endothelial and fibroblast cells, leading to the progression of inflammation and mucus secretion. Eosinophils are therefore potent activators and modulators of diseases such as bronchial asthma, atopic dermatitis, and colitis ulcerosa. *See* Hogan SP, *Int Arch Allergy Immunol*. 2007, 143(Suppl 1):3-14; Simon D et al., *Allergy*. 2004, 59:561-570; Wedemeyer J & Vosskuhle K., *Best Pract Res Clin Gastroenterol*. 2008, 22:537-549. Further, in asthmatics, levels of eosinophil granule proteins such as eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO) largely correlate with asthma severity. *See* Parra A, et al., *J Investig Allergol Clin Immunol*. 1999; 9:27-34. Eosinophilic inflammation of the upper airways may also occur independent of allergy, as observed in chronic rhinosinusitis (CRS) subjects. *See* Hutcheson PS, et al., *J Rhinol Allergy*. 2010, 24:405-408. Such individuals represent a unique subgroup who are largely resistant to medical and surgical interventions and who could show immediate benefit by therapy that targets eosinophilic expansion and effector functions.

BRIEF SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a lipopeptide, comprising:

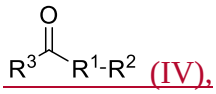
alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[(4-Hydroxy-2-pyrrolidinyl)carbonyl]-5-methyl-3-pyrrolin-2-one, or

alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[4-hydroxypyrrolidine-2-carbonyl]-1*H*-[pyrrole-2,5-dione], or

alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[pyrrolidine-2-carbonyl]-1*H*-[pyrrole-2,5-dione],

or a salt thereof, including any isomers of the foregoing.

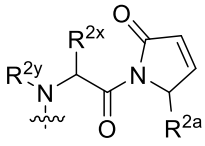
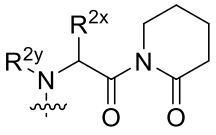
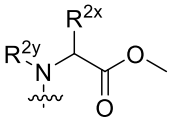
[0005b] In another aspect of the present disclosure, there is provided a lipopeptide of formula (IV):



(IV),

or a salt thereof, including any isomers of the foregoing, wherein:

R^1 is at least one optionally substituted amino acid moiety;

R^2 is ,  or , wherein

R^{2a} is H, oxo or optionally substituted alkyl;

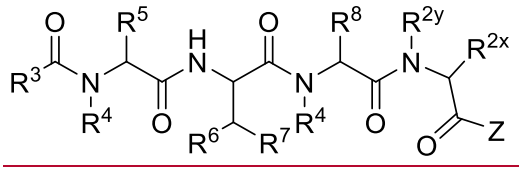
R^{2x} is alkyl, optionally substituted with –OH or –COOH;

R^{2y} is H or alkyl; or

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form an optionally substituted 5-membered heterocycle; and

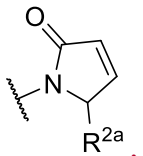
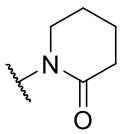
R^3 is alkenyl.

[0005c] In a further aspect of the present disclosure, there is provided a lipopeptide of formula (IV-A):



(IV-A),

or a salt thereof, including any isomers of the foregoing, wherein:

Z is ,  or alkoxy, wherein

R^{2a} is H, oxo or optionally substituted alkyl;

R^{2x} is alkyl, optionally substituted with –OH or –COOH;

R^{2y} is H or alkyl; or

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form an optionally substituted 5-membered heterocycle;

R^3 is alkenyl;

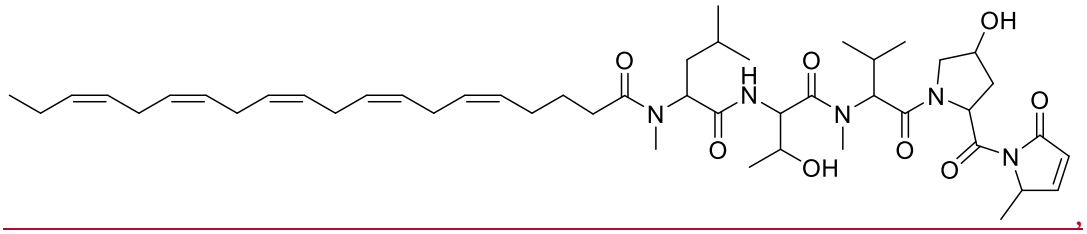
R^4 is H or alkyl;

each R^5 and R^8 is independently a hydrophobic side chain of Ala, Val, Ile, Leu, Met, Phe, Tyr, Trp, or Gly, wherein the hydrophobic side chain is optionally substituted;

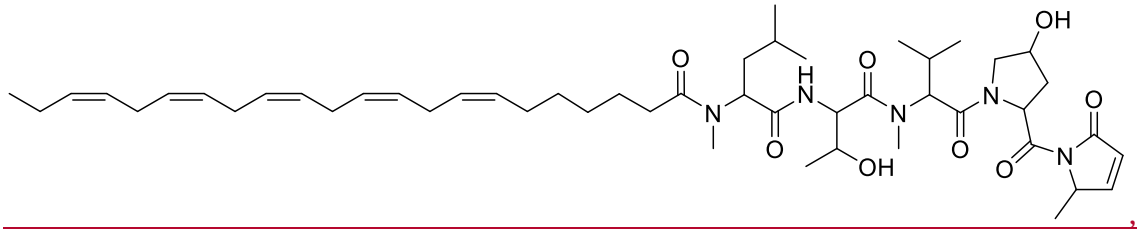
R^6 is H or alkyl; and

R^7 is –OH, –O(C=O)alkyl, –SH, or –S(C=O)alkyl.

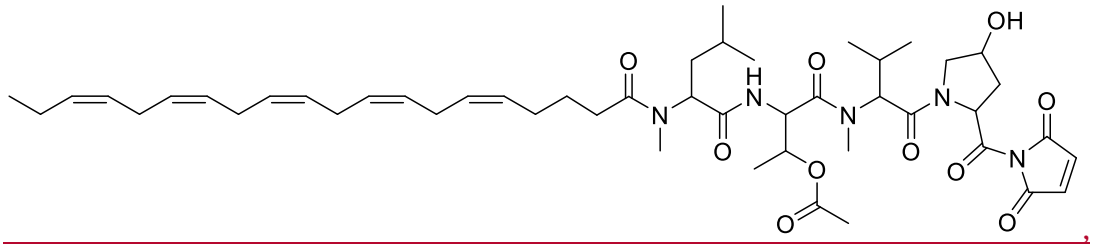
[0005d] In another aspect of the present disclosure, there is provided a lipopeptide, wherein the lipopeptide is:



