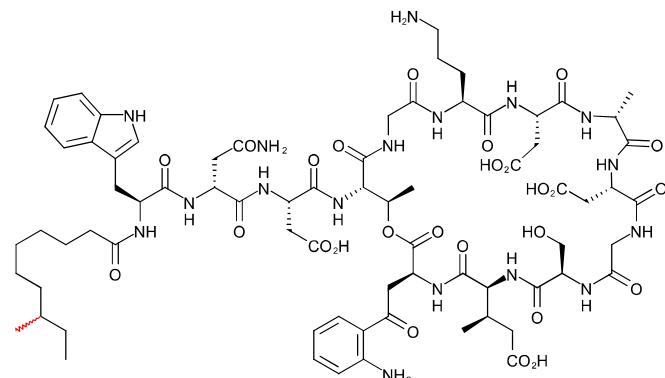
### Note

The C8 stereochemistry of the *anteiso*-undecanoyl fatty acid is unspecified.



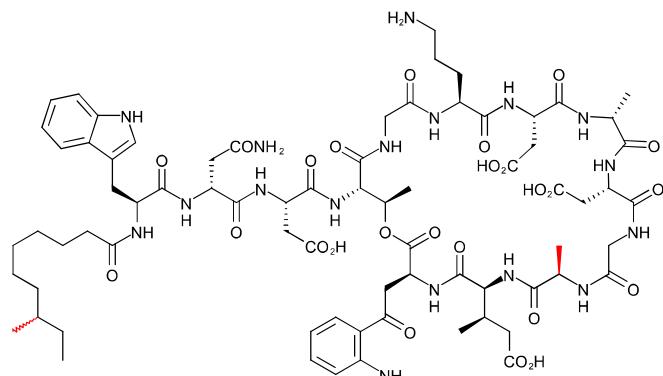
**207. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> 1118 = 1	<i>S. Aureus</i> 1695 = 2
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 2
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 2
<i>E. faecalis</i> 312 = 64	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 128	
<i>S. pneumoniae</i> 402 = 0.125	



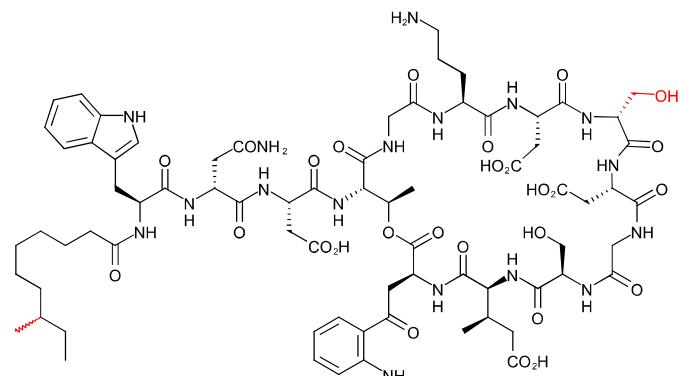
**208. CB-181,220, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 0.5	<i>S. Aureus</i> 399 = 0.5
<i>S. Aureus</i> 1118 = 0.5	<i>S. Aureus</i> 1695 = 2
<i>S. Aureus</i> 1616 = 8	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 16	<i>E. faecalis</i> 201 = 2
<i>E. faecalis</i> 312 = 32	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 128	
<i>S. pneumoniae</i> 402 = 0.125	



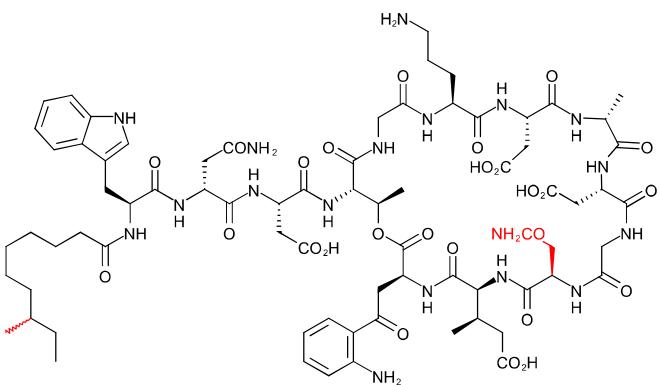
**209. CB-182,122, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> 1118 = 0.5	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 8	<i>E. faecium</i> 14 = 2
<i>E. faecium</i> 384 = 8	<i>E. faecalis</i> 201 = 1
<i>E. faecalis</i> 312 = 32	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 128	
<i>S. pneumoniae</i> 402 = 0.125	



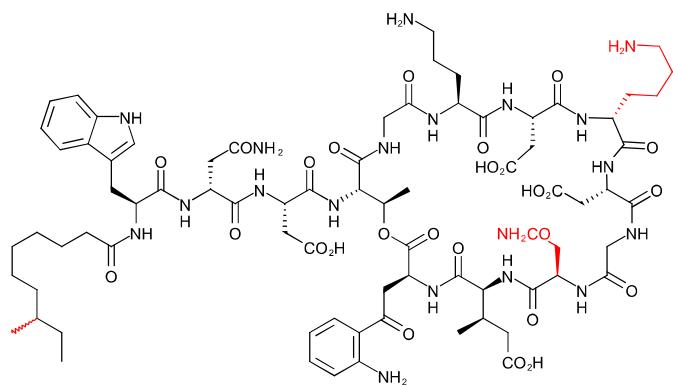
**210. CB-182,166, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 2	<i>S. Aureus</i> 399 = 0.5
<i>S. Aureus</i> 1118 = 1	<i>S. Aureus</i> 1695 = 8
<i>S. Aureus</i> 1616 = 32	<i>E. faecium</i> 14 = 8
<i>E. faecium</i> 384 = 64	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 128	
<i>S. pneumoniae</i> 402 = 0.5	



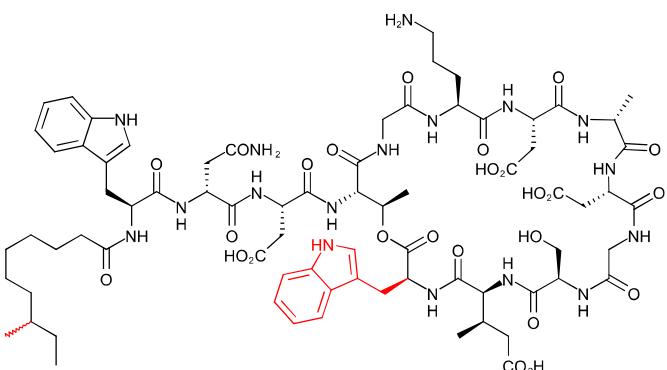
**211. CB-182,290, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> 1118 = 1	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 64	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 32	
<i>S. pneumoniae</i> 402 = 0.5	



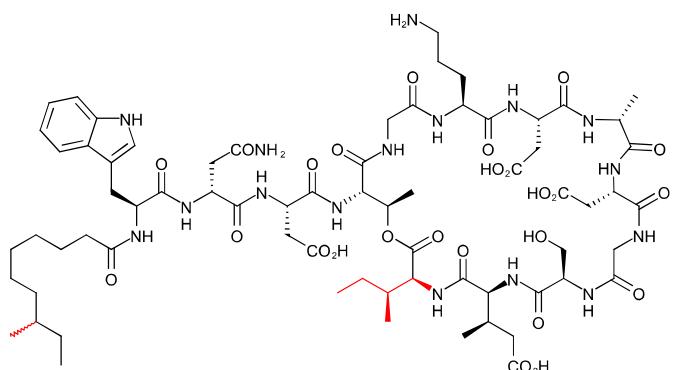
**212. CB-182,296, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> 1118 = 1	<i>S. Aureus</i> 1695 = 8
<i>S. Aureus</i> 1616 = 32	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 16
<i>E. faecalis</i> 312 = 256	<i>E. coli</i> 35 > 256
<i>E. coli</i> 256 ( $\Delta lamB106$ ) > 256	
<i>E. coli</i> 257 ( <i>imp-4213</i> ) = 128	
<i>S. pneumoniae</i> 402 = 1	



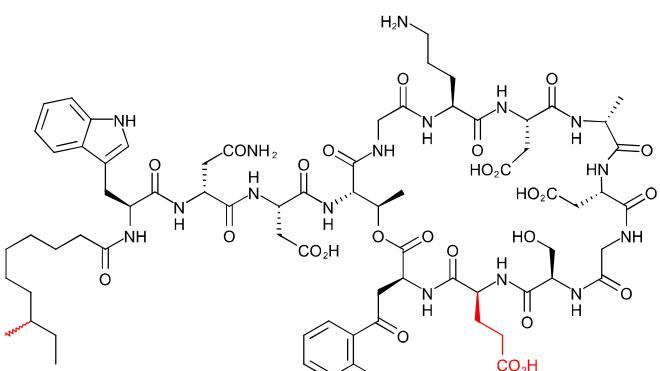
**213. CB-182,098, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 1



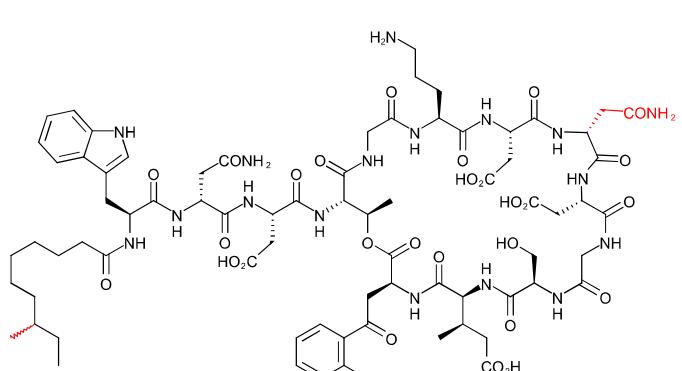
**214. CB-182,107, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 4



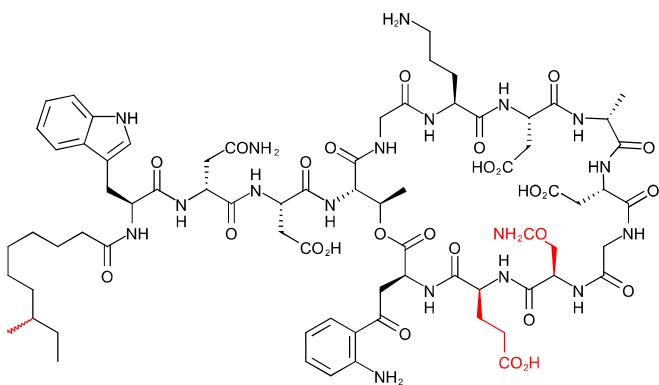
**215. CB-182,130, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 8



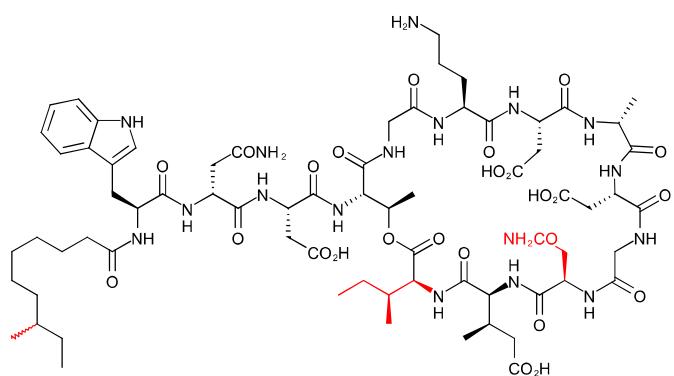
**216. CB-182,257, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 8



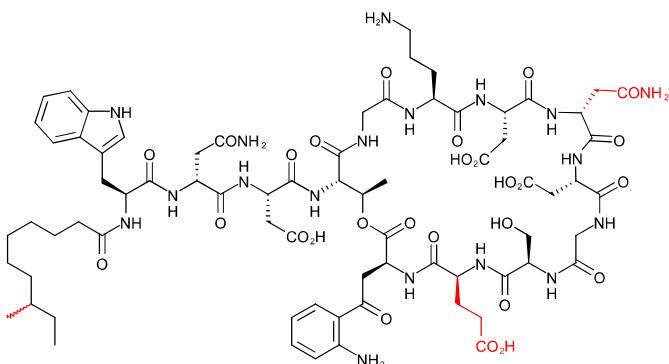
**217. CB-182,251, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 32



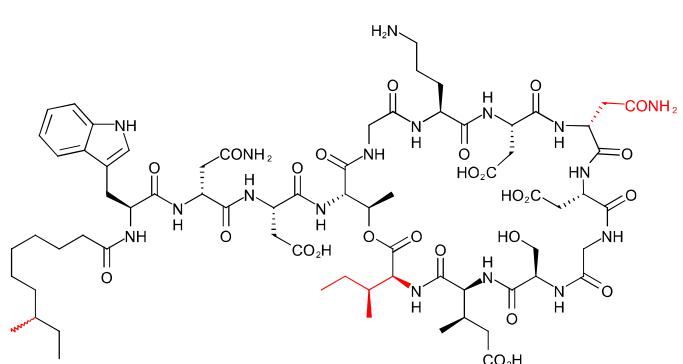
**218. CB-182,286, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 4



**219. CB-182,269, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 128



**220. CB-182,263, MIC ( $\mu\text{g/mL}$ )**

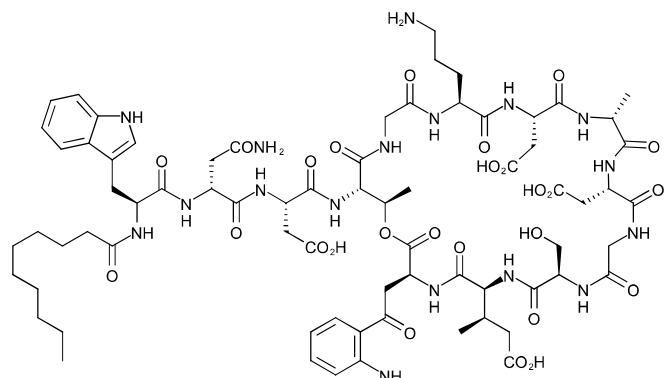
*S. aureus* 42 = 16

# Genetically Engineered Lipopeptide Antibiotics Related to A54145 and Daptomycin with Improved Properties

Nguyen, K. T., He, X., Alexander, D. C., Li, C., Gu, J.-Q., Mascio, C., Van Praagh, A., Mortin, L., Chu, M., Silverman, J., Brian, P., Baltz, R. H., *Antimicrob. Agents Chemother.*, 2010, 54, 4, 1404-1413.

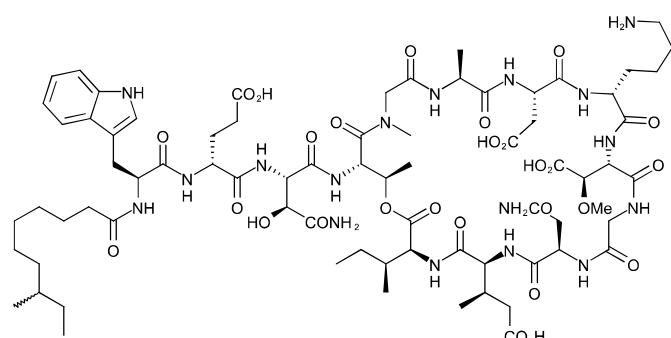
## Note

The C8 stereochemistry of the *anteiso*-undecanoyl fatty acid is unspecified.