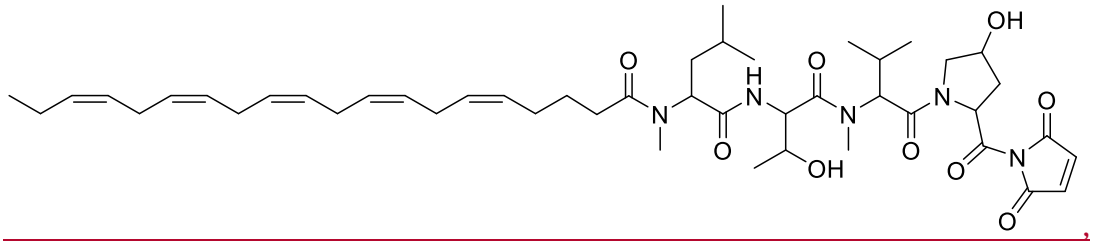
,



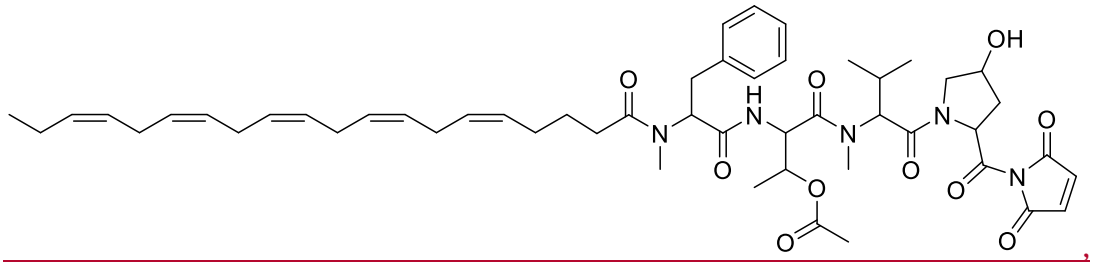
,

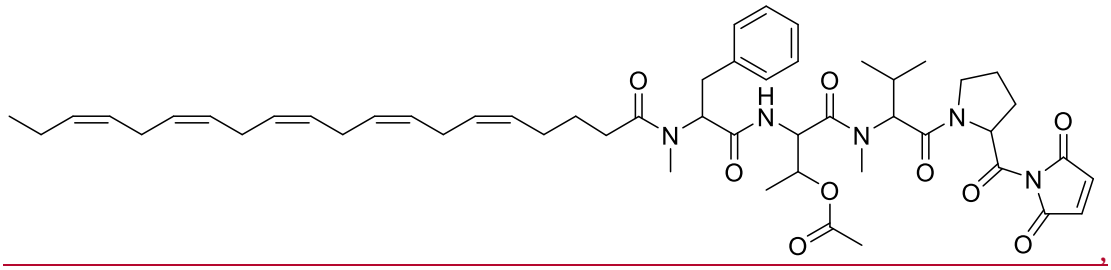


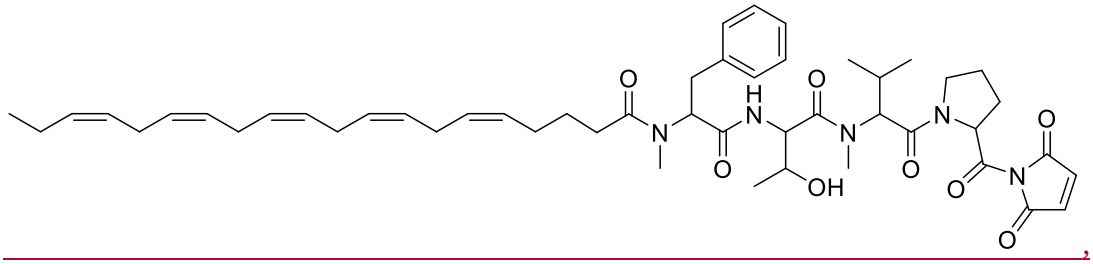
,

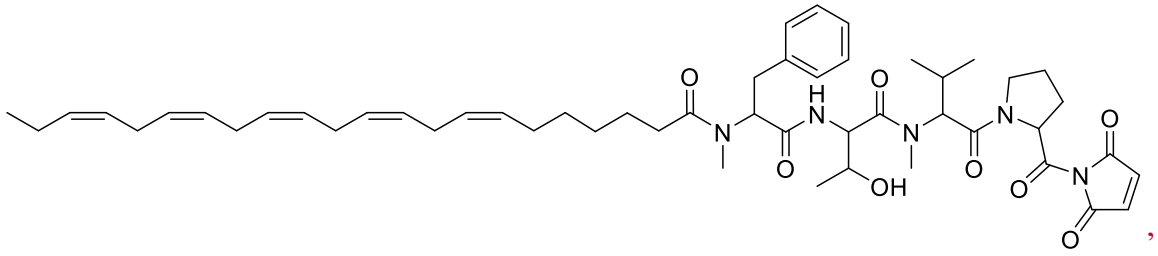


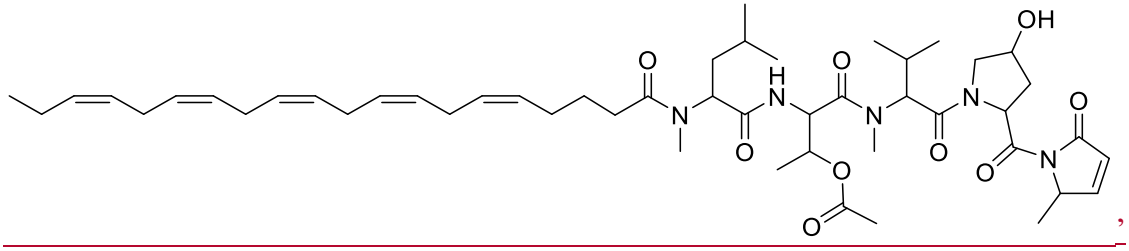
,


,


,

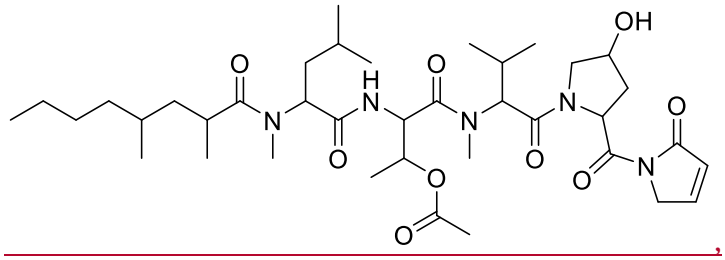

,


,

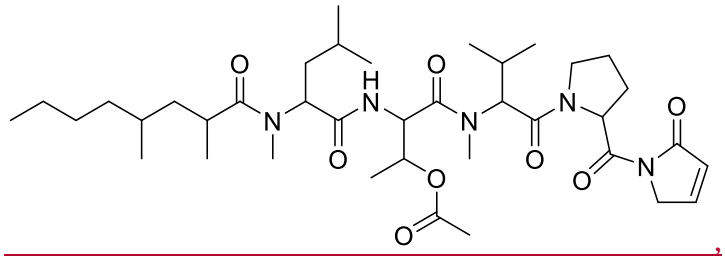

,

or a salt thereof, including any isomers of the foregoing.

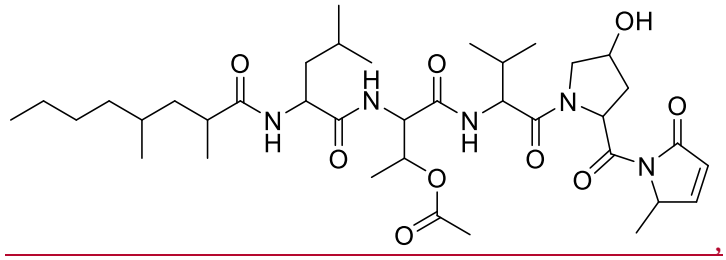
[0005e] In a further aspect of the present disclosure, there is provided a lipopeptide, wherein the lipopeptide is:



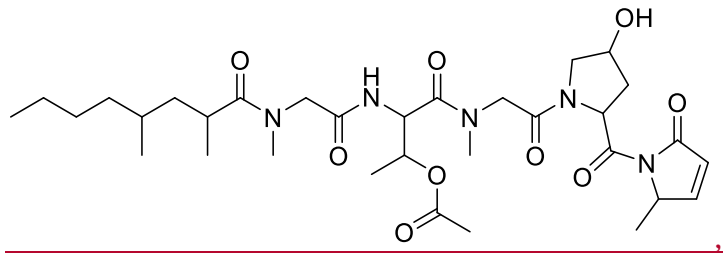
,



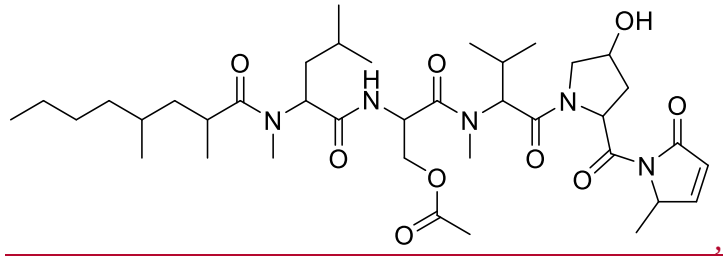
,



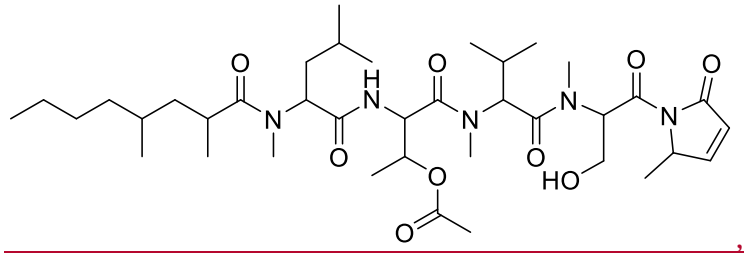
,



,

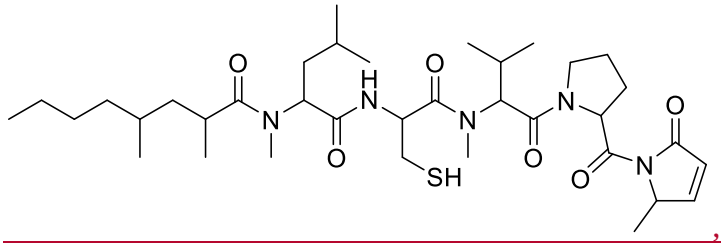


,

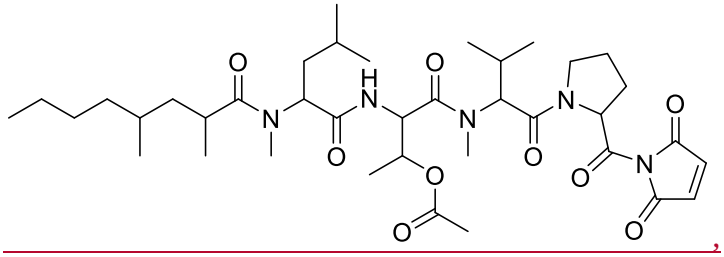


,

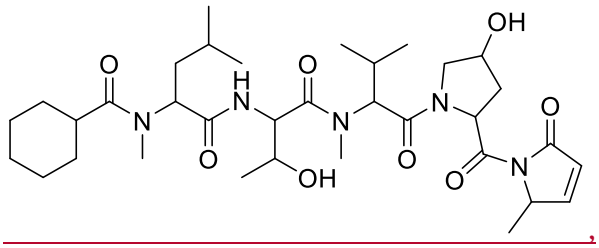
2d



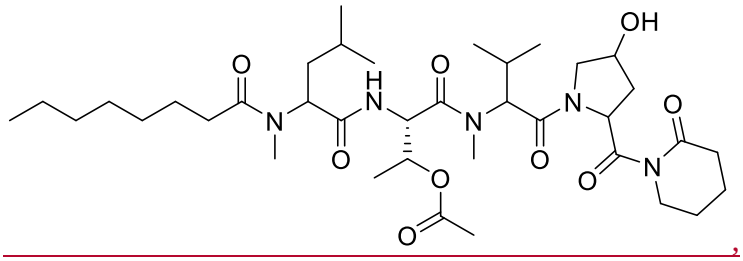
,



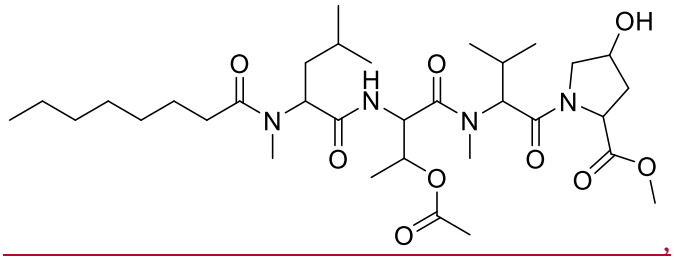
,



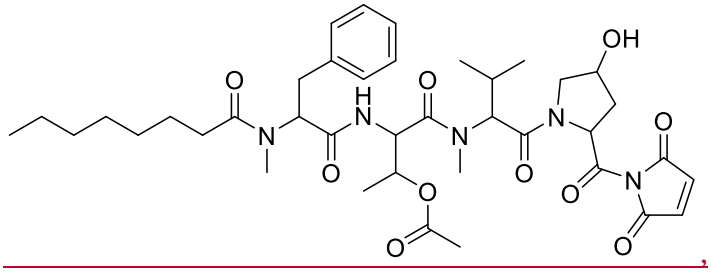
,



,

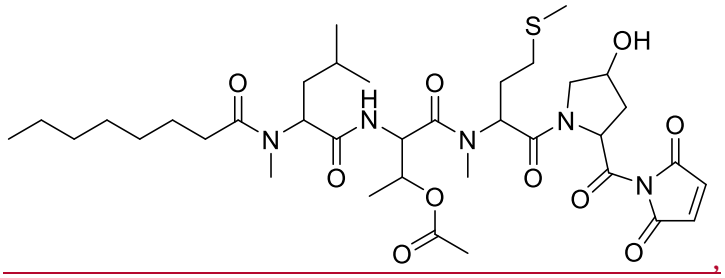


,

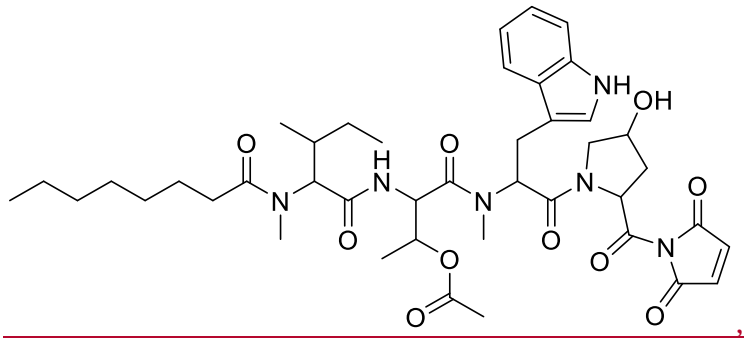


,

2e



,



,

or a salt thereof, including any isomers of the foregoing.

[0005f] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising at least one lipopeptide disclosed herein, and at least one pharmaceutically acceptable excipient.

[0005g] In a further aspect of the present disclosure, there is provided a use of a composition comprising at least one lipopeptide disclosed herein, in the manufacture of a medicament for treating an eosinophilic inflammatory condition, disorder or disease in a human in need thereof.

[0005h] In another aspect of the present disclosure, there is provided a use of a composition comprising at least one lipopeptide disclosed herein, in the manufacture of a medicament for treating an eosinophilic respiratory condition, disorder or disease in a human in need thereof.

[0005i] In a further aspect of the present disclosure, there is provided a use of a salmonid oil composition or a composition comprising at least one lipopeptide disclosed herein, in the manufacture of a medicament for reducing eosinophil effector function in a human in need thereof.

[0005j] In another aspect of the present disclosure, there is provided an article of manufacture, comprising:

a container comprising a composition comprising at least one lipopeptide disclosed herein; and

a label containing instructions for use of such composition.

[0005k] In a further aspect of the present disclosure, there is provided a kit, comprising:

a dosage form of a composition comprising a composition comprising at least one lipopeptide disclosed herein; and

a package insert containing instructions for use of such composition.

[0005l] In another aspect of the present disclosure, there is provided a salmonid oil composition or a composition comprising at least one lipopeptide disclosed herein, for use in therapy.

[0006] In some ~~aspect~~examples, provided herein respiratory treatments, such as asthma treatments, using lipopeptides. In some ~~embodiment~~examples, the lipopeptides are microcolins, and structural analogues thereof. In some variations, microcolin A or microcolin B, or a combination thereof, is administered in the respiratory treatments.

[0007] In some ~~embodiment~~examples, the asthma is bronchial asthma. In certain ~~embodiment~~examples, the treatments provided target a subgroup of patients (*e.g.*, asthma patients) that are largely resistant to medical and surgical interventions, including steroid therapies.

[0008] In certain ~~aspect~~examples, provided is a method for treating an inflammatory condition, disorder or disease in a human in need thereof, comprising: orally administering to the human an effective dose of a composition comprising at least one lipopeptide, including for example, at least one microcolin, or structural analogues thereof, to treat the inflammatory condition, disorder or disease.

[0009] In certain ~~aspect~~examples, provided is a method for treating a respiratory condition, disorder or disease in a human in need thereof, comprising: orally administering to the human an effective dose a composition comprising at least one lipopeptide, including for example, at least one microcolin, or structural analogues thereof, to treat the respiratory condition, disorder or disease.

[0010] In certain ~~aspect~~examples, provided is a method for reducing eosinophil effector function in a human in need thereof, comprising administering to the human a composition comprising at least one lipopeptide, including for example, at least one microcolin, or structural analogues thereof, to reduce eosinophil effector function.

[0011] In other ~~aspect~~examples, provided is an article of manufacture, comprising: a container comprising a composition comprising at least one lipopeptide, including for example, at least one microcolin, or structural analogues thereof; and a label containing instructions for use of such composition.