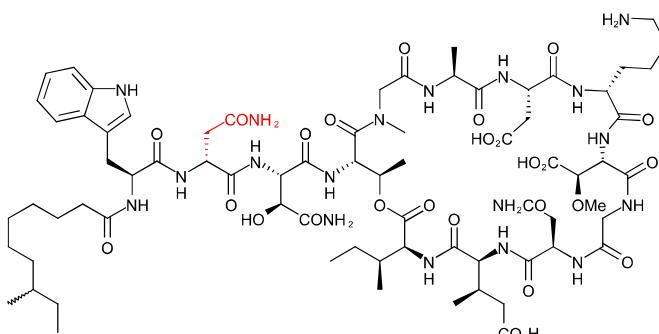
### **221. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 0.5
<i>S. Aureus</i> MW2 = 1	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 2
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 2
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> BAS849 = 128
<i>S. pneumoniae</i> 402 = 0.25	



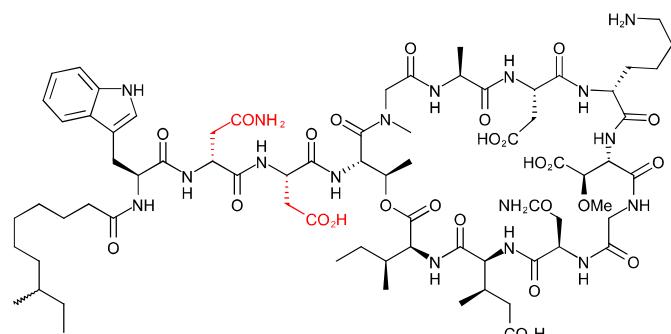
### **222. A54145E, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 0.5	<i>S. Aureus</i> 399 = 2
<i>S. Aureus</i> MW2 = 1	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 16	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> BAS849 = 16
<i>S. pneumoniae</i> 402 = 0.25	



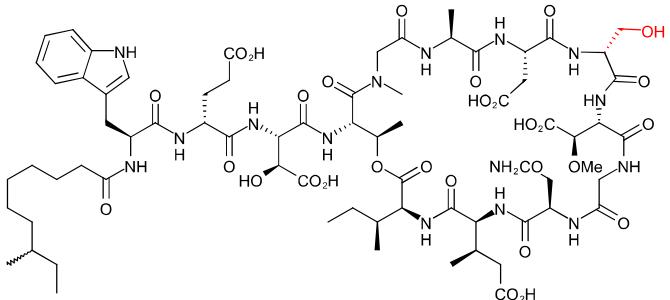
### **223. CB-182,575, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 2	<i>S. Aureus</i> 399 = 2
<i>S. Aureus</i> MW2 = 1	<i>S. Aureus</i> 1695 = 16
<i>S. Aureus</i> 1616 = 32	<i>E. faecium</i> 14 = 8
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 16
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> BAS849 = 64
<i>S. pneumoniae</i> 402 = 2	



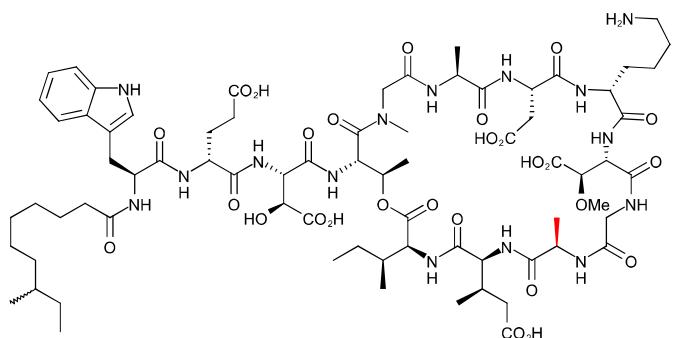
### **224. CB-182,561, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 0.5
<i>S. Aureus</i> MW2 = 1	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 16	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 64	<i>E. coli</i> BAS849 = 16
<i>S. pneumoniae</i> 402 = 1	



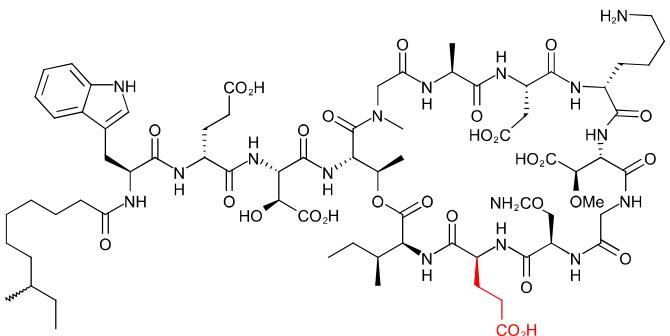
**225. CB-182,549, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> MW2 = 0.5	<i>S. Aureus</i> 1695 = 4
<i>S. Aureus</i> 1616 = 8	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> BAS849 = 16
<i>S. pneumoniae</i> 402 = 0.25	



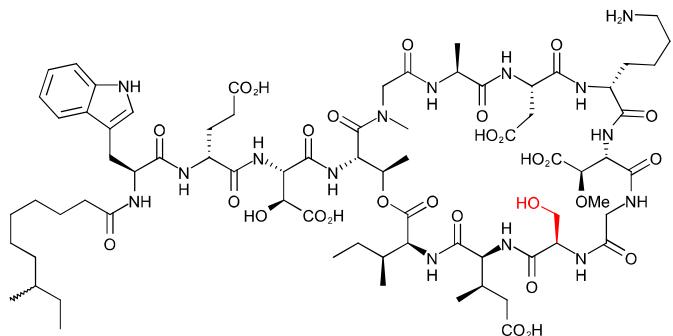
**226. CB-182,548, MIC ( $\mu\text{g/mL}$ )**

<i>S. Aureus</i> 42 = 1	<i>S. Aureus</i> 399 = 1
<i>S. Aureus</i> MW2 = 1	<i>S. Aureus</i> 1695 = 8
<i>S. Aureus</i> 1616 = 16	<i>E. faecium</i> 14 = 4
<i>E. faecium</i> 384 = 32	<i>E. faecalis</i> 201 = 4
<i>E. faecalis</i> 312 = 128	<i>E. coli</i> BAS849 = 16
<i>S. pneumoniae</i> 402 = 0.5	



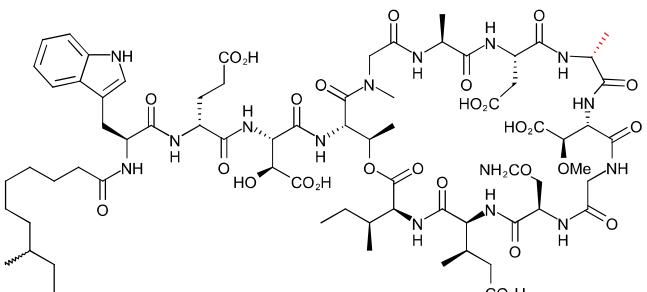
**227. A54145D, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 2  
*S. aureus* 42, +surf. = 4



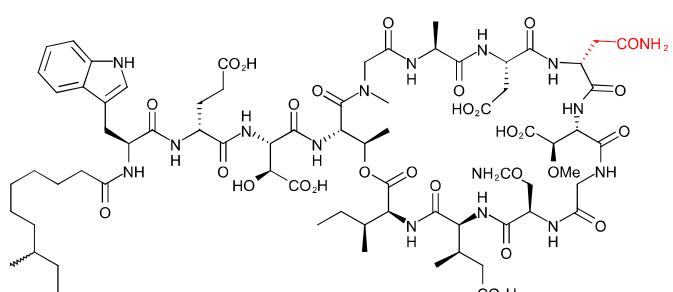
**228. CB-182,332, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 2  
*S. aureus* 42, +surf. = 16



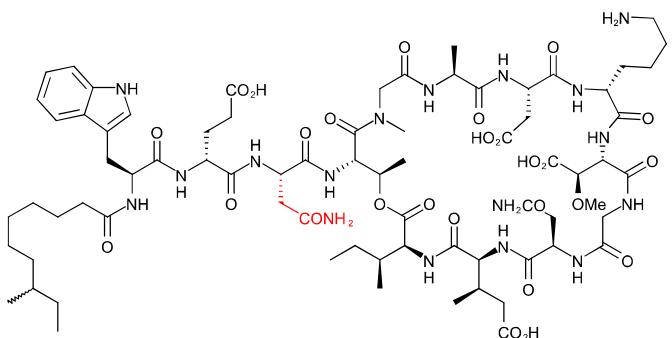
**229. CB-182,571, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 1  
*S. aureus* 42, +surf. = 32



**230. CB-182,510, MIC ( $\mu\text{g/mL}$ )**

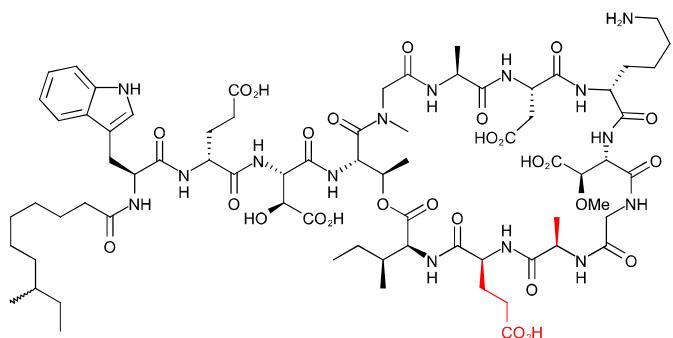
*S. aureus* 42, -surf. = 8  
*S. aureus* 42, +surf. = 64



**231. CB-182,363, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 2

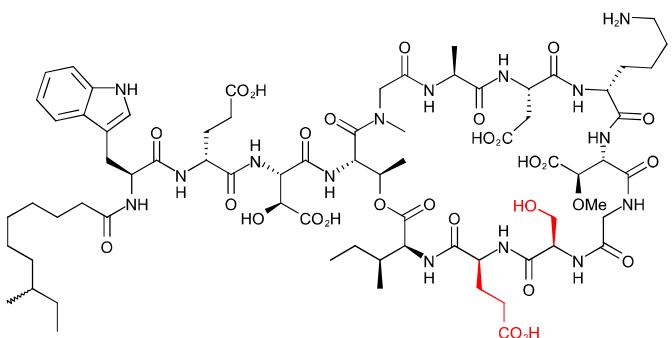
*S. aureus* 42, +surf. = 16



**232. CB-182,509, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8

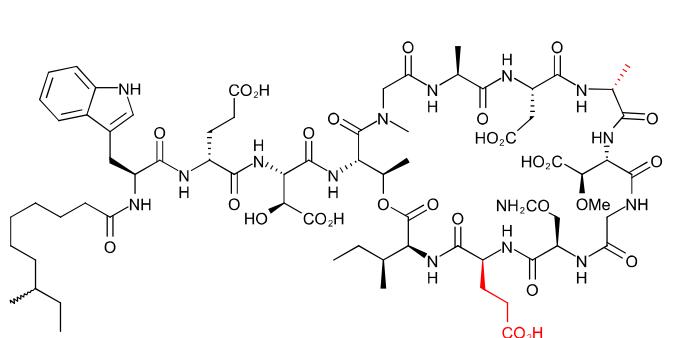
*S. aureus* 42, +surf. = 16



**233 CB-182,336, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 64

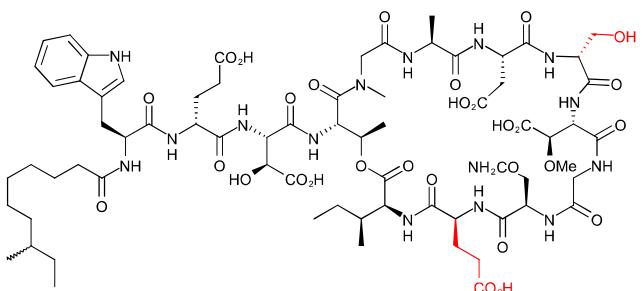
*S. aureus* 42, +surf. = 128



**234. CB-182,567, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 4

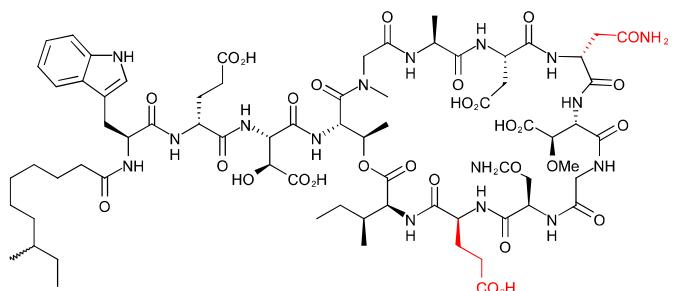
*S. aureus* 42, +surf. = 8



**235. CB-182,532, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8

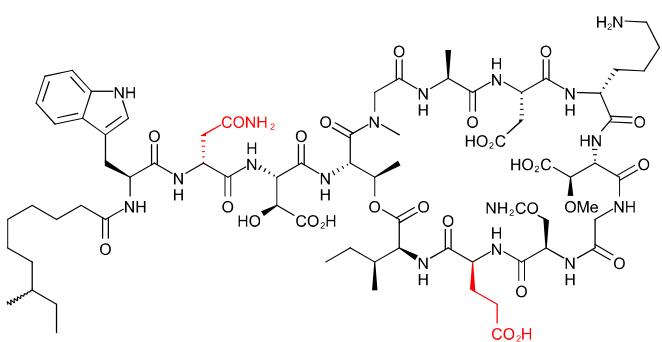
*S. aureus* 42, +surf. = 8



**236. CB-182,531, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 16

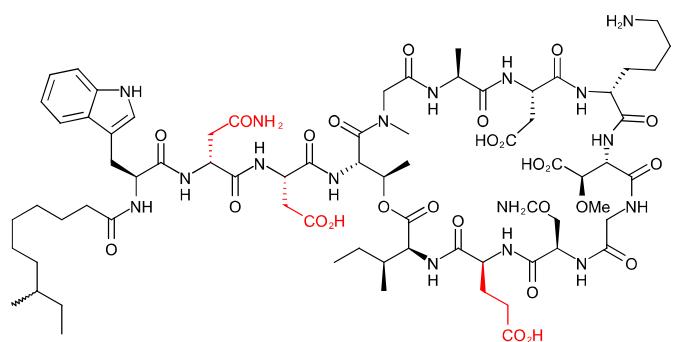
*S. aureus* 42, +surf. = 16



**237. CB-182,444, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8

*S. aureus* 42, +surf. = 8



**238. CB-182,560, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42, -surf. = 8

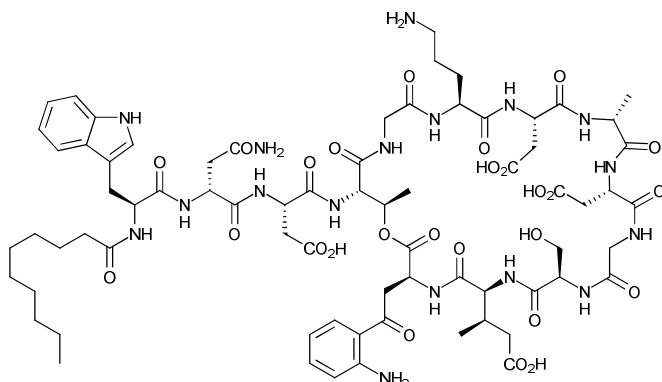
*S. aureus* 42, +surf. = 16

**A combined solid- and solution-phase approach provides convenient access to analogues of the calcium-dependent lipopeptide antibiotics**

't Hart P., Kleijn, L.H., de Bruin, G., Oppedijk, S. F., Kemmink, J., Martin, N. I.,  
*Org. Biomol. Chem.*, 2014, 12, 6, 913-918.

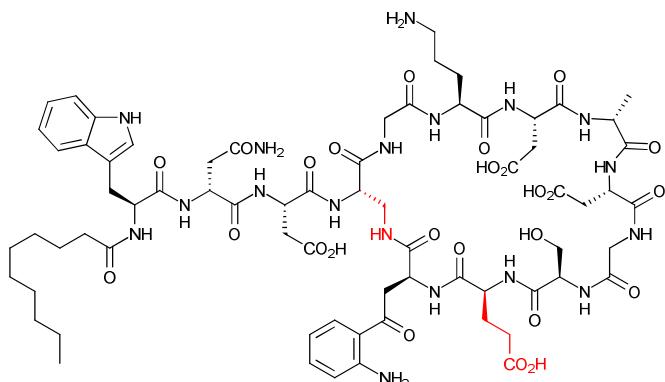
**Note**

1. Culture broth supplemented with 50 mg/L Ca<sup>2+</sup>.
2. Highest concentration tested = 804 μM.



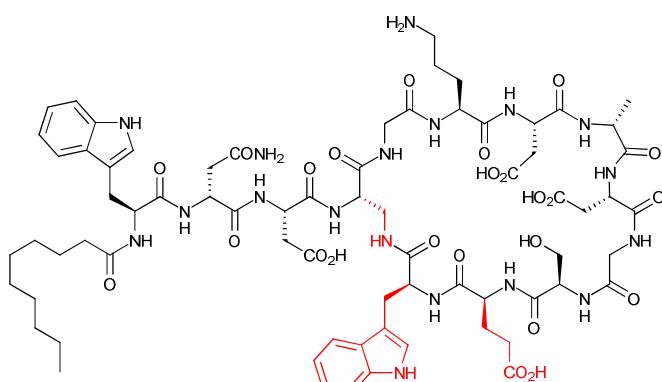
**239. Daptomycin (1), MIC (μM)**

*S. aureus* ATCC29213 = 1.23



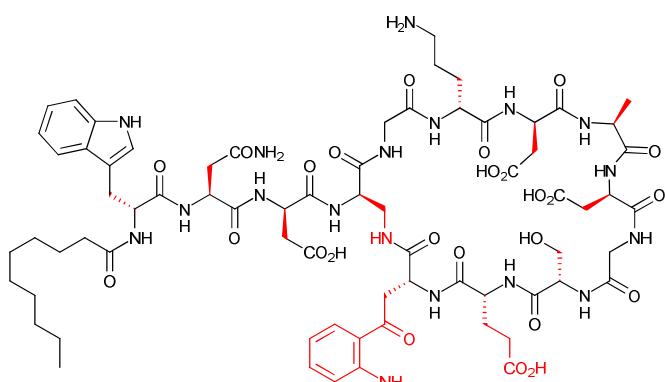
**240. Compound 2, MIC (μM)**

*S. aureus* ATCC29213 = 201.2



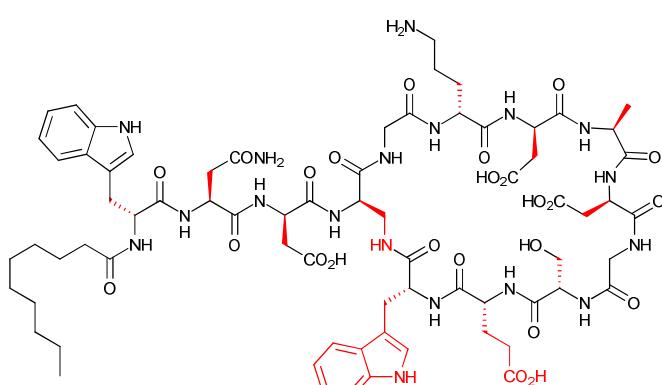
**241. Compound 3, MIC (μM)**

*S. aureus* ATCC29213 = 100.8



**242. Compound ent-2, MIC (μM)**

*S. aureus* ATCC29213 = not active



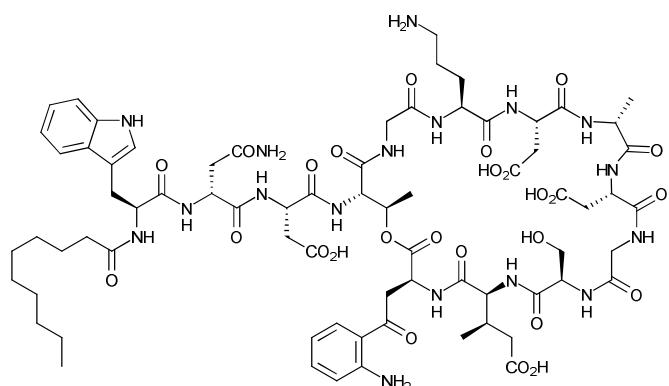
**243. Compound ent-3, MIC (μM)**

*S. aureus* ATCC29213 = not active

## Solid-phase total synthesis of daptomycin and analogs

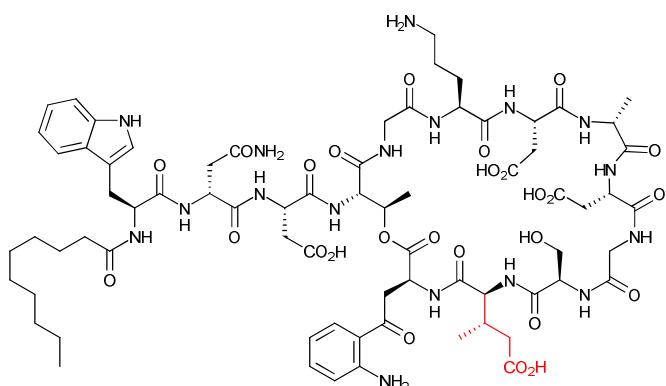
Lohani, C. R., Taylor, R., Palmer, M., Taylor, S. D.,

*Org. Lett.*, 2015, 17, 3, 748-751.