[0012] In yet other ~~aspect~~examples, provided is a kit, comprising: a dosage form of a composition comprising at least one lipopeptide, including for example, at least one microcolin, or structural analogues thereof; and a package insert containing instructions for use of such composition.

[0013] In some variations of the foregoing ~~aspect~~examples, the dosage form is a syrup, chewable, capsule or soft gel. In other variations, the compositions provided herein are formulated for aerosol delivery.

DETAILED DESCRIPTION

[0014] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0015] In some aspects, provided herein are methods for treating inflammatory conditions, disorders or diseases in humans in need thereof by orally administering a composition comprising at least one lipopeptide.

[0016] In some embodiments, the lipopeptide is microcolin. In one embodiment, the lipopeptide is microcolin A. In other embodiments, the lipopeptide is [2,4-alkylsubstituted octanoyl]-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[(4-hydroxy-2-pyrrolidinyl)carbonyl]-5-methyl-3-pyrrolin-2-one.

CLAIMS

What is claimed is:

1. A lipopeptide, comprising:

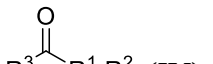
alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[(4-Hydroxy-2-pyrrolidinyl)carbonyl]-5-methyl-3-pyrrolin-2-one, or

alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[4-hydroxypyrrolidine-2-carbonyl]-1*H*-[pyrrole-2,5-dione], or

alkenyl-[N-methyl aminoacid with hydrophobic side chain]-[aminoacid with polar uncharged sidechain]-[N-methyl aminoacid with hydrophobic side chain]-N-[pyrrolidine-2-carbonyl]-1*H*-[pyrrole-2,5-dione],

or a salt thereof, including any isomers of the foregoing.

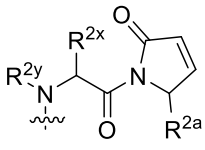
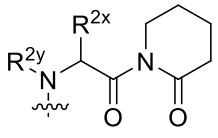
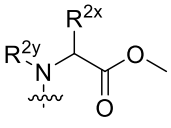
2. A lipopeptide of formula (IV):



(IV),

or a salt thereof, including any isomers of the foregoing, wherein:

R^1 is at least one optionally substituted amino acid moiety;

R^2 is ,  or , wherein

R^{2a} is H, oxo or optionally substituted alkyl;

R^{2x} is alkyl, optionally substituted with –OH or –COOH;

R^{2y} is H or alkyl; or

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form an optionally substituted 5-membered heterocycle; and

R^3 is alkenyl.

3. The lipopeptide of claim 2, or a salt thereof, including any isomers of the foregoing, wherein R^1 is a sequence of three optionally substituted amino acid moieties.

4. The lipopeptide of claim 2, or a salt thereof, including any isomers of the foregoing, wherein R^1 is $–R^{1a}\text{-}R^{1b}\text{-}R^{1c}–$, wherein:

R^{1a} is an optionally substituted amino acid moiety with a hydrophobic side chain;

R^{1b} is an optionally substituted amino acid moiety with a polar uncharged side chain; and

R^{1c} is an optionally substituted amino acid moiety with a hydrophobic side chain.

5. The lipopeptide of claim 2, or a salt thereof, including any isomers of the foregoing, wherein R^1 is $–R^{1a}\text{-}R^{1b}\text{-}R^{1c}–$, wherein:

R^{1a} is an optionally substituted Leu or Phe;

R^{1b} is optionally substituted Thr; and

R^{1c} is is optionally substituted Val.

6. The lipopeptide of claim 2, wherein R^1 is:

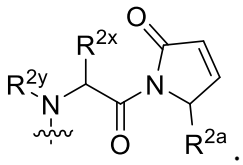
Leu-Thr-Val, wherein each Leu and Val is N-methylated;

Leu-OAcThr-Val, wherein each Leu and Val is N-methylated;

Phe-OAcThr-Val, wherein each Phe and Val is N-methylated; or

Phe-Thr-Val, wherein each Phe and Val is N-methylated.

7. The lipopeptide of any one of claims 1 to 6, or a salt thereof, including any isomers of the foregoing, wherein:

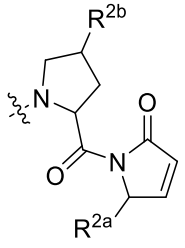
R^2 is 

.

8. The lipopeptide of claim 7, or a salt thereof, including any isomers of the foregoing, wherein:

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form an optionally substituted 5-membered heterocycle.

9. The lipopeptide of any one of claims 1 to 8, or a salt thereof, including any isomers of the foregoing, wherein:

R^2 is  .

10. The lipopeptide of claim 9, or a salt thereof, including any isomers of the foregoing, wherein:

R^{2b} is H or OH.

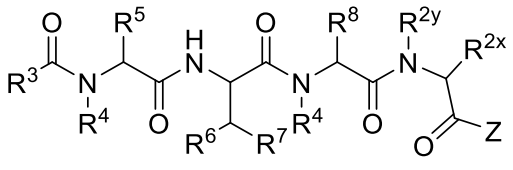
11. The lipopeptide of any one of claims 2 to 10, or a salt thereof, including any isomers of the foregoing, wherein:

R^{2a} is alkyl or oxo.

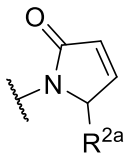
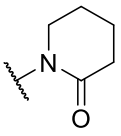
12. The lipopeptide of any one of claims 2 to 11, or a salt thereof, including any isomers of the foregoing, wherein:

R^3 is C_2-C_{30} alkenyl.

13. A lipopeptide of formula (IV-A):

 (IV-A),

or a salt thereof, including any isomers of the foregoing, wherein:

Z is ,  or alkoxy, wherein

R^{2a} is H, oxo or optionally substituted alkyl;

R^{2x} is alkyl, optionally substituted with –OH or –COOH;

R^{2y} is H or alkyl; or

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form an optionally substituted 5-membered heterocycle;

R^3 is alkenyl;

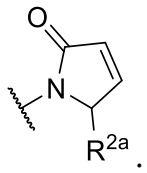
R^4 is H or alkyl;

each R^5 and R^8 is independently a hydrophobic side chain of Ala, Val, Ile, Leu, Met, Phe, Tyr, Trp, or Gly, wherein the hydrophobic side chain is optionally substituted;

R^6 is H or alkyl; and

R^7 is –OH, –O(C=O)alkyl, –SH, or –S(C=O)alkyl.

14. The lipopeptide of claim 13, or a salt thereof, including any isomers of the foregoing, wherein:

Z is 

.

15. The lipopeptide of claim 14, or a salt thereof, including any isomers of the foregoing, wherein:

R^{2a} is alkyl or oxo.

16. The lipopeptide of any one of claims 13 to 15, or a salt thereof, including any isomers of the foregoing, wherein:

R^{2x} and R^{2y} are taken together with the atoms to which they are attached to form 5-membered heterocycle substituted with –OH.

17. The lipopeptide of any one of claims 13 to 16, or a salt thereof, including any isomers of the foregoing, wherein:

R^3 is C_2-C_{30} alkenyl.

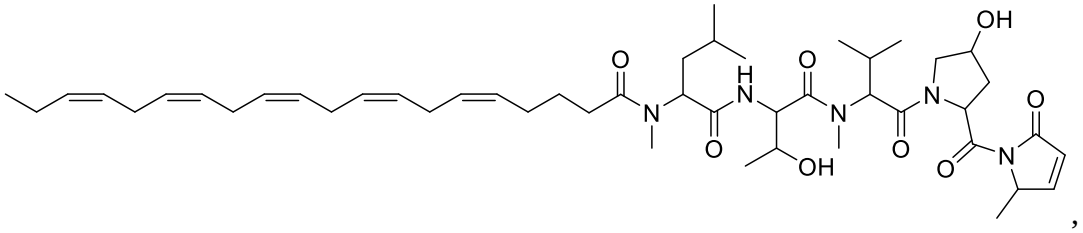
18. The lipopeptide of any one of claims 13 to 17, or a salt thereof, including any isomers of the foregoing, wherein:

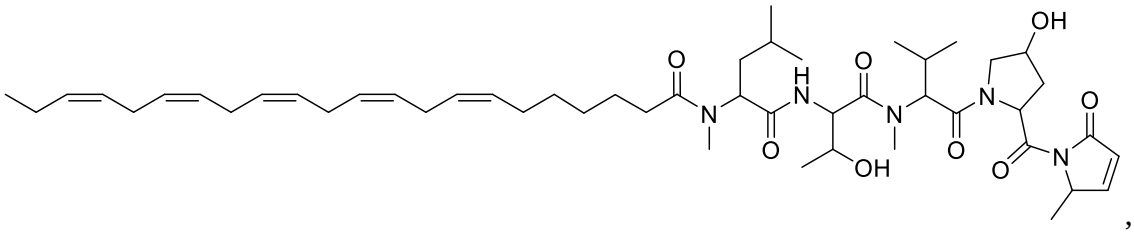
R^5 is the hydrophobic side chain of Leu or Phe.

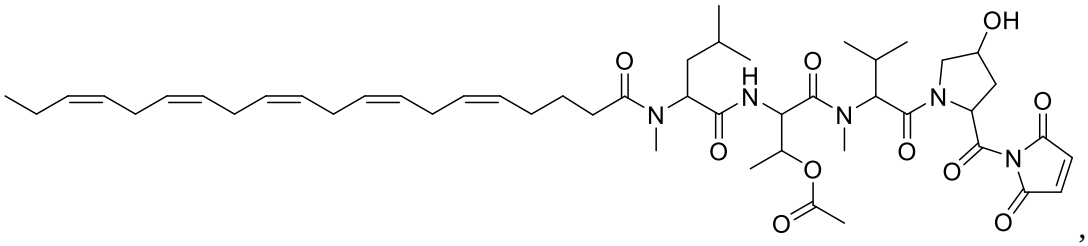
19. The lipopeptide of any one of claims 13 to 18, or a salt thereof, including any isomers of the foregoing, wherein:

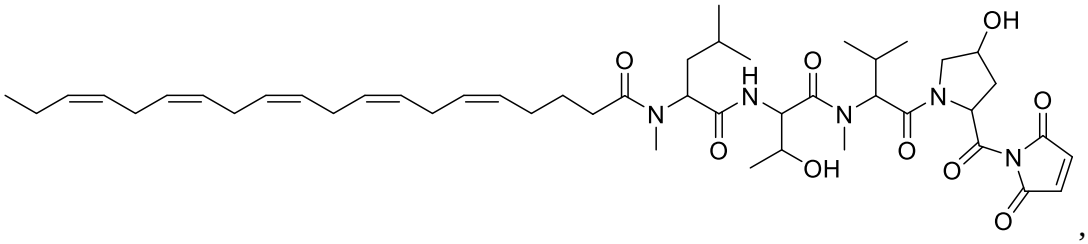
R^7 is –OH, –O(C=O)CH_3, –SH, or –S(C=O)CH_3.

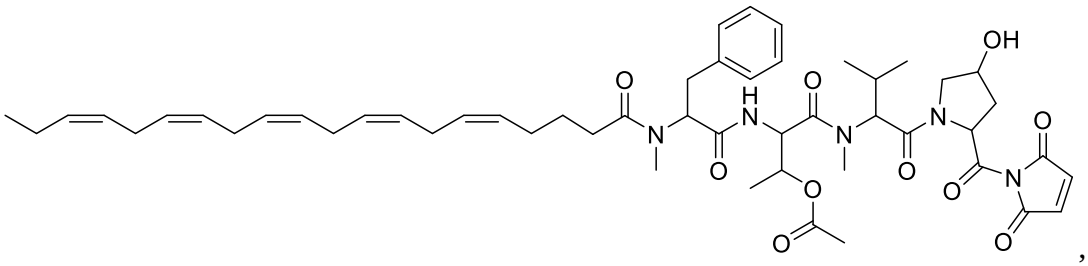
20. A lipopeptide, wherein the lipopeptide is:

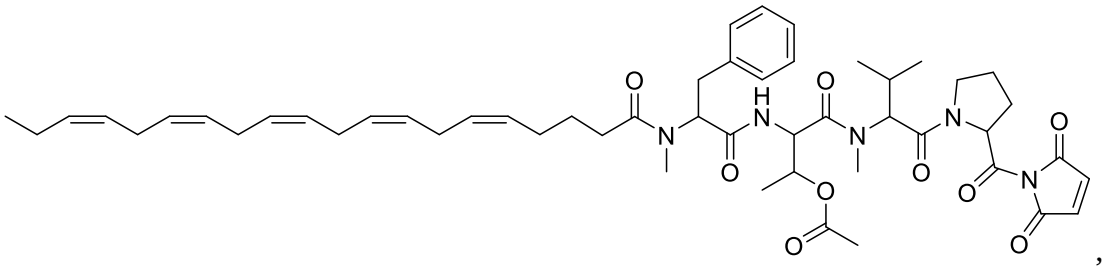

,

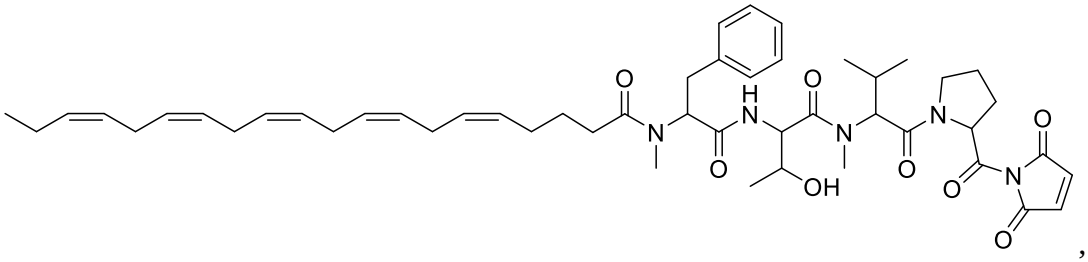

,

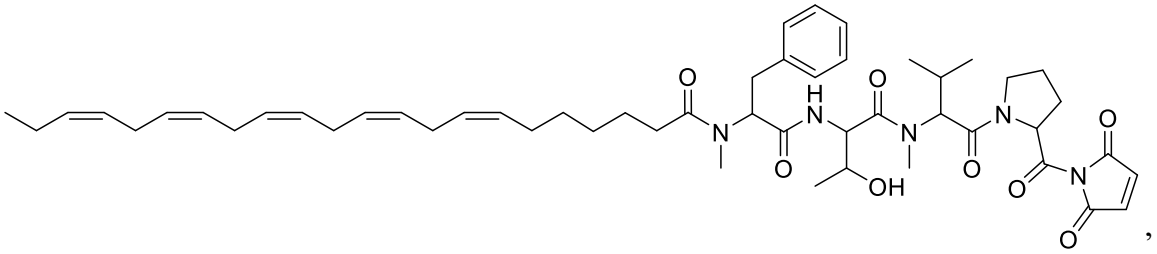

,

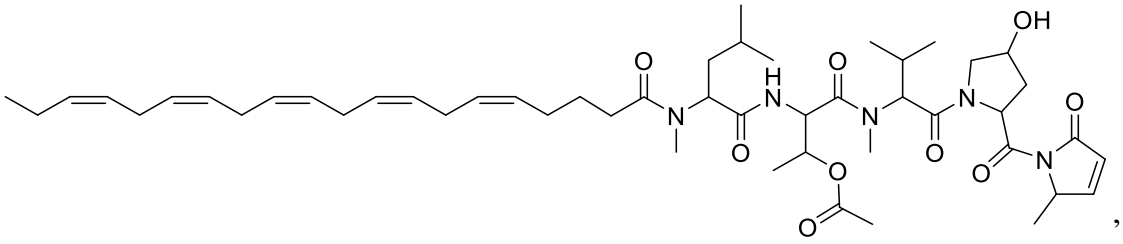

,


,


,

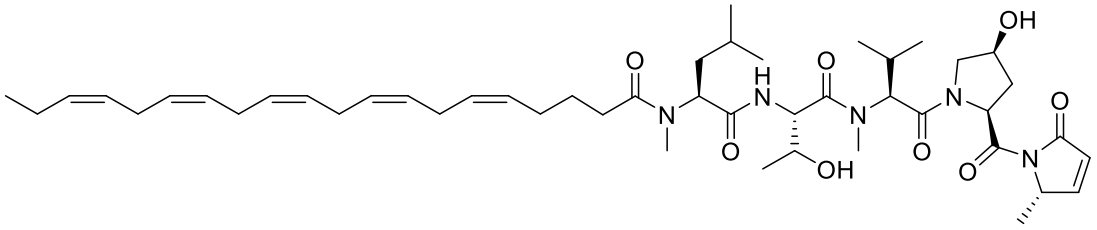

,

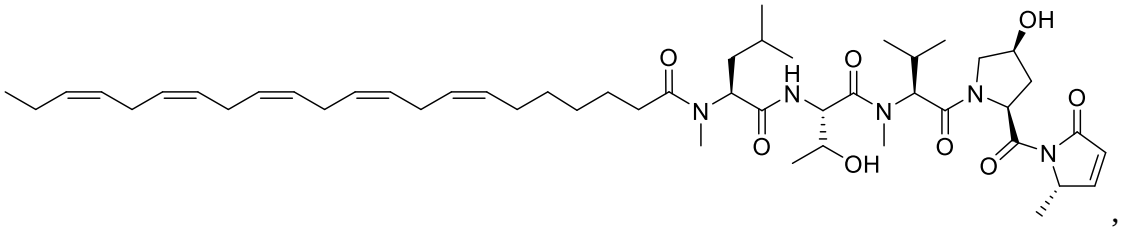

,

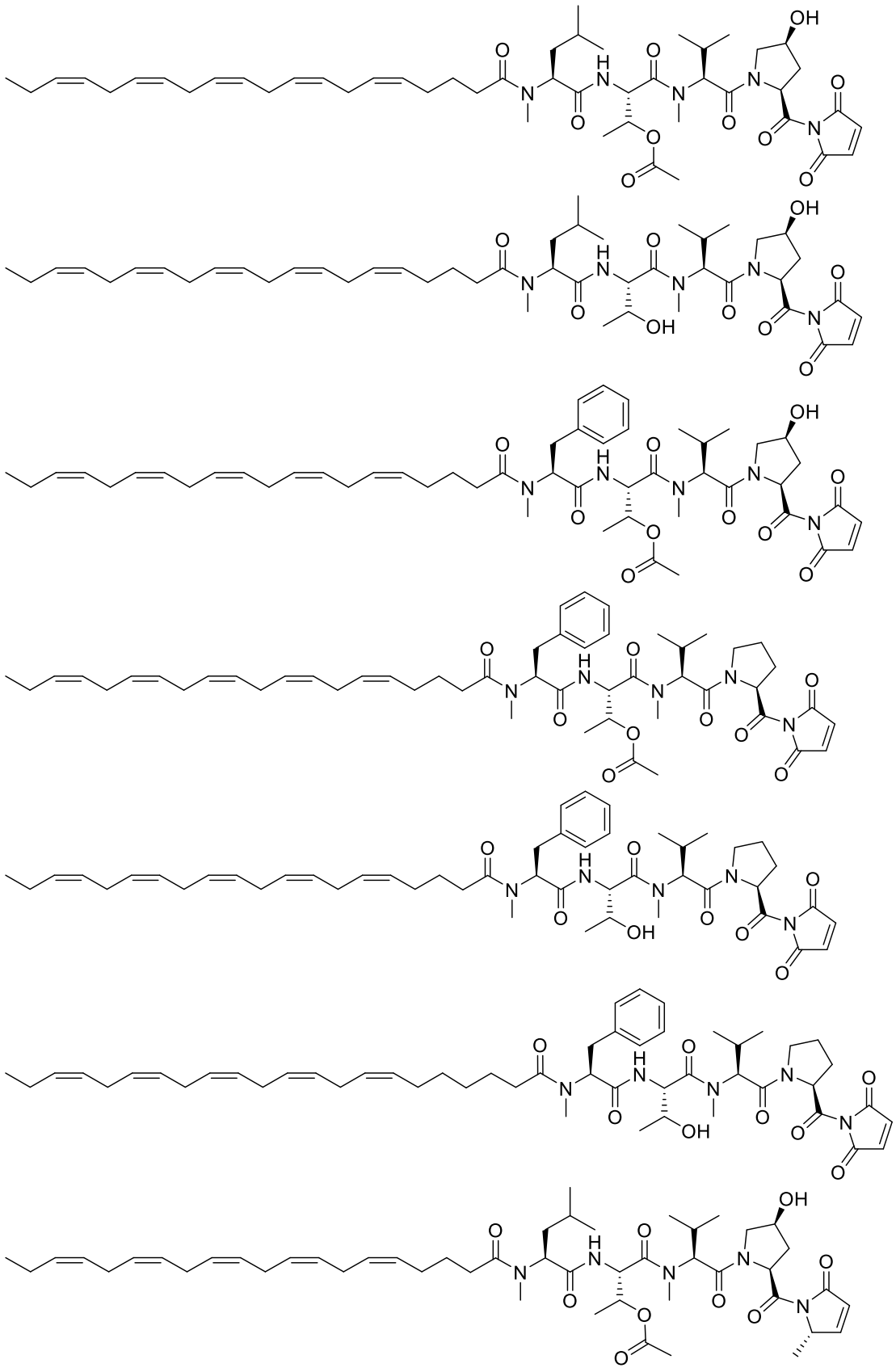

,

or a salt thereof, including any isomers of the foregoing.

21. The lipopeptide of claim 20, wherein the lipopeptide is:

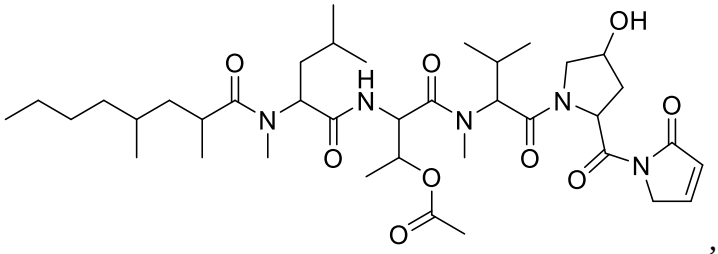

,

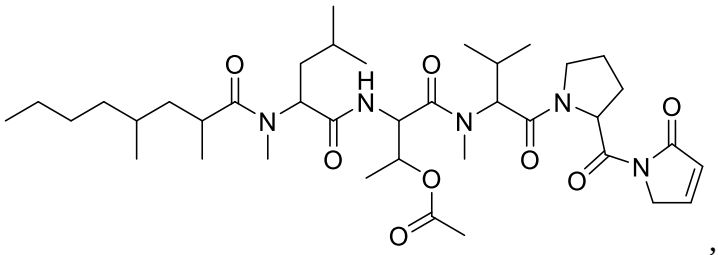

,

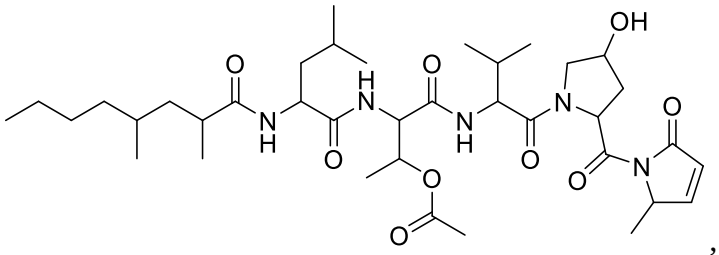


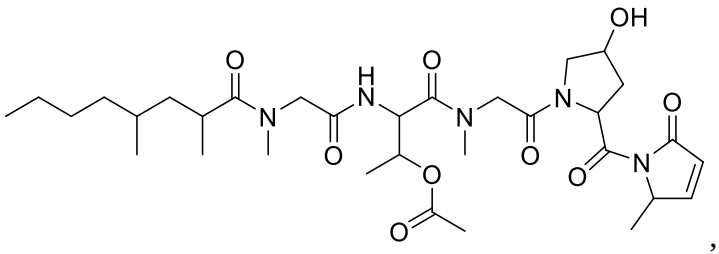
or a salt thereof, including any isomers of the foregoing.