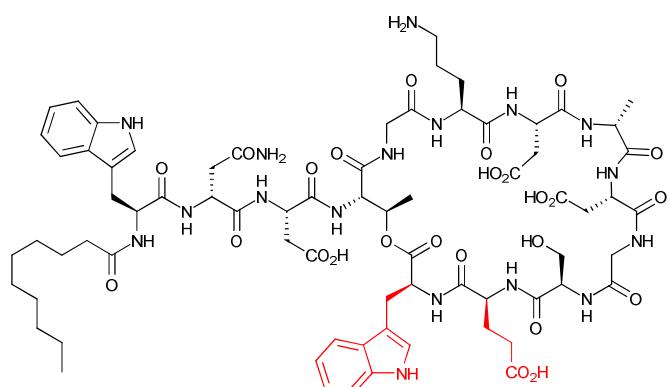
**244. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

- B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 0.75  
*B. subtilis* ATCC1046, 25 mM  $\text{Ca}^{2+}$  = 0.5  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = 0.5  
*B. subtilis* PY79, 5 mM  $\text{Ca}^{2+}$  = 0.75



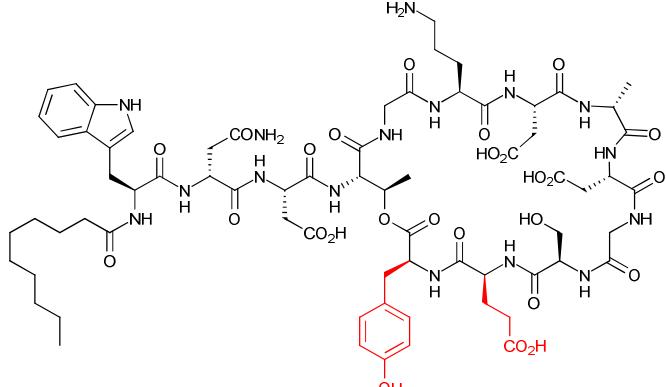
**245. Dap-(2S,3S)-MeGlu, MIC ( $\mu\text{g/mL}$ )**

- B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 40  
*B. subtilis* ATCC1046, 25 mM  $\text{Ca}^{2+}$  = 5.0  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = 5.0  
*B. subtilis* PY79, 5 mM  $\text{Ca}^{2+}$  > 40



**246. Dap-E12/W13, MIC ( $\mu\text{g/mL}$ )**

- B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 1.0  
*B. subtilis* ATCC1046, 25 mM  $\text{Ca}^{2+}$  = ND  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = ND  
*B. subtilis* PY79, 5 mM  $\text{Ca}^{2+}$  = 3.0

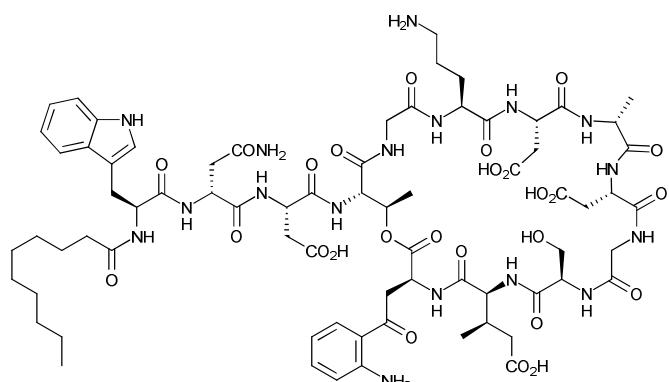


**247. Dap-E12/Y13, MIC ( $\mu\text{g/mL}$ )**

- B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 35  
*B. subtilis* ATCC1046, 25 mM  $\text{Ca}^{2+}$  = 3.0  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = 1.3  
*B. subtilis* PY79, 5 mM  $\text{Ca}^{2+}$  = ND

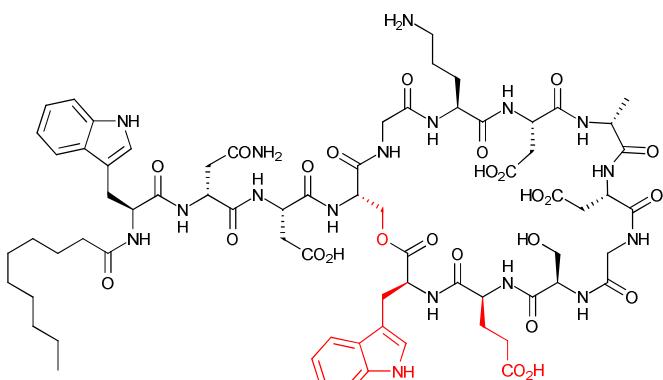
## Solid-phase synthesis and in vitro biological activity of a Thr4→Ser4 analog of daptomycin

Lohani, C. R., Taylor, R., Palmer, M., Taylor, S. D.,  
*Bioorg. Med. Chem. Lett.*, 2015, 25, 5490-5494.



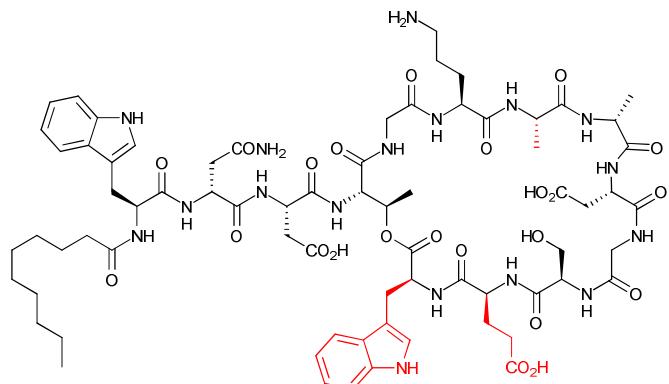
**248. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.8 mM  $\text{Ca}^{2+}$  = 1.0  
*B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 0.75  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = 0.5



**249. Dap-S4-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.8 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  = 65  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  = 3



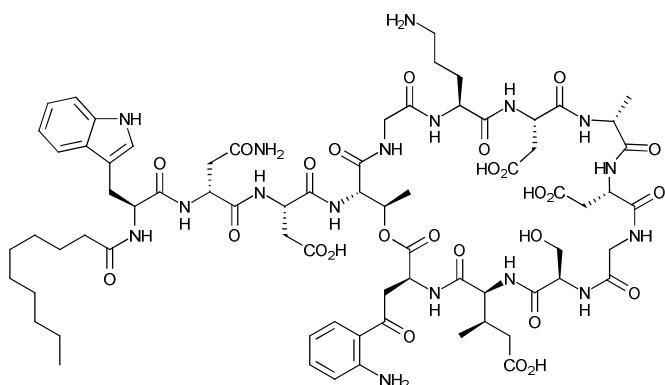
**250. Dap-A7-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.8 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 100 mM  $\text{Ca}^{2+}$  > 100

# Structure-Activity Relationship Studies on Daptomycin

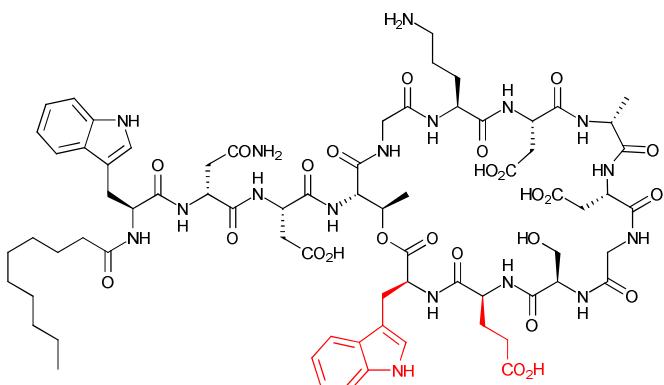
Barnawi, G.

Masters Thesis, 2018, University of Waterloo, Canada.



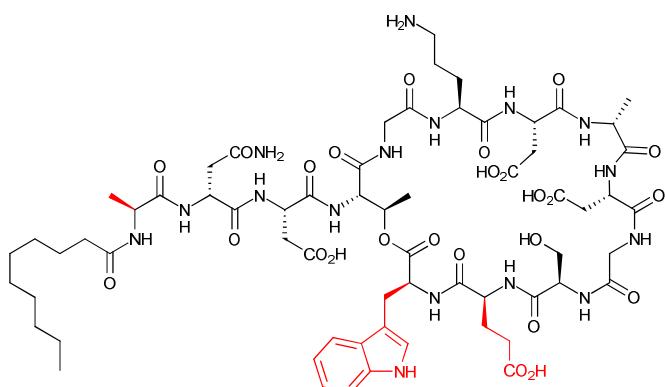
**251. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 0.75  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5  
*B. subtilis* PY79, 1.25 mM  $\text{Ca}^{2+}$  = 0.75  
*B. subtilis* PY79, 5.0 mM  $\text{Ca}^{2+}$  = 0.75



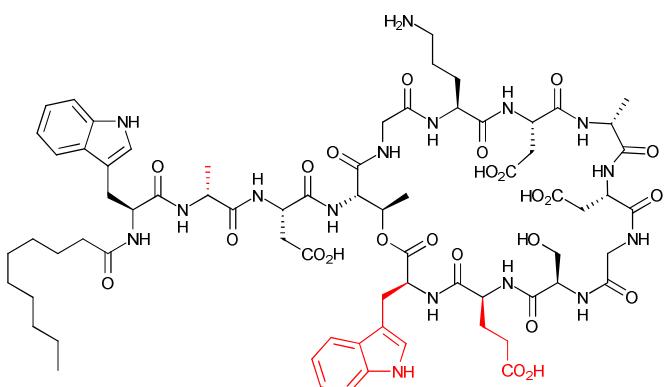
**252. Dap-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 3.5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 1.0  
*B. subtilis* PY79, 1.25 mM  $\text{Ca}^{2+}$  = 4.5  
*B. subtilis* PY79, 5.0 mM  $\text{Ca}^{2+}$  = 3.0



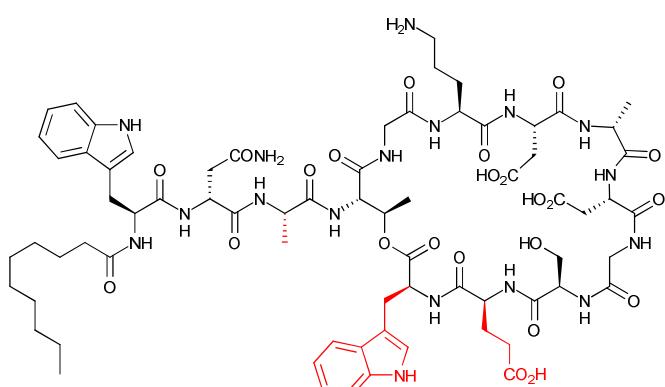
**253. Dap-A1-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 30



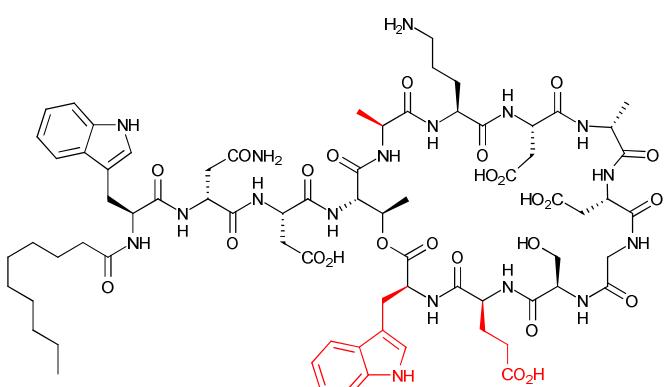
**254. Dap-D-A2-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 15  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 3



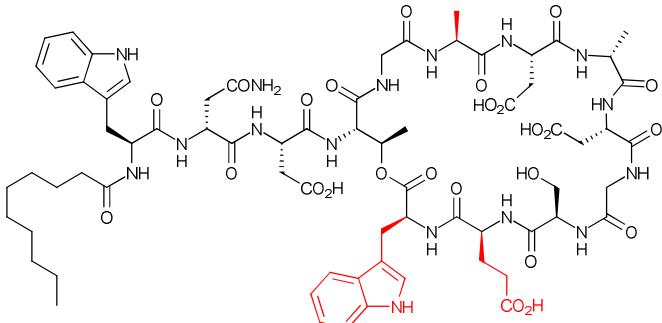
**255. Dap-A3-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 30



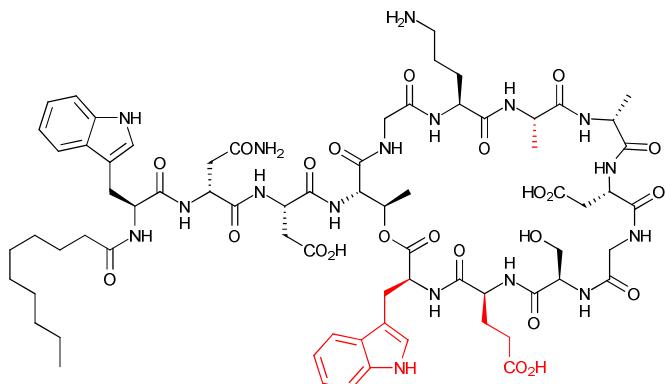
**256. Dap-A5-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 35  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 4



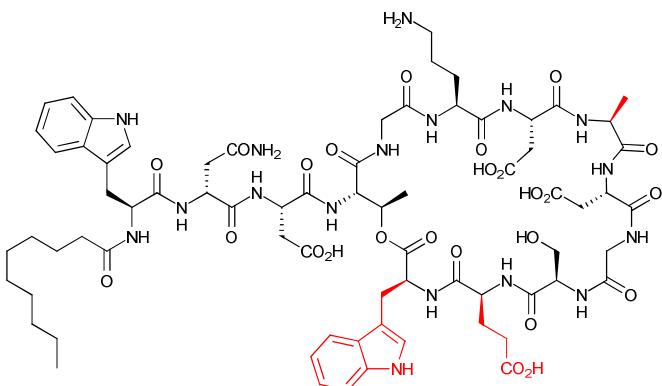
**257. Dap-A6-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5



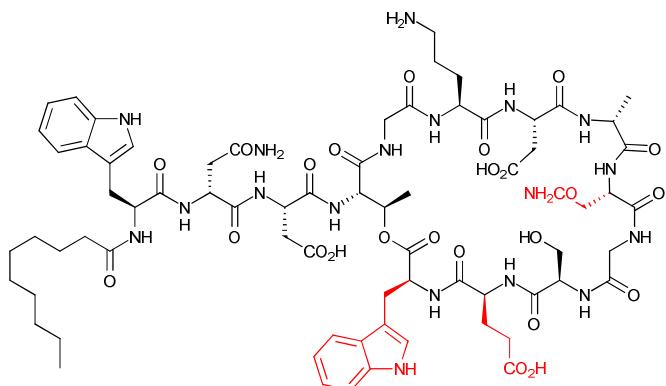
**258. Dap-A7-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  > 100



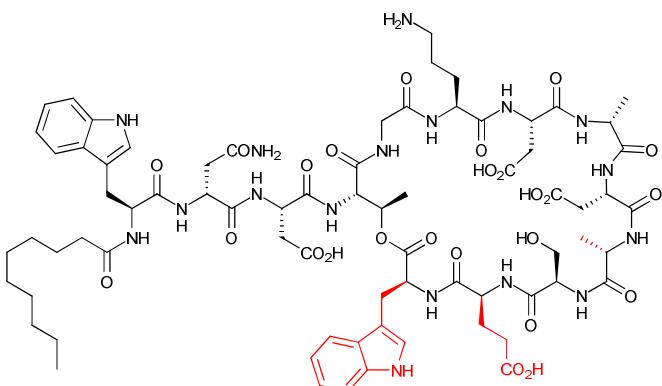
**259. Dap-L-A8-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 35



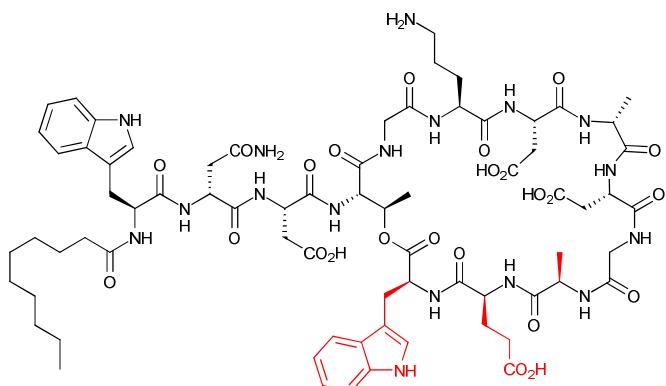
**260. Dap-L-N9-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 35



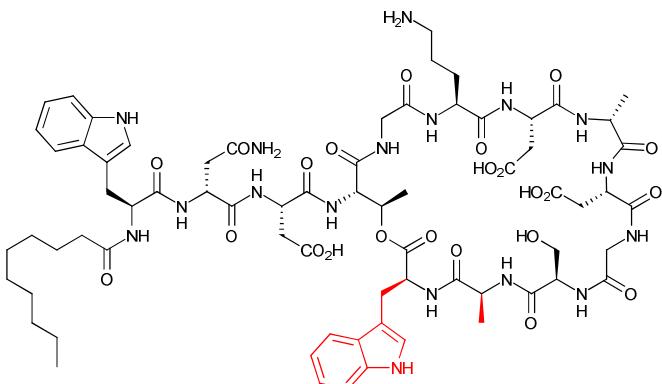
**261. Dap-A10-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  > 100



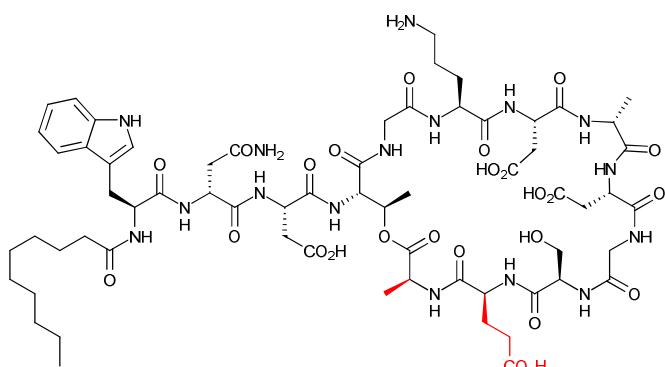
**262. Dap-D-A11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5



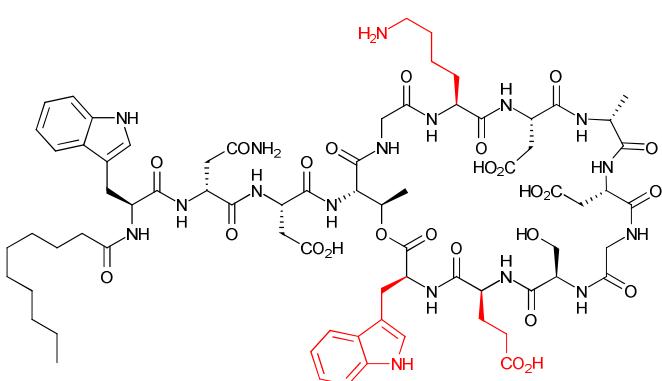
**263. Dap-A12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 35  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 4



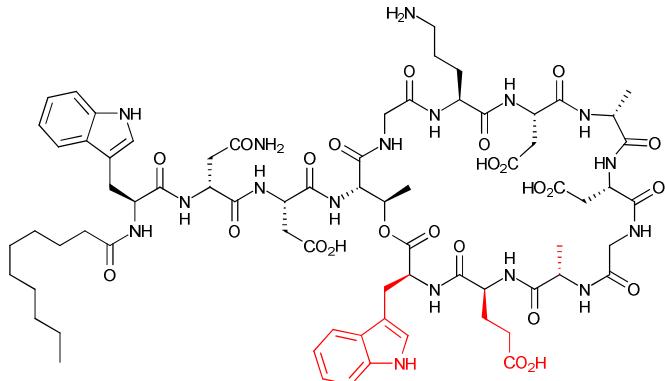
**264. Dap-E12-A13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 100



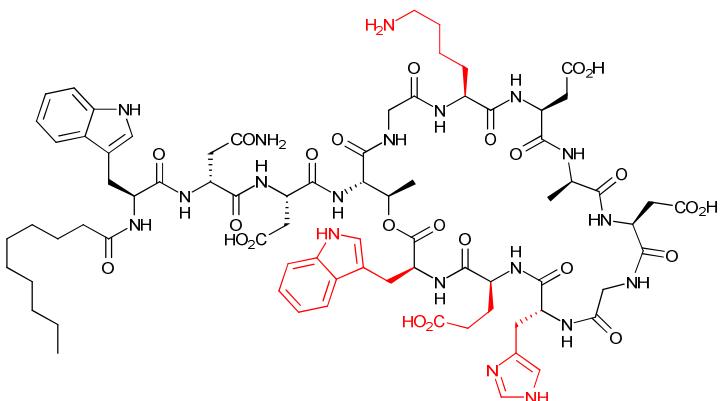
**265. Dap-K6-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 1.5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5  
*B. subtilis* PY79, 1.25 mM  $\text{Ca}^{2+}$  = 1.5  
*B. subtilis* PY79, 5.0 mM  $\text{Ca}^{2+}$  = 0.75



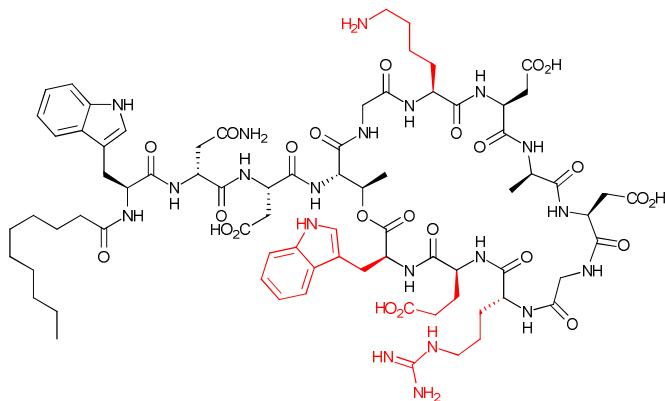
**266. Dap-A11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5



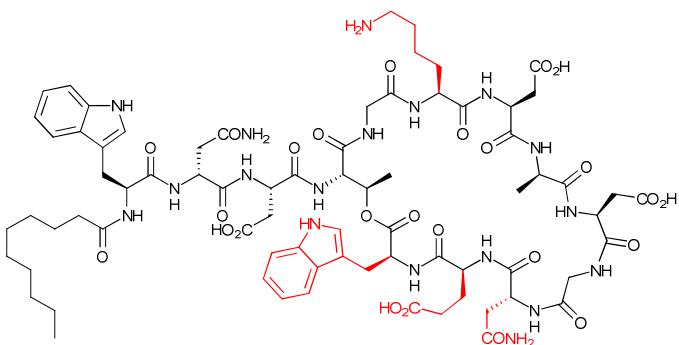
**267. Dap-K6-D-H11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 1.5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 1



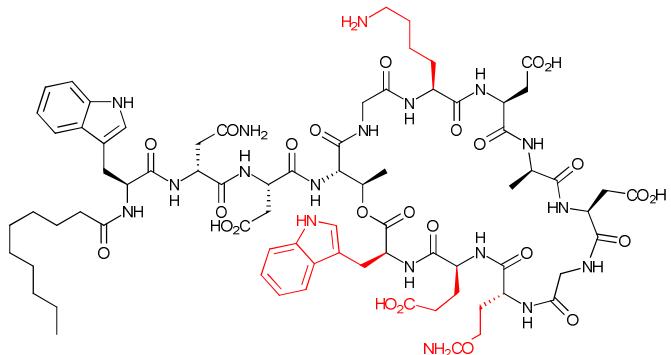
**268. Dap-K6-D-R11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 2.5  
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 0.5



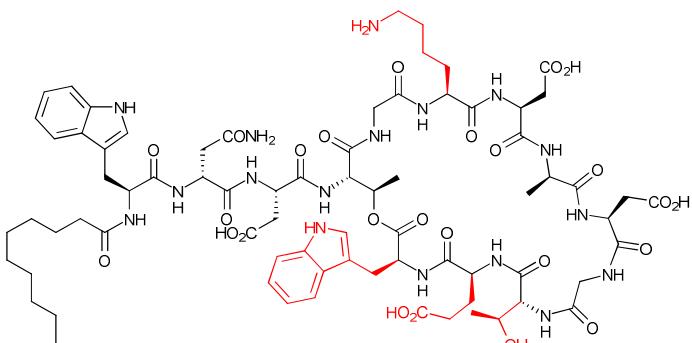
**269. Dap-K6-D-N11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 2.5  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 0.5



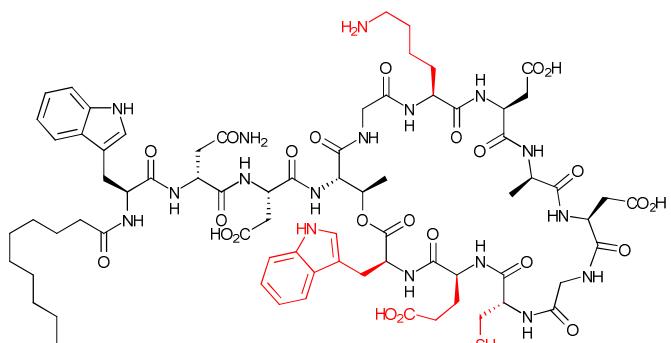
**270. Dap-K6-D-Q11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 30  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 1.5



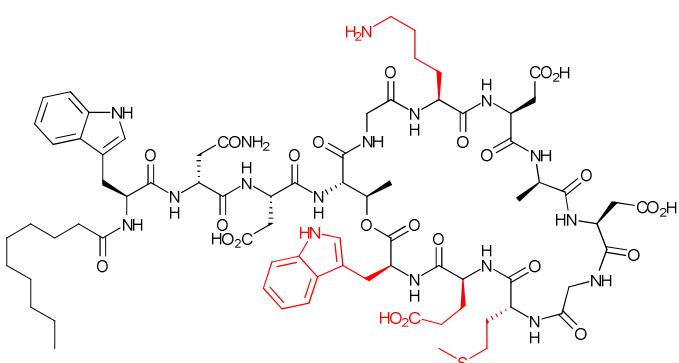
**271. Dap-K6-D-T11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 4  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 0.85



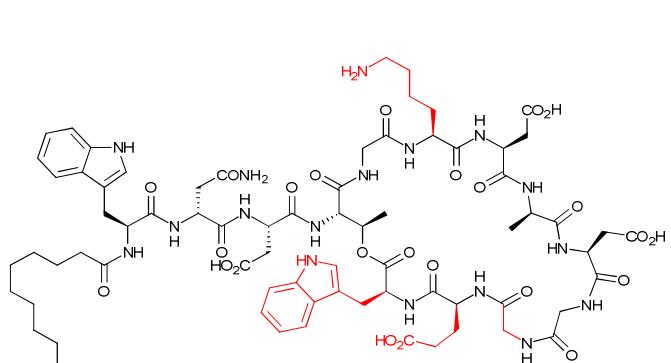
**272. Dap-K6-D-C11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 4  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 1.5



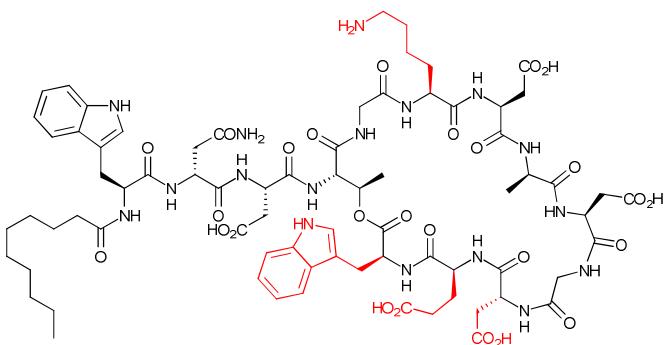
**273. Dap-K6-D-M11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 4  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 0.5



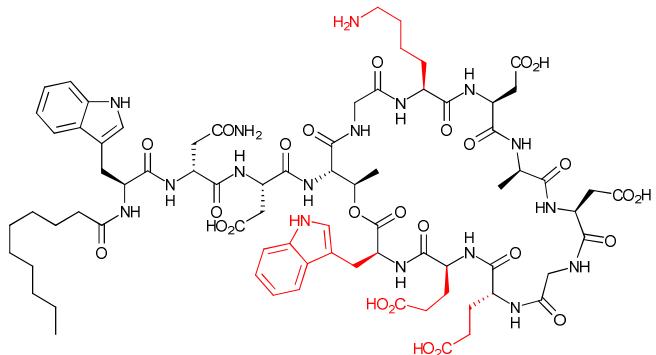
**274. Dap-K6-G11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 4  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 2.5



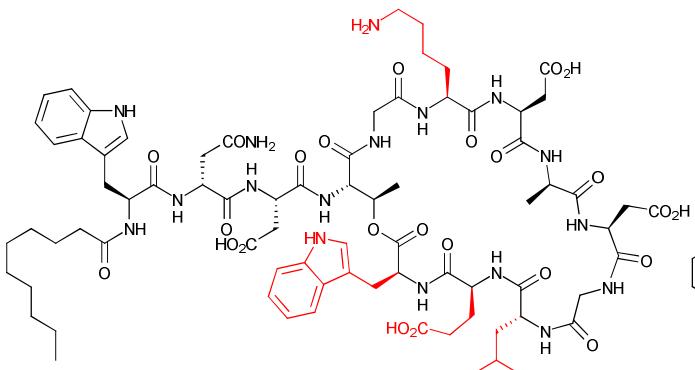
**275. Dap-K6-D-D11-E12-W13, MIC (μg/mL)**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 30  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 7.5



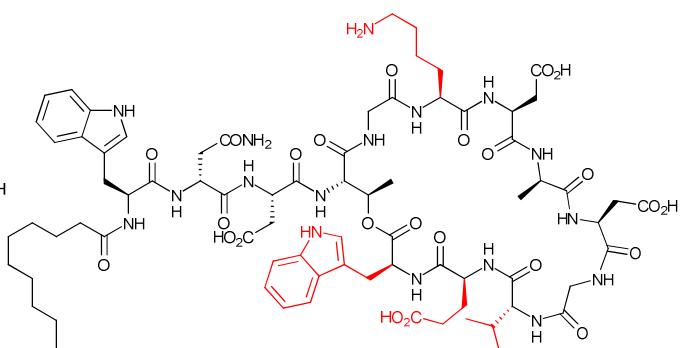
**276. Dap-K6-D-E11-E12-W13, MIC (μg/mL)**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 75  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 30



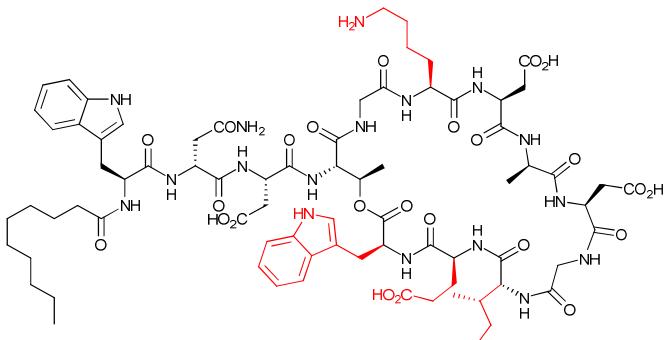
**277. Dap-K6-D-L11-E12-W13, MIC (μg/mL)**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 30  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 1.5