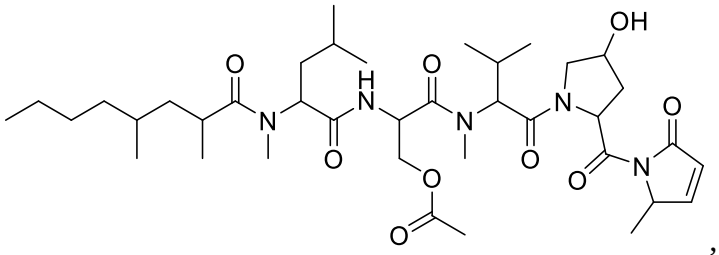
22. A lipopeptide, wherein the lipopeptide is:

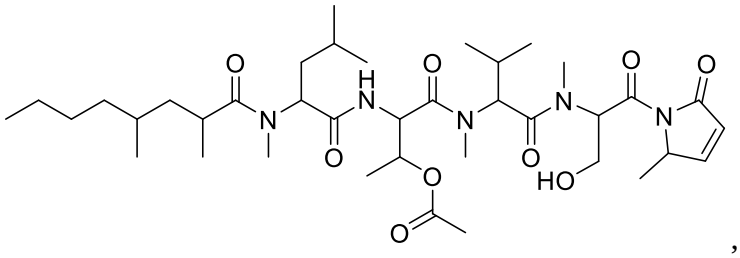

,

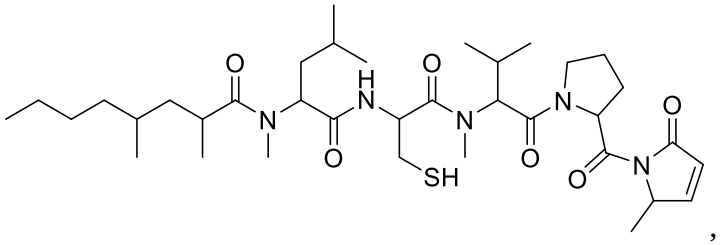
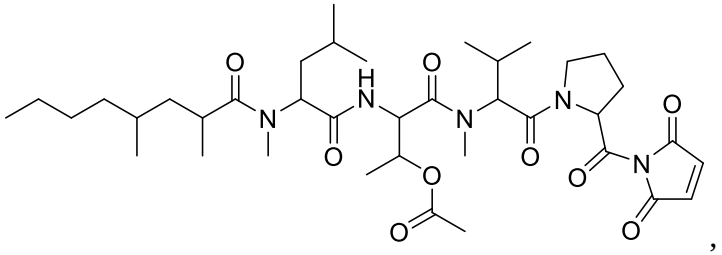
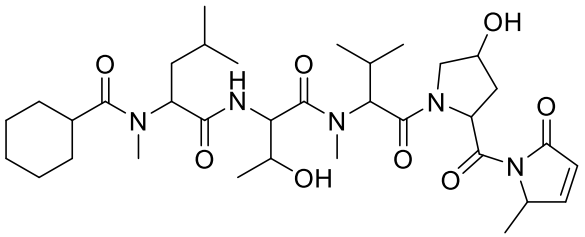
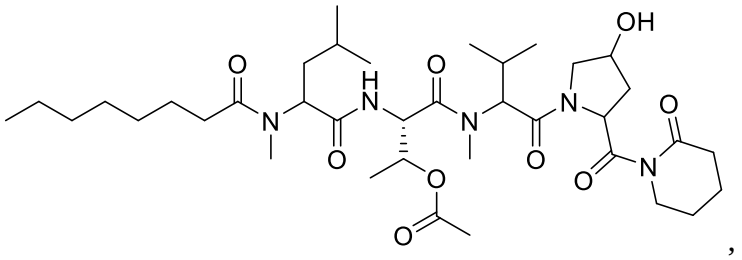
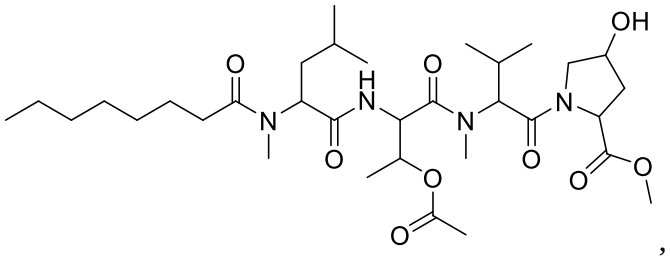
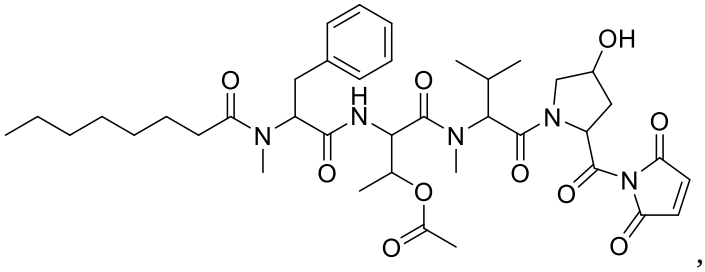

,

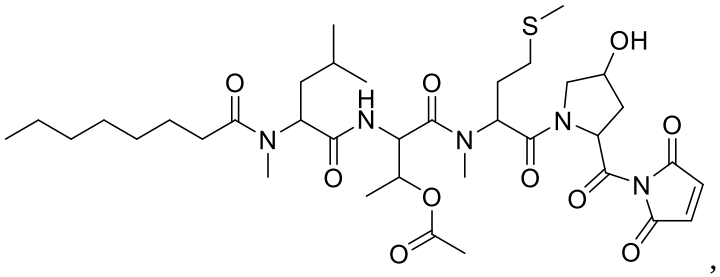

,

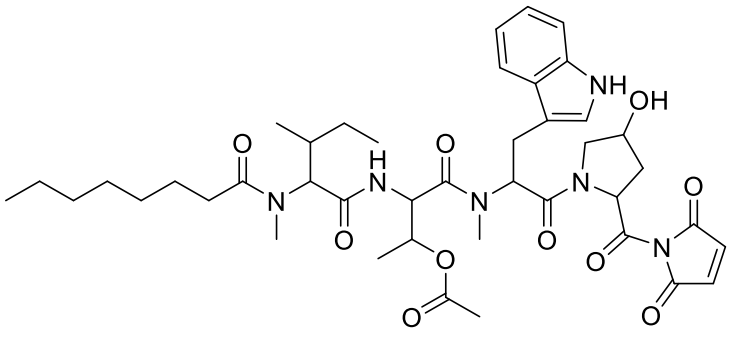

,


,


,

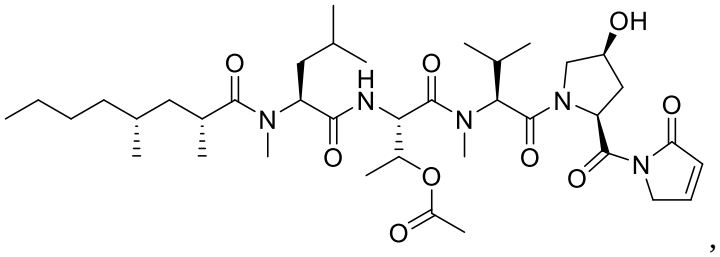

,

,

,

,

,

,

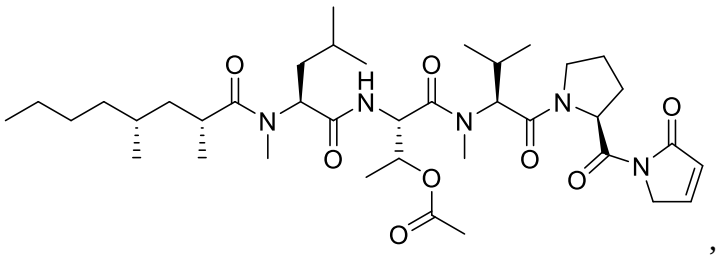

,

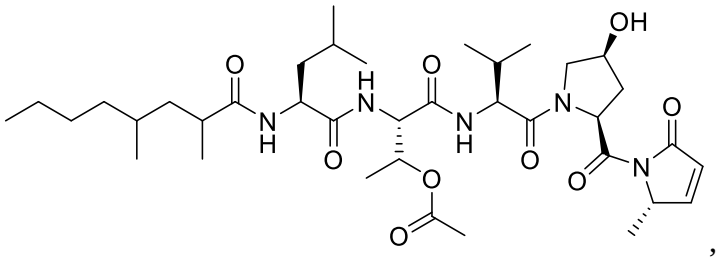

,

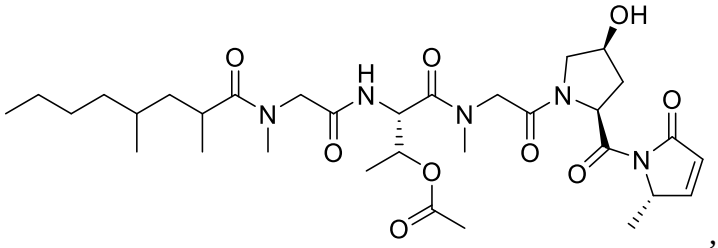
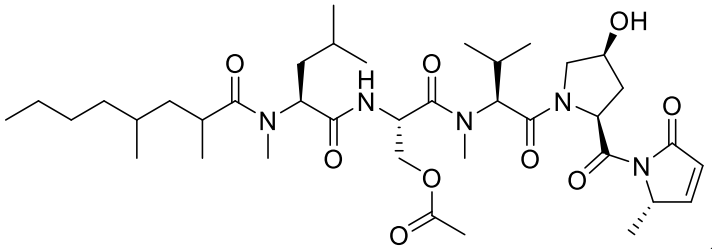
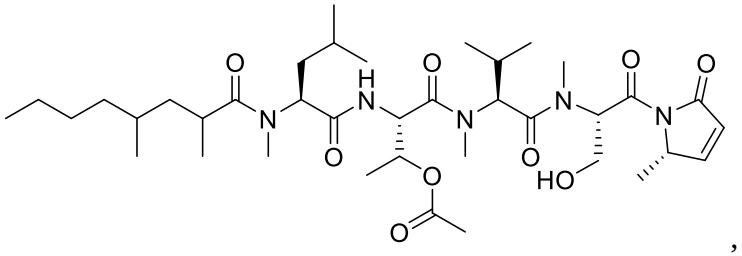
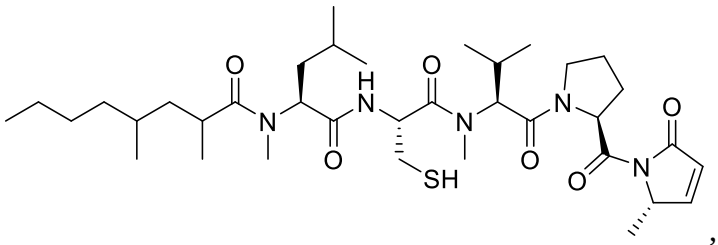
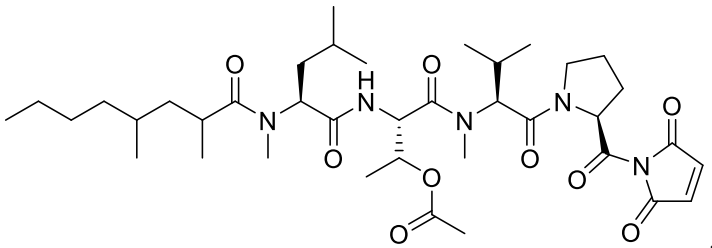
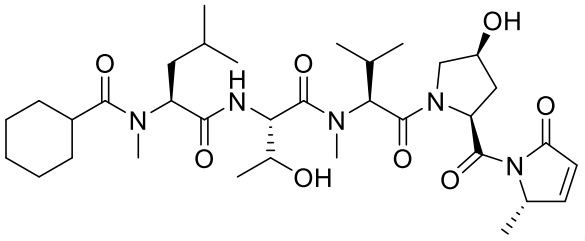
or a salt thereof, including any isomers of the foregoing.

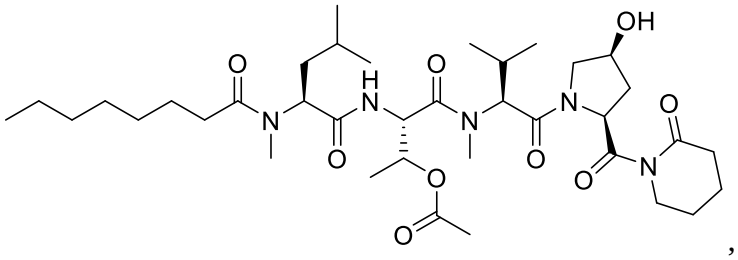
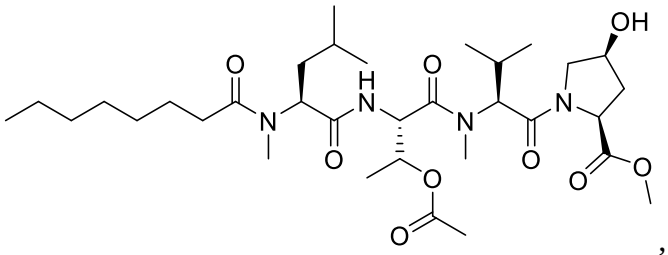
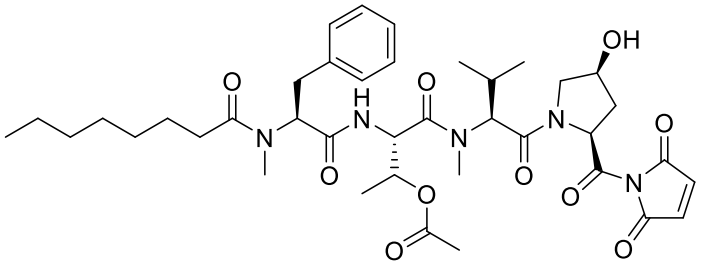
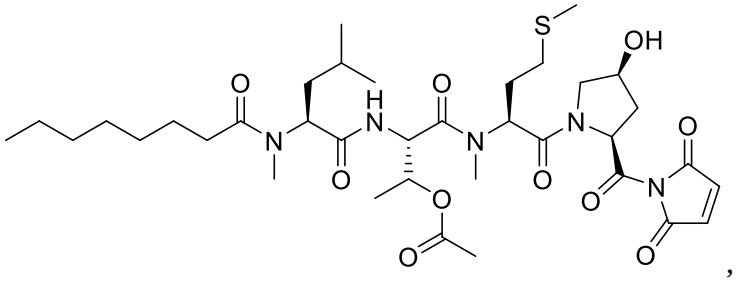
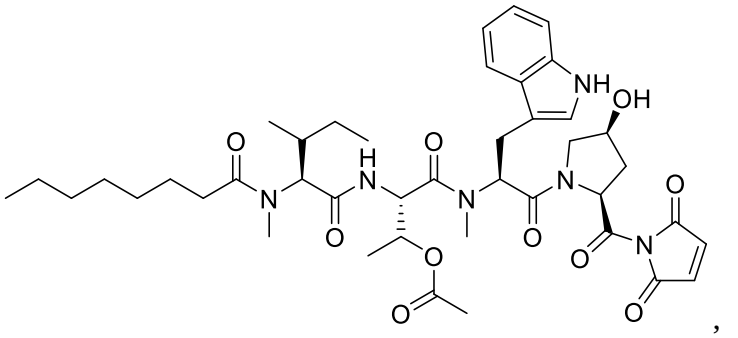
23. The lipopeptide of claim 22, wherein the lipopeptide is:


,


,


,


,

,

,

,

,

,


,

,

,

,

,
or a salt thereof, including any isomers of the foregoing.

24. A pharmaceutical composition, comprising at least one lipopeptide of any one of claims 1 to 23, and at least one pharmaceutically acceptable excipient.

25. Use of a composition comprising at least one lipopeptide of any one of claims 1 to 23, in the manufacture of a medicament ~~A method~~ for treating an eosinophilic inflammatory condition,

disorder or disease in a human in need thereof~~, comprising: administering to the human an effective dose of a composition comprising at least one lipopeptide of any one of claims 1 to 23 to treat the eosinophilic inflammatory condition, disorder or disease~~.

26. The ~~method~~use of claim 25, wherein the eosinophilic inflammatory condition, disorder or disease is a chronic inflammatory disorder of the airways.

27. The ~~method~~use of claim 25, wherein the eosinophilic inflammatory condition, disorder or disease is asthma.

28. The ~~method~~use of claim 25, wherein the eosinophilic inflammatory condition, disorder or disease is bronchial asthma.

29. Use of a composition comprising at least one lipopeptide of any one of claims 1 to 23, in the manufacture of a medicament ~~A method~~ for treating an eosinophilic respiratory condition, disorder or disease in a human in need thereof~~, comprising