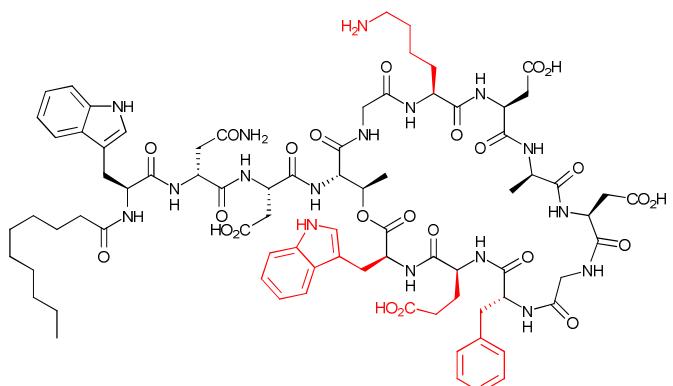
**278. Dap-K6-D-V11-E12-W13, MIC (μg/mL)**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 30  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 0.85



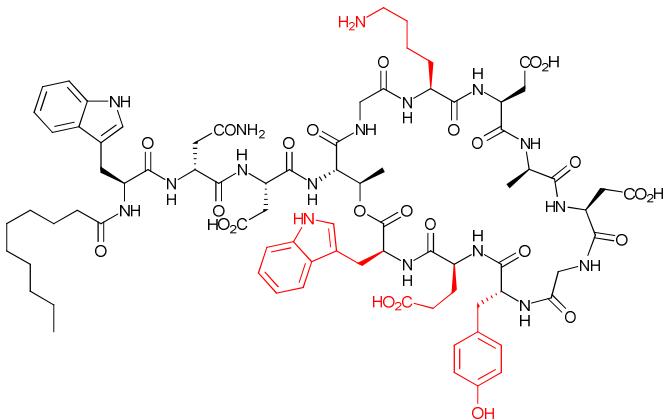
**279. Dap-K6-D-*allo*-Ile11-E12-W13, MIC (μg/mL)**

*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 30  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 4



**280. Dap-K6-D-F11-E12-W13, MIC (μg/mL)**

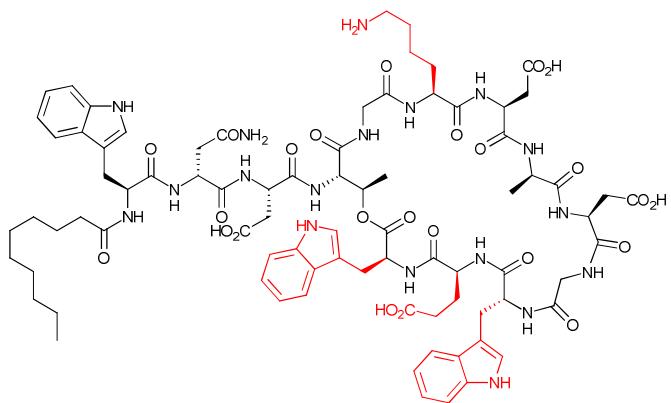
*B. subtilis* ATCC1046, 1.25 mM Ca<sup>2+</sup> = 100  
*B. subtilis* ATCC1046, 5.0 mM Ca<sup>2+</sup> = 4



**281. Dap-K6-D-Y11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  = 75

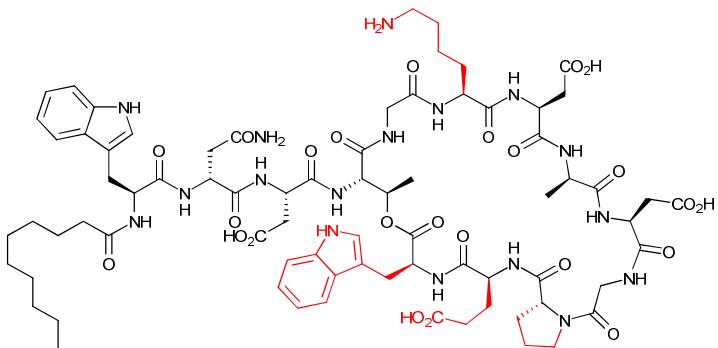
*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 10



**282. Dap-K6-D-W11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100

*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  > 100



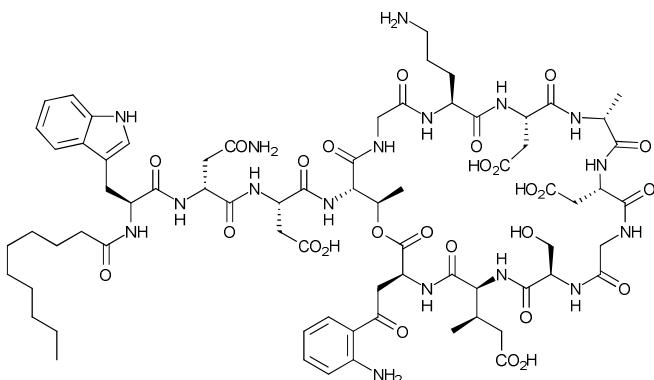
**283. Dap-K6-D-P11-E12-W13, MIC ( $\mu\text{g/mL}$ )**

*B. subtilis* ATCC1046, 1.25 mM  $\text{Ca}^{2+}$  > 100

*B. subtilis* ATCC1046, 5.0 mM  $\text{Ca}^{2+}$  = 30

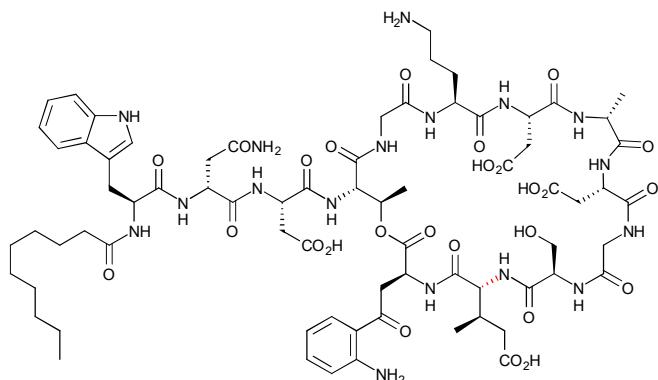
**A Versatile Boc Solid Phase Synthesis of Daptomycin and Analogues Using Site Specific, On-Resin Ozonolysis to Install the Kynurenine Residue**

Xu, B., Hermant, Y., Yang, S.-H., Harris, P. W., Brimble, M. A.  
*Chem. Eur. J.*, 2019, 25, 14101-14107.



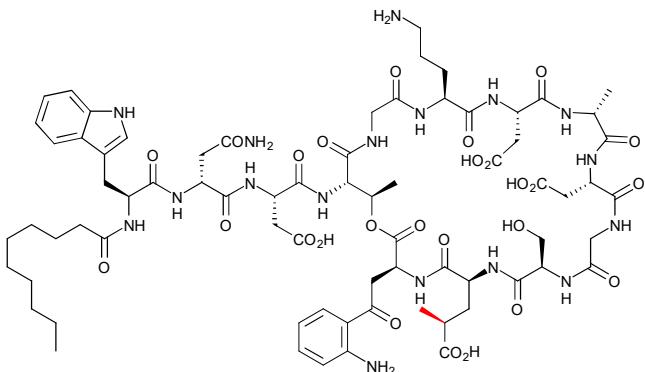
**284. Daptomycin (1), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> = 1.0*



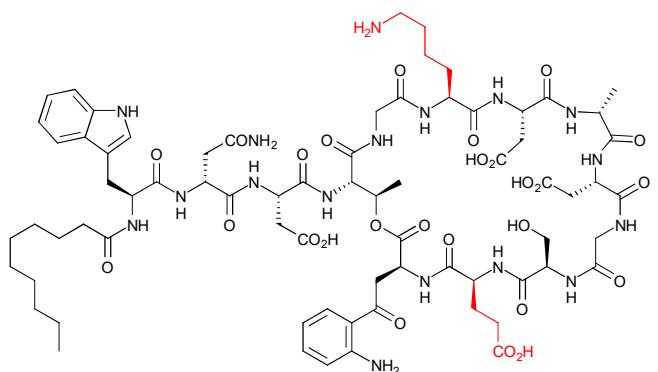
**285. Dapt-(2R,3R)-MeGlu (16), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> > 128*



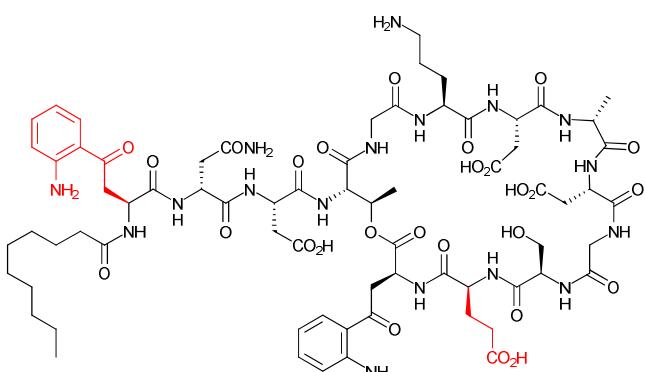
**286. Dapt-(2S,4S)-MeGlu (17), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> > 128*



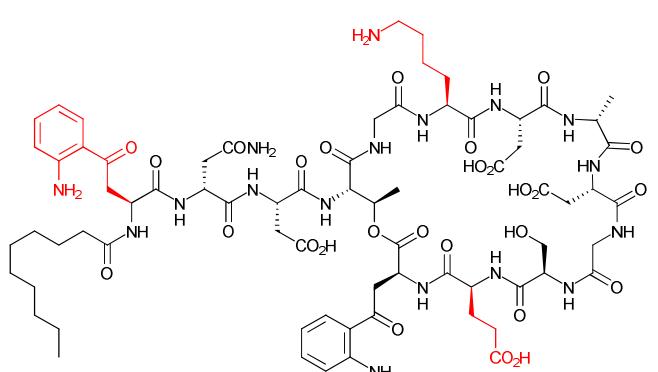
**287. Dapt-Lys6/Glu12 (18), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> = 64*



**288. Dapt-Kyn1/Glu12 (19), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> > 128*



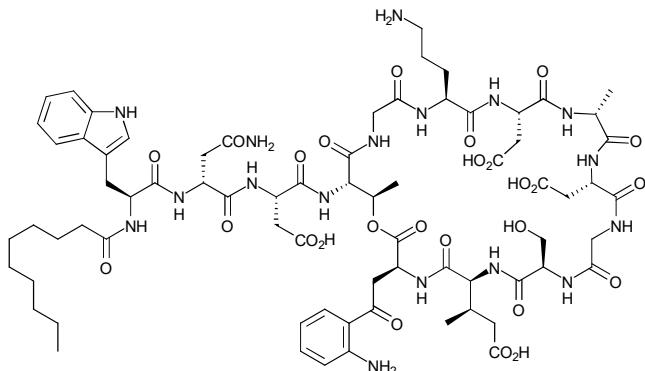
**289. Dapt-Kyn1/Lys6/Glu12 (20), MIC ( $\mu\text{g/mL}$ )**

*S. Aureus ATCC29213, 1.25 mM Ca<sup>2+</sup> > 128*

## Structure-activity relationship of daptomycin analogues with substitution at (2S,3R) 3-methyl glutamic acid position

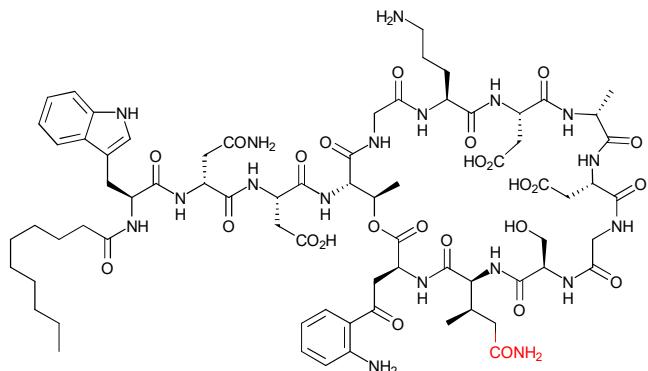
Lin, D., Iam, H. Y., Han, W., Cotroneo, N., Pandya, B. A., Li, X.

*Bioorg. Med. Chem. Lett.*, 2017, 27, 456-459.



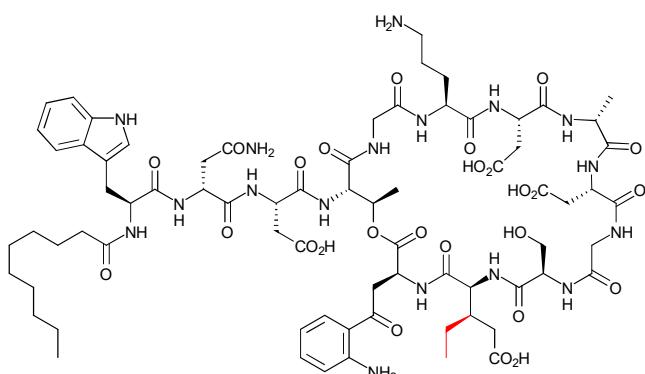
**290. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 0.5



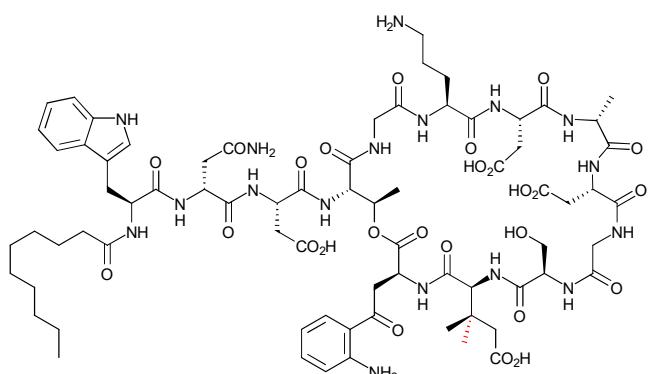
**291. (2S,3R)-MeGln12, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 32



**292. (2S,3R)-EtGlu12, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 8

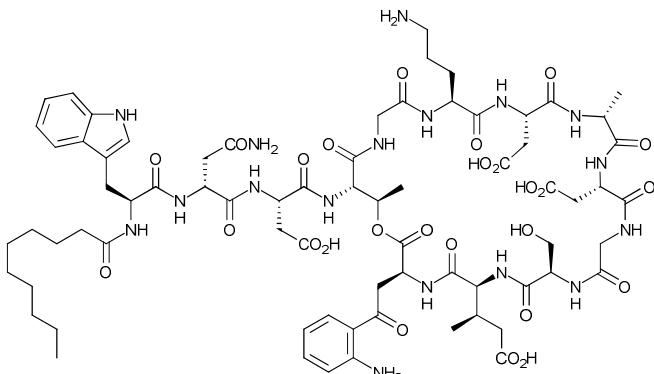


**293 3,3'-Dimethyl-Glu12, MIC ( $\mu\text{g/mL}$ )**

*S. aureus* 42 = 64

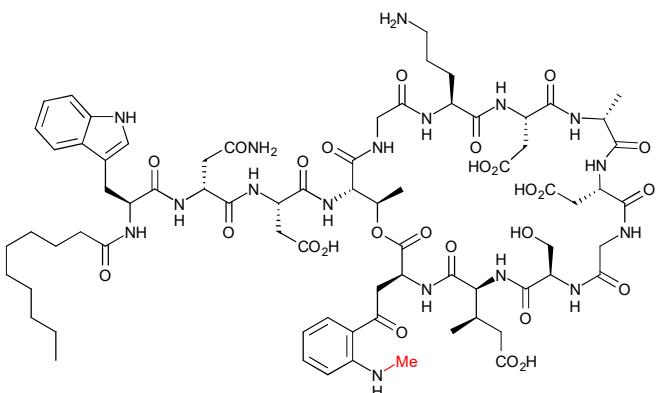
## Methylation of Daptomycin Leading to the Discovery of Kynomycin, a Cyclic Lipodepsipeptide Active against Resistant Pathogens

Chow, H. Y., Hiu, K., Po, L., Gao, P., Blasco, P., Wang, X., Li, C., Ye, L., Jin, K., Chen, K., Chan, E. W. C., You, X., Kao, R. Y. T., Chen, S., Li, X.  
*J. Med. Chem.*, **2020**, 63, 3161-3171.



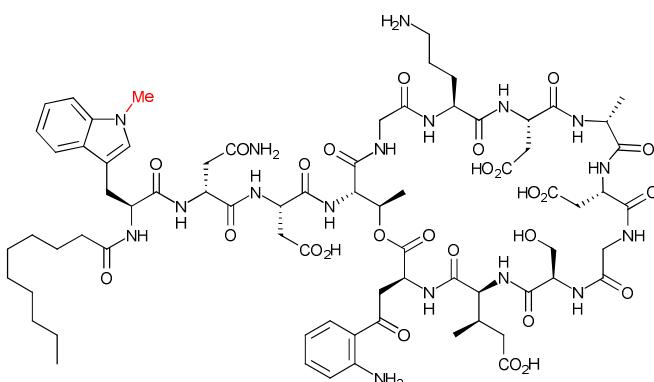
**294. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 2	MRSA SA14 = 0.5
MRSA SA86 = 0.5	MRSA SA88 = 0.5
SA ATCC29213 = 0.5	<i>S. faecalis</i> = 0.5
<i>Enterococc.</i> ET6 = 4	<i>Enterococc.</i> ET60 = 2
<i>Enterococc.</i> ATCC29212 = 4	
No hemolytic activity (rat RBCs) at 320 $\mu\text{g/mL}$	
Cytotoxicity (HEK cells), 40 mg/mL: some	
Cytotoxicity (HEK cells), 80 mg/mL: some	



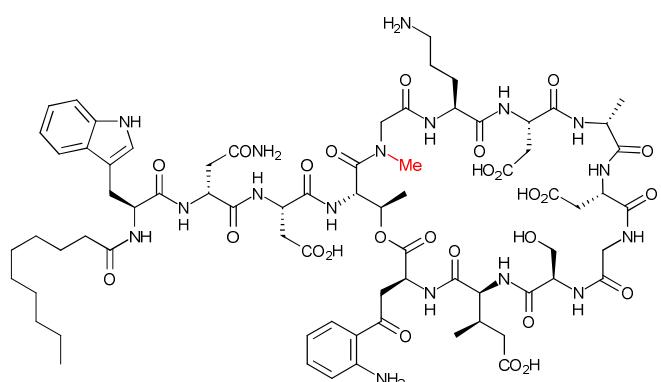
**295. Me-Kyn-13 (Kynomycin), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 0.5	MRSA SA14 = 0.25
MRSA SA86 = 0.25	MRSA SA88 = 0.25
SA ATCC29213 = 0.25	<i>S. faecalis</i> = 0.5
<i>Enterococc.</i> ET6 = 1	<i>Enterococc.</i> ET60 = 1
<i>Enterococc.</i> ATCC29212 = 1	
No hemolytic activity (rat RBCs) at 320 $\mu\text{g/mL}$	
Cytotoxicity (HEK cells), 40 mg/mL: none	
Cytotoxicity (HEK cells), 80 mg/mL: minor	



**296. Me-Trp-1, MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 2	MRSA SA14 = 0.5
MRSA SA86 = 0.5	MRSA SA88 = 0.25
SA ATCC29213 = 0.5	<i>S. faecalis</i> = ND
<i>Enterococc.</i> ET6 = 1	<i>Enterococc.</i> ET60 = 1
<i>Enterococc.</i> ATCC29212 = 2	



**297. Sar-5, MIC ( $\mu\text{g/mL}$ )**

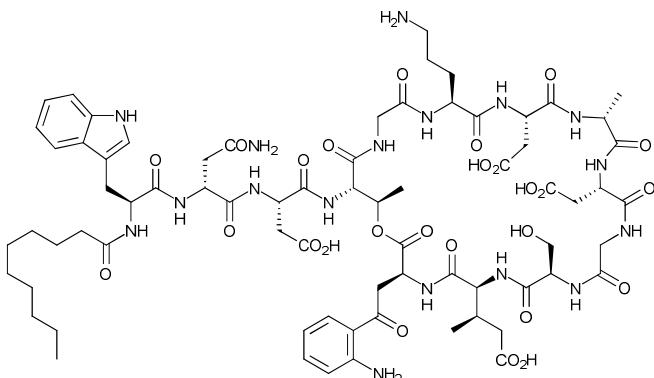
MRSA SA11 = 0.5	MRSA SA14 = 0.25
MRSA SA86 = 0.5	MRSA SA88 = 0.5
SA ATCC29213 = 0.5	<i>S. faecalis</i> = 2
<i>Enterococc.</i> ET6 = 8	<i>Enterococc.</i> ET60 = 4
<i>Enterococc.</i> ATCC29212 = 8	

## Establishing the Structure–Activity Relationship of Daptomycin

Chow, H. Y., Po, K. H. L., Jin, K., Qiao, G., Sun, Z., Ma, W., Ye, X.,

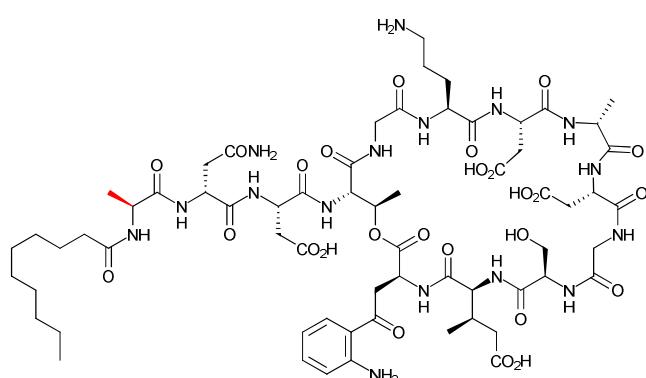
Zhou, N., Chen, S., Li, X.

ACS Med. Chem. Lett., 2020, DOI: 10.1021/acsmedchemlett.0c00175.



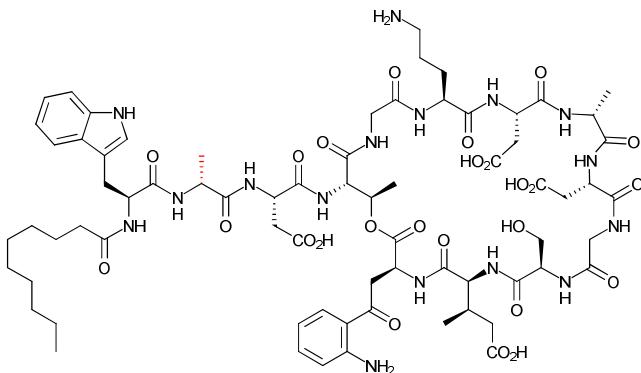
**298. Daptomycin, MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 0.5	MRSA SA14 = 0.5
MRSA SA86 = 0.5	MRSA SA88 = 0.25
SA ATCC29213 = 0.25	<i>S. faecalis</i> = 4
<i>Enterococc.</i> ET6 = 2	<i>Enterococc.</i> ET60 = 2
<i>Enterococc.</i> ATCC29212 = 4	



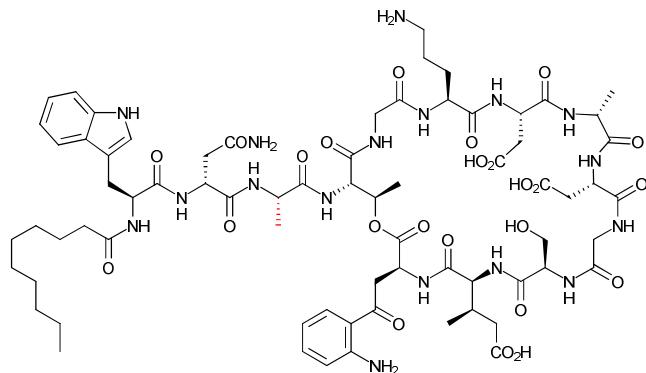
**299. L-Ala1 (1), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 $\geq$ 32	MRSA SA88 $\geq$ 32
SA ATCC29213 $\geq$ 32	<i>S. faecalis</i> $\geq$ 64
<i>Enterococc.</i> ET6 $\geq$ 64	<i>Enterococc.</i> ET60 $\geq$ 64
<i>Enterococc.</i> ATCC29212 $\geq$ 64	



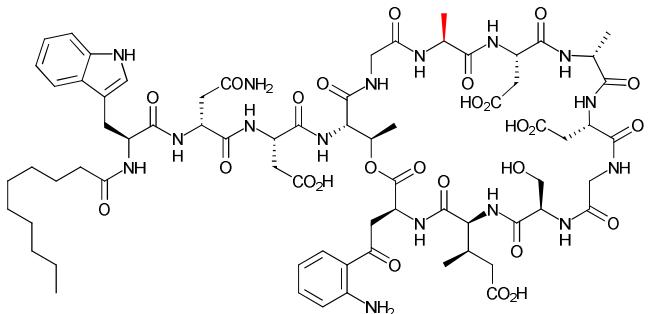
**300. D-Ala2 (2), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 $\geq$ 32	MRSA SA88 = 16
SA ATCC29213 $\geq$ 32	<i>S. faecalis</i> = 16
<i>Enterococc.</i> ET6 = 64	<i>Enterococc.</i> ET60 = 32
<i>Enterococc.</i> ATCC29212 = 64	



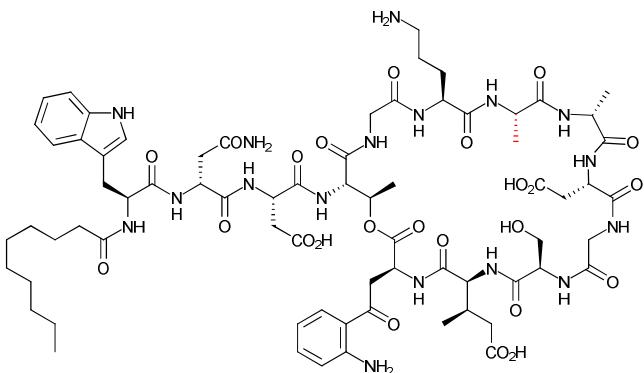
**301. L-Ala3 (3), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 = 16	MRSA SA88 = 16
SA ATCC29213 = 16	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 $\geq$ 32
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



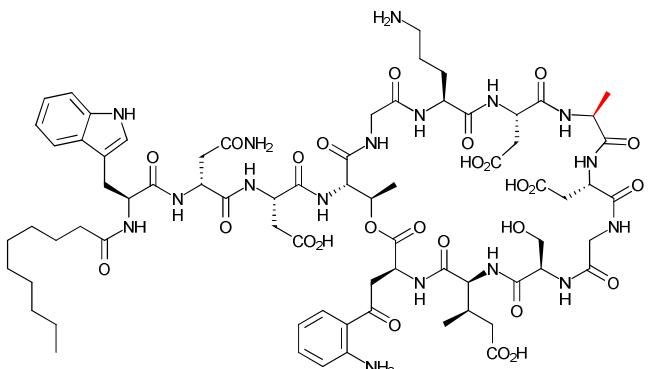
**302. L-Ala6 (4), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 0.5	MRSA SA14 = 0.25
MRSA SA86 = 0.5	MRSA SA88 = 1
SA ATCC29213 = 0.5	<i>S. faecalis</i> = 4
<i>Enterococc.</i> ET6 = 2	<i>Enterococc.</i> ET60 = 1
<i>Enterococc.</i> ATCC29212 = 4	



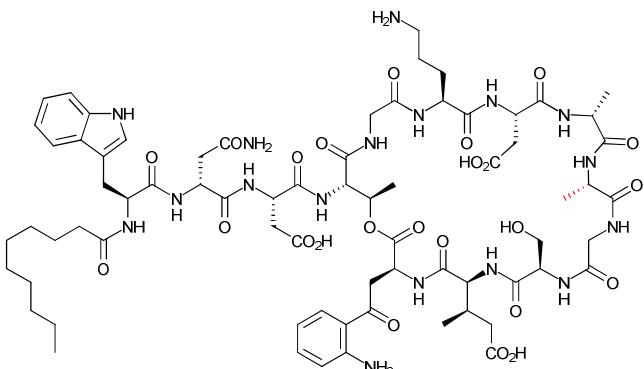
**303. L-Ala7 (5), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 64	MRSA SA14 $\geq$ 64
MRSA SA86 $\geq$ 64	MRSA SA88 $\geq$ 64
SA ATCC29213 $\geq$ 64	<i>S. faecalis</i> $\geq$ 64
<i>Enterococc.</i> ET6 $\geq$ 64	<i>Enterococc.</i> ET60 $\geq$ 64
<i>Enterococc.</i> ATCC29212 $\geq$ 64	



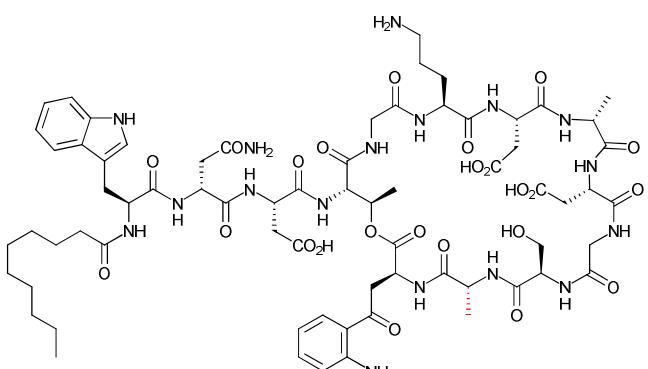
**304. L-Ala8 (6), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 64	MRSA SA14 $\geq$ 64
MRSA SA86 $\geq$ 64	MRSA SA88 $\geq$ 64
SA ATCC29213 $\geq$ 64	<i>S. faecalis</i> $\geq$ 64
<i>Enterococc.</i> ET6 $\geq$ 64	<i>Enterococc.</i> ET60 $\geq$ 64
<i>Enterococc.</i> ATCC29212 $\geq$ 64	



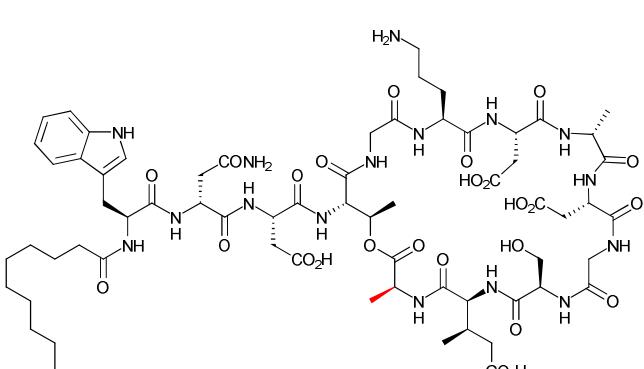
**305. L-Ala9 (7), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 64	MRSA SA14 $\geq$ 64
MRSA SA86 $\geq$ 64	MRSA SA88 $\geq$ 64
SA ATCC29213 $\geq$ 64	<i>S. faecalis</i> $\geq$ 64
<i>Enterococc.</i> ET6 $\geq$ 64	<i>Enterococc.</i> ET60 $\geq$ 64
<i>Enterococc.</i> ATCC29212 $\geq$ 64	



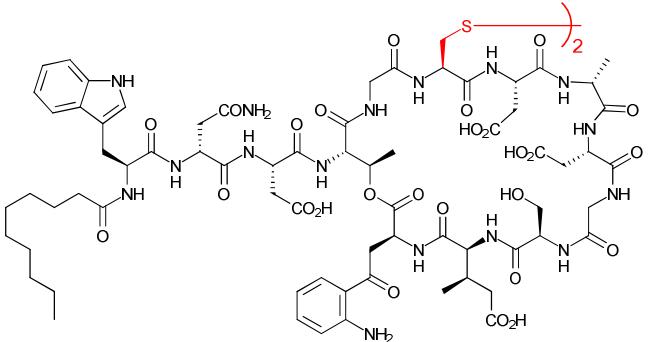
**306. L-Ala12 (8), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 64	MRSA SA14 $\geq$ 64
MRSA SA86 $\geq$ 64	MRSA SA88 $\geq$ 64
SA ATCC29213 $\geq$ 64	<i>S. faecalis</i> $\geq$ 64
<i>Enterococc.</i> ET6 $\geq$ 64	<i>Enterococc.</i> ET60 $\geq$ 64
<i>Enterococc.</i> ATCC29212 $\geq$ 64	



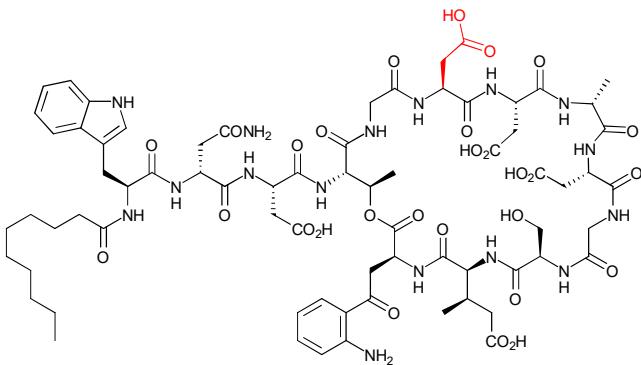
**307. L-Ala13 (9), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 $\geq$ 32	MRSA SA88 $\geq$ 32
SA ATCC29213 = 0.25	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 $\geq$ 32
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



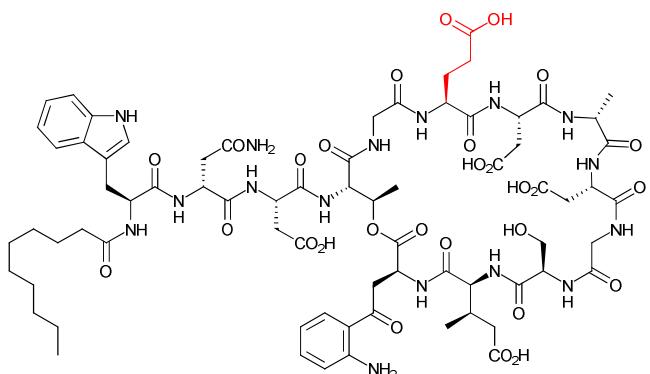
**308. L-Cys6 - dimer (10), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 8                    MRSA SA14 = 4  
 MRSA SA86 = 8                    MRSA SA88 = 16  
 SA ATCC29213 = 16              *S. faecalis* = 4  
*Enterococc.* ET6 = 16            *Enterococc.* ET60 = 16  
*Enterococc.* ATCC29212 = 16



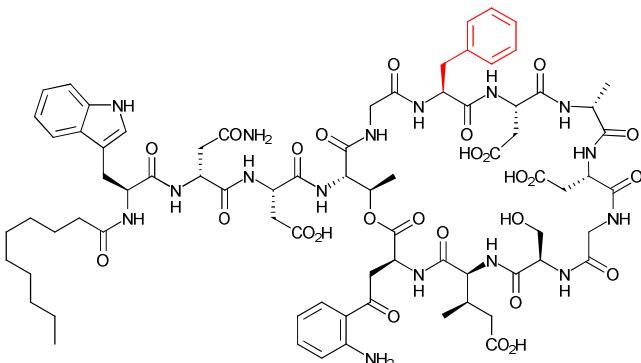
**309. L-Asp6 (11), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                MRSA SA14  $\geq$  32  
 MRSA SA86 = 16                MRSA SA88 = 8  
 SA ATCC29213 = 16            *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32            *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



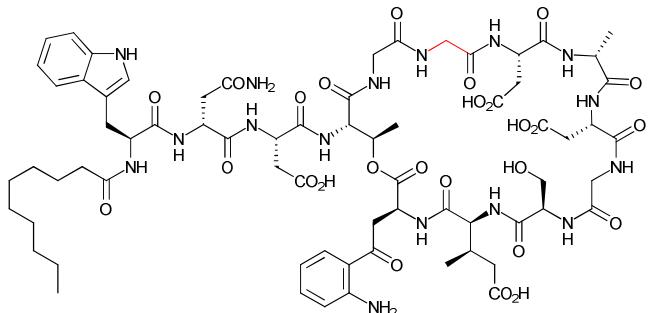
**310. L-Glu6 (12), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                MRSA SA88 = 16  
 SA ATCC29213 = 16              *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32            *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



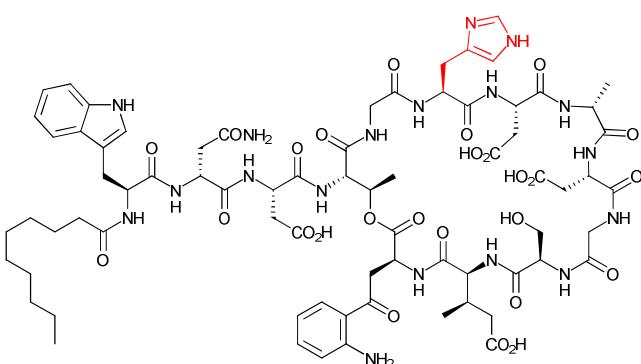
**311. L-Phe6 (13), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                MRSA SA14  $\geq$  32  
 MRSA SA86 = 16                MRSA SA88 = 16  
 SA ATCC29213 = 16            *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32            *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



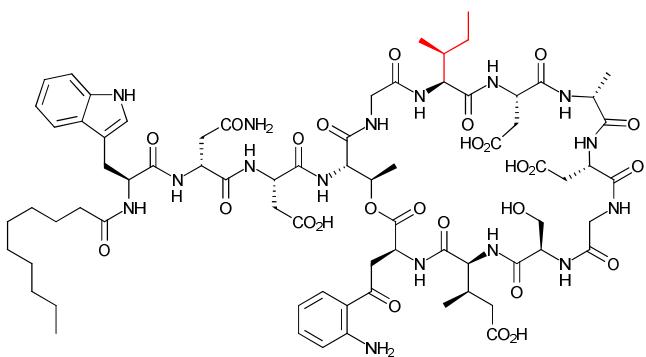
**312. Gly6 (14), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32            *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32            *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



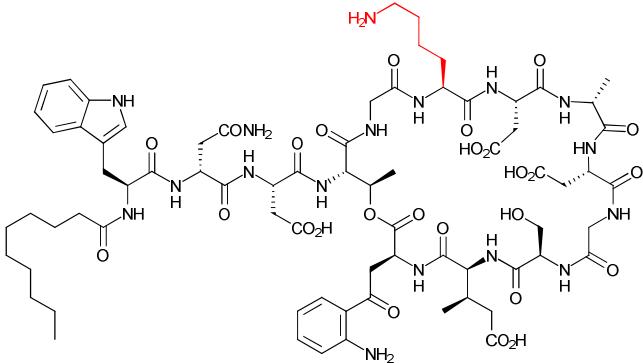
**313. L-His6 (15), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 16                MRSA SA14 = 16  
 MRSA SA86 = 8                MRSA SA88 = 8  
 SA ATCC29213 = 8            *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32            *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



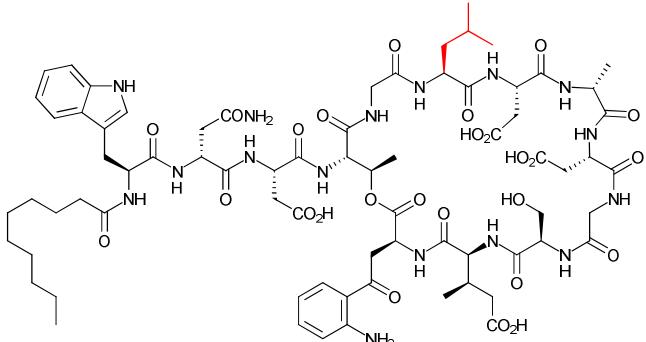
**314. L-Ile6 (16), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 = 8	MRSA SA88 = 4
SA ATCC29213 = 8	<i>S. faecalis</i> $\geq 64$
<i>Enterococc.</i> ET6 $\geq 64$	<i>Enterococc.</i> ET60 = 32
<i>Enterococc.</i> ATCC29212 $\geq 64$	



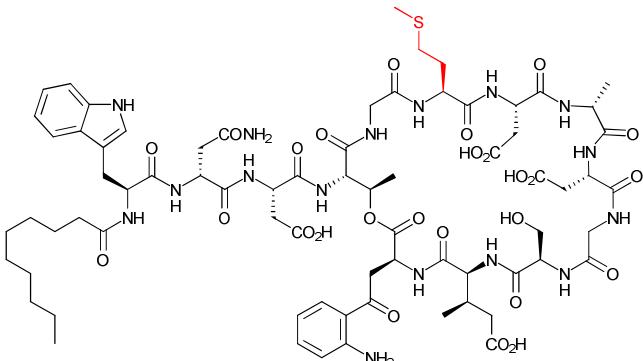
**315. L-Lys6 (17), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 16	MRSA SA14 $\geq 32$
MRSA SA86 = 1	MRSA SA88 = 1
SA ATCC29213 = 1	<i>S. faecalis</i> = 8
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 = 16
<i>Enterococc.</i> ATCC29212 $\geq 32$	



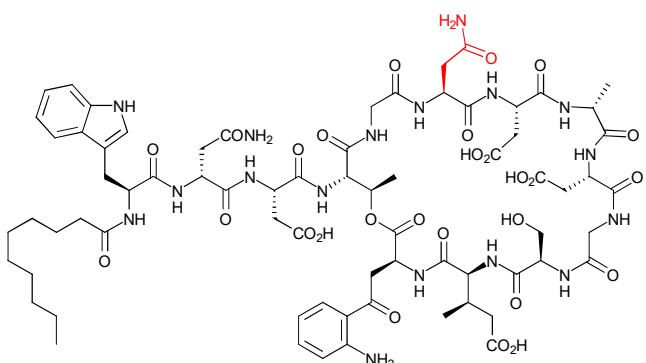
**316. L-Leu6 (18), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 1	MRSA SA14 = 0.5
MRSA SA86 = 4	MRSA SA88 = 2
SA ATCC29213 = 4	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 = 16
<i>Enterococc.</i> ATCC29212 $\geq 32$	



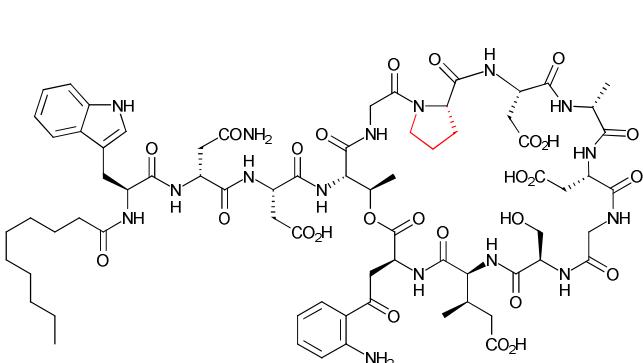
**317. L-Met6 (19), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 $\geq 32$	MRSA SA88 $\geq 32$
SA ATCC29213 $\geq 32$	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



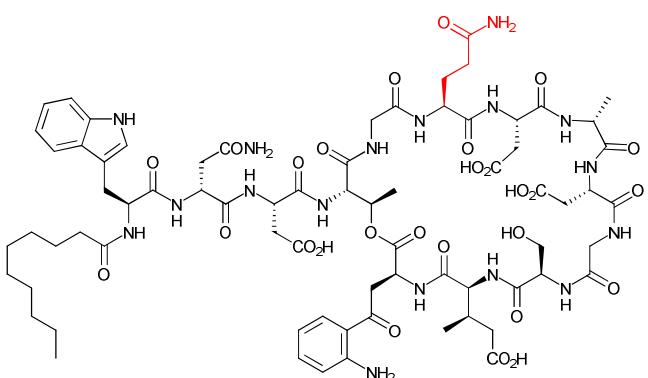
**318. L-Asn6 (20), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 $\geq 32$	MRSA SA88 $\geq 32$
SA ATCC29213 $\geq 32$	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



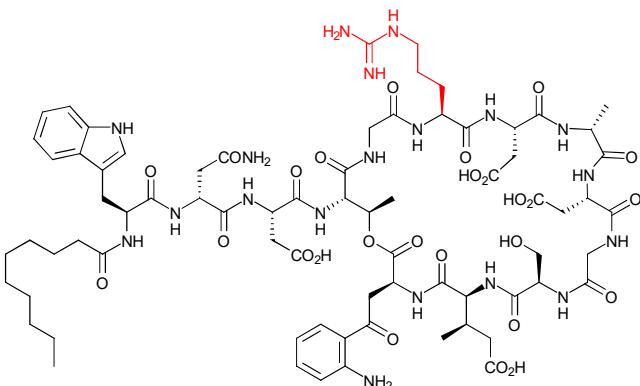
**319. L-Pro6 (21), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 $\geq 32$	MRSA SA88 $\geq 32$
SA ATCC29213 $\geq 32$	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



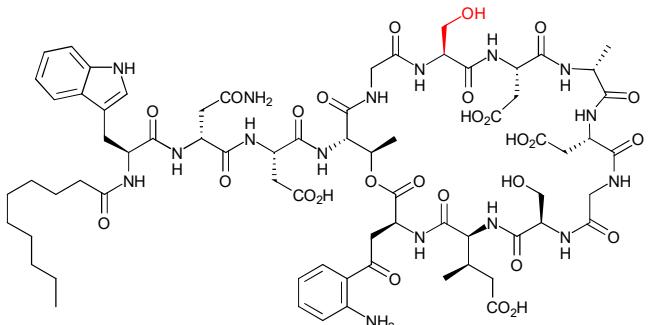
**320. L-Gln6 (22), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 = 4	MRSA SA88 = 4
SA ATCC29213 = 4	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



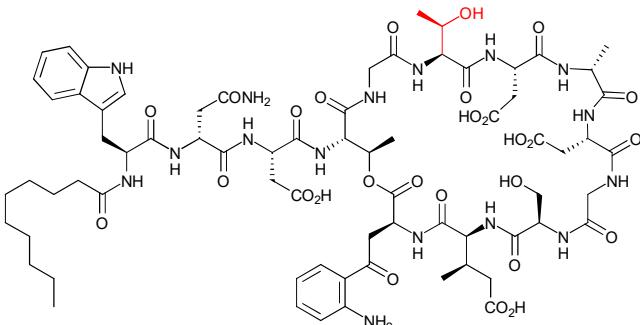
**321. L-Arg6 (23), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 8	MRSA SA14 = 16
MRSA SA86 = 2	MRSA SA88 = 1
SA ATCC29213 = 2	<i>S. faecalis</i> = 8
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 = 16
<i>Enterococc.</i> ATCC29212 $\geq 32$	



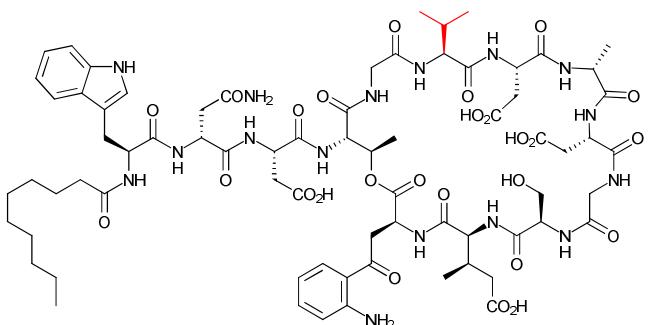
**322. L-Ser6 (24), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 4	MRSA SA14 = 4
MRSA SA86 = 2	MRSA SA88 = 1
SA ATCC29213 = 2	<i>S. faecalis</i> = 4
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



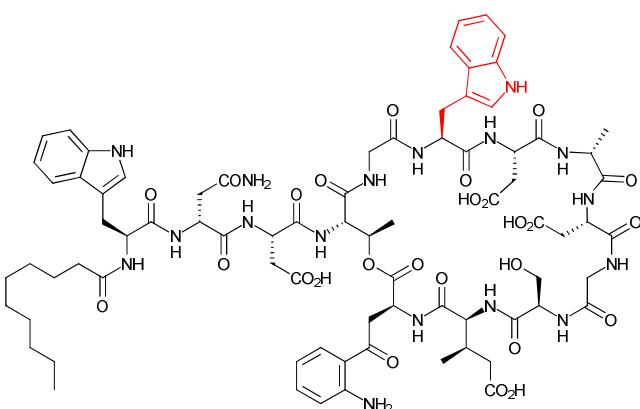
**323. L-Thr6 (25), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 16	MRSA SA14 = 16
MRSA SA86 = 2	MRSA SA88 = 2
SA ATCC29213 = 2	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



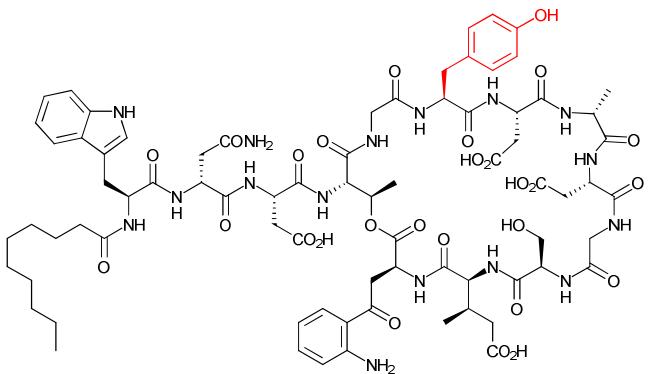
**324. L-Val6 (26), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq 32$	MRSA SA14 $\geq 32$
MRSA SA86 = 8	MRSA SA88 = 8
SA ATCC29213 = 8	<i>S. faecalis</i> $\geq 32$
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



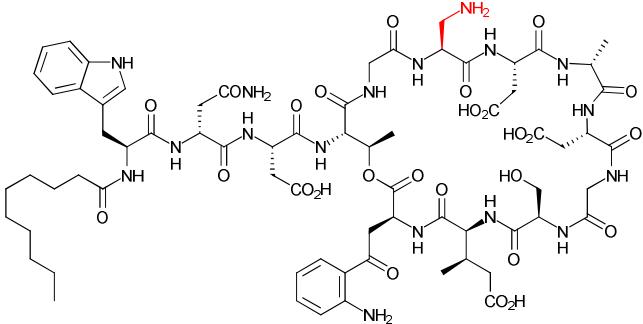
**325. L-Trp6 (27), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 2	MRSA SA14 = 1
MRSA SA86 = 4	MRSA SA88 = 2
SA ATCC29213 = 4	<i>S. faecalis</i> = 2
<i>Enterococc.</i> ET6 $\geq 32$	<i>Enterococc.</i> ET60 $\geq 32$
<i>Enterococc.</i> ATCC29212 $\geq 32$	



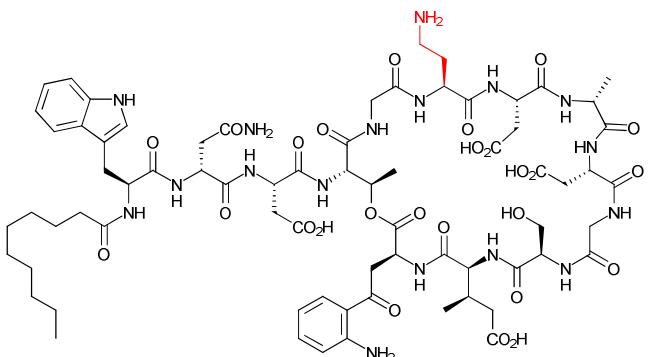
**326. L-Tyr6 (28), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 1	MRSA SA14 = 0.5
MRSA SA86 = 4	MRSA SA88 = 4
SA ATCC29213 = 1	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 = 16
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



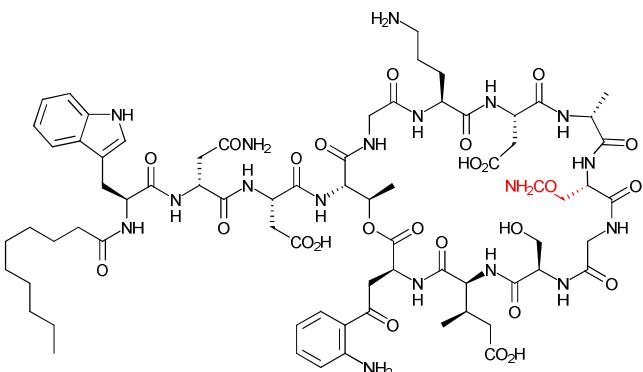
**327. L-Dap6 (29), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 8	MRSA SA14 = 1
MRSA SA86 = 1	MRSA SA88 = 0.5
SA ATCC29213 = 1	<i>S. faecalis</i> = ND
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 = 8
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



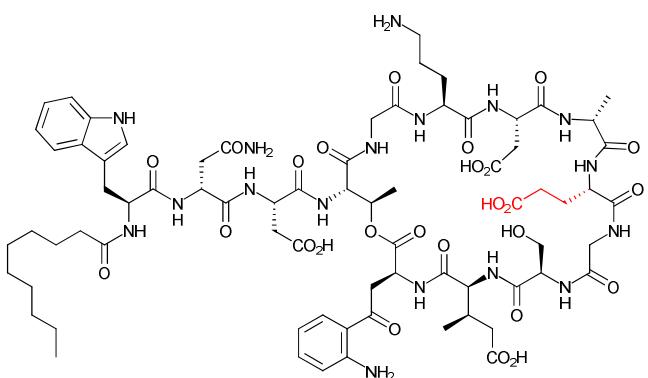
**328. L-Dab6 (30), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 2	MRSA SA14 = 0.5
MRSA SA86 = 0.25	MRSA SA88 = 0.25
SA ATCC29213 = 0.25	<i>S. faecalis</i> = ND
<i>Enterococc.</i> ET6 = 16	<i>Enterococc.</i> ET60 = 8
<i>Enterococc.</i> ATCC29212 = 16	



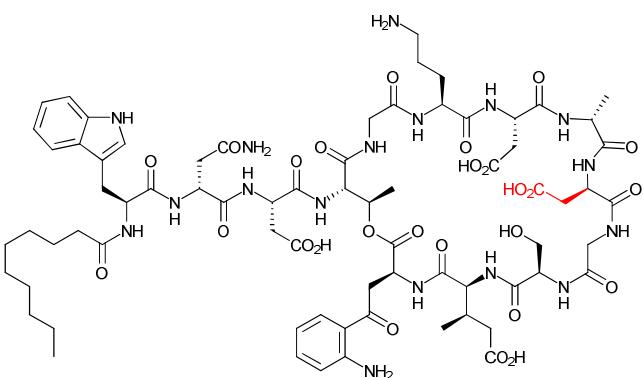
**329. L-Asn9 (31), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 = 32	MRSA SA88 = 16
SA ATCC29213 = 16	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 $\geq$ 32
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



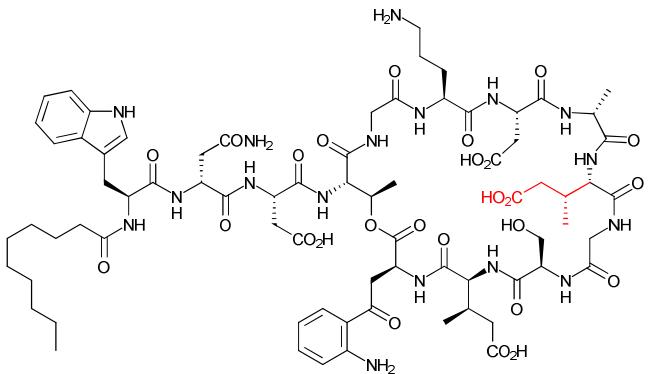
**330. L-Glu9 (32), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 $\geq$ 32	MRSA SA88 $\geq$ 32
SA ATCC29213 $\geq$ 32	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 $\geq$ 32
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



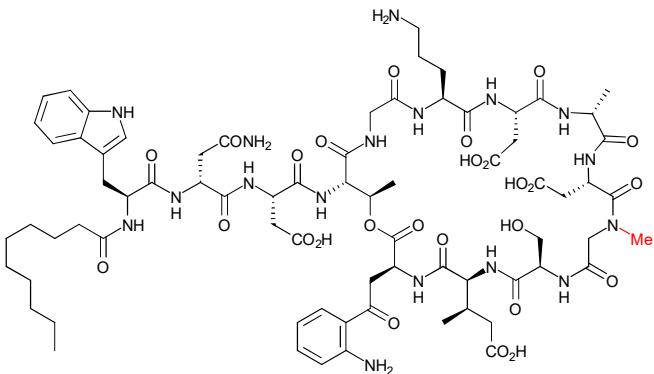
**331. D-Asp9 (33), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 $\geq$ 32	MRSA SA14 $\geq$ 32
MRSA SA86 = 16	MRSA SA88 = 16
SA ATCC29213 = 16	<i>S. faecalis</i> $\geq$ 32
<i>Enterococc.</i> ET6 $\geq$ 32	<i>Enterococc.</i> ET60 $\geq$ 32
<i>Enterococc.</i> ATCC29212 $\geq$ 32	



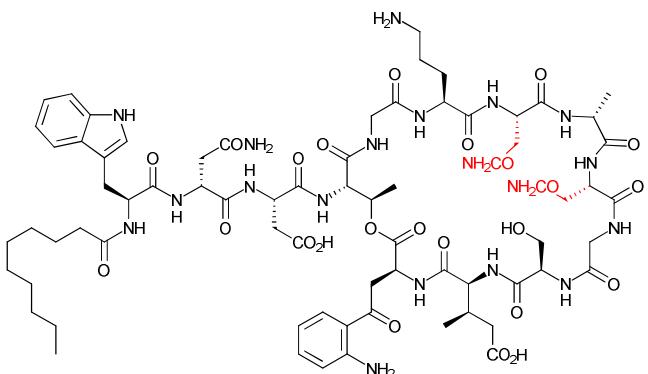
**332. (2S,3R)-MeGlu9 (34), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                    MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                    MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32                *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32              *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



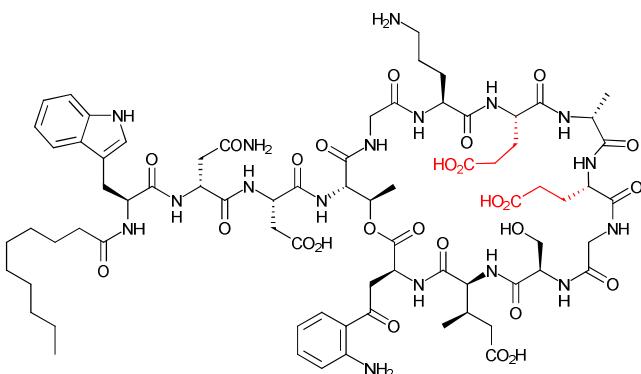
**333. Sar10 (35), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                    MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                    MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32                *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32              *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



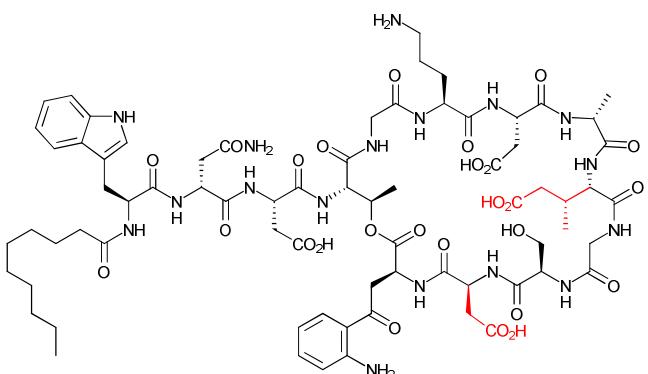
**334. L-Asn7, L-Asn9 (36), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                    MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                    MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32                *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32              *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



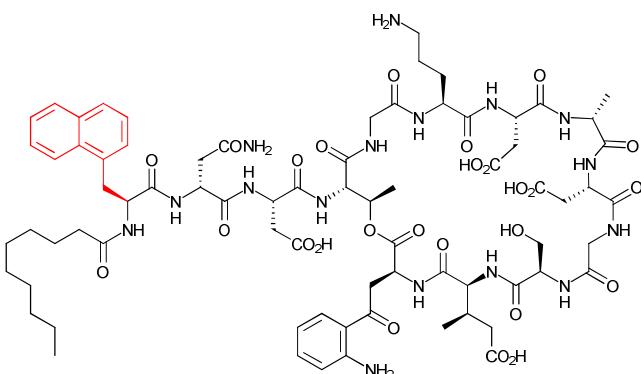
**335. L-Glu7, L-Glu9 (37), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                    MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                    MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32                *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32              *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



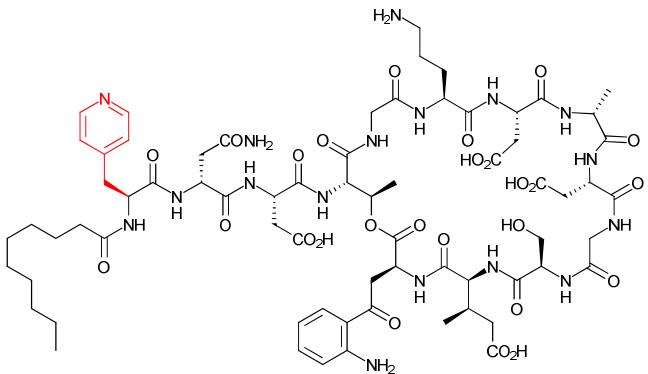
**336. (2S,3R)-MeGlu9, Asp12 (38), MIC ( $\mu\text{g/mL}$ )**

MRSA SA11  $\geq$  32                    MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32                    MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32                *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32              *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32

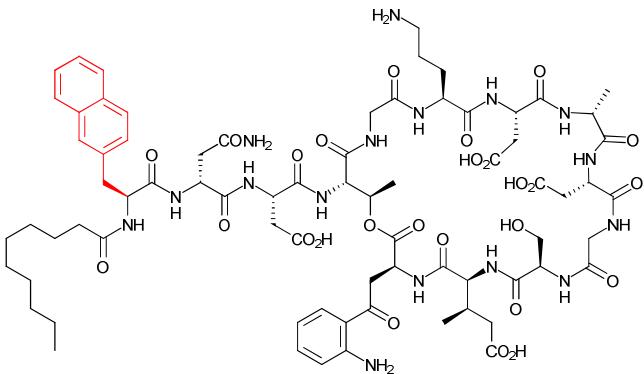


**337.  $\beta$ -(1-Naphthyl)-L-Ala1 (39), MIC ( $\mu\text{g/mL}$ )**

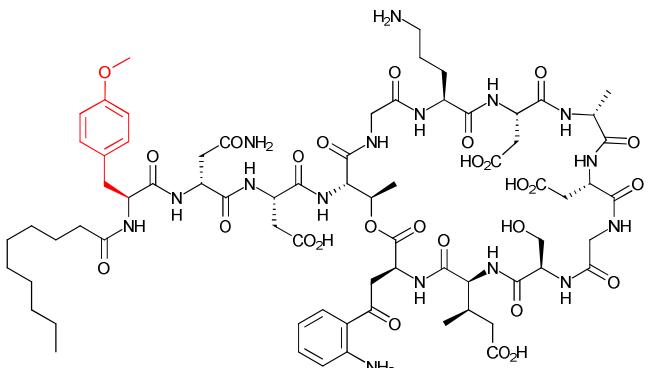
MRSA SA11 = 1                      MRSA SA14 = 0.25  
 MRSA SA86 = 0.25                MRSA SA88 = 0.125  
 SA ATCC29213 = 0.25            *S. faecalis* = 0.5  
*Enterococc.* ET6 = 2              *Enterococc.* ET60 = 2  
*Enterococc.* ATCC29212 = 2



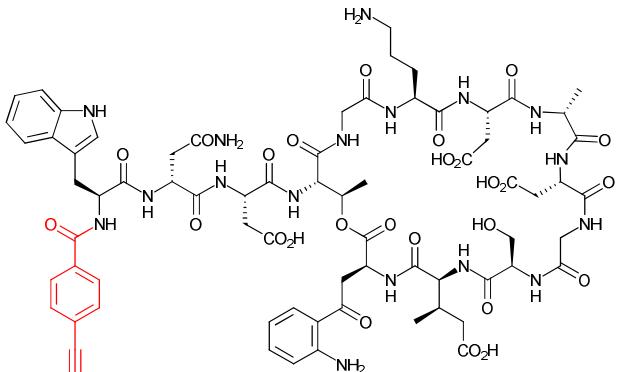
**338.  $\beta$ -(4-Pyridyl)-L-Ala1 (40), MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11  $\geq$  32      MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32      MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32      *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32      *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



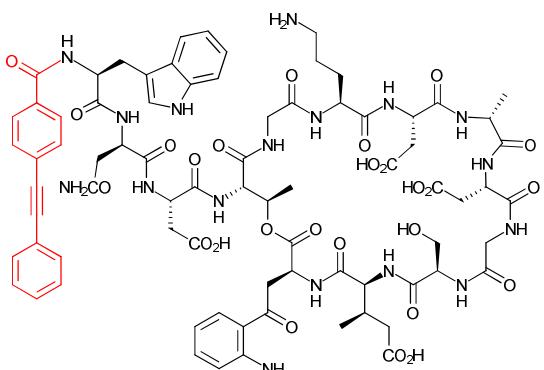
**339.  $\beta$ -(2-Naphthyl)-L-Ala1 (41), MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11 = 0.5      MRSA SA14 = 0.125  
 MRSA SA86 = 0.06      MRSA SA88 = 0.125  
 SA ATCC29213 = 0.25      *S. faecalis* = 0.25  
*Enterococc.* ET6 = 4      *Enterococc.* ET60 = 0.5  
*Enterococc.* ATCC29212 = 1



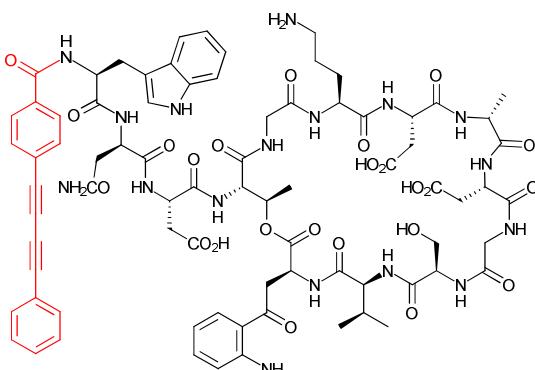
**340. TyrOMe1 (42), MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11 = 16      MRSA SA14 = 4  
 MRSA SA86 = 2      MRSA SA88 = 2  
 SA ATCC29213 = 2      *S. faecalis* = 8  
*Enterococc.* ET6  $\geq$  32      *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



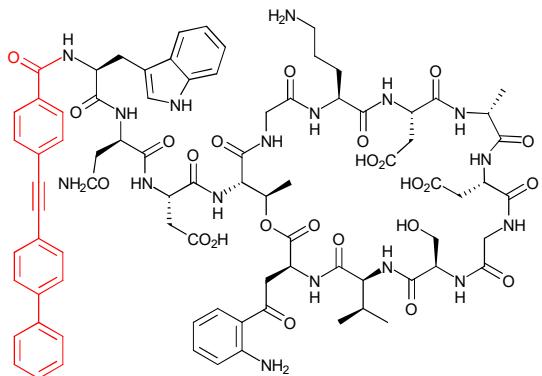
**341. Compound 43, MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11  $\geq$  32      MRSA SA14  $\geq$  32  
 MRSA SA86  $\geq$  32      MRSA SA88  $\geq$  32  
 SA ATCC29213  $\geq$  32      *S. faecalis*  $\geq$  32  
*Enterococc.* ET6  $\geq$  32      *Enterococc.* ET60  $\geq$  32  
*Enterococc.* ATCC29212  $\geq$  32



**342. Compound 44, MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11 = 0.25      MRSA SA14 = 0.5  
 MRSA SA86 = 0.5      MRSA SA88 = 0.5  
 SA ATCC29213 = 0.5      *S. faecalis* = 1  
*Enterococc.* ET6 = 8      *Enterococc.* ET60 = 2  
*Enterococc.* ATCC29212 = 8



**343. Compound 45, MIC ( $\mu\text{g/mL}$ )**  
 MRSA SA11 = 1      MRSA SA14 = 0.5  
 MRSA SA86 = 0.5      MRSA SA88 = 0.5  
 SA ATCC29213 = 0.5      *S. faecalis* = 1  
*Enterococc.* ET6 = 4      *Enterococc.* ET60 = 1  
*Enterococc.* ATCC29212 = 1



**344. Compound 46, MIC ( $\mu\text{g/mL}$ )**

MRSA SA11 = 1	MRSA SA14 = 1
MRSA SA86 = 2	MRSA SA88 = 1
SA ATCC29213 = 2	<i>S. faecalis</i> = 2
<i>Enterococc.</i> ET6 = 0.5	<i>Enterococc.</i> ET60 = 2
<i>Enterococc.</i> ATCC29212 = 0.5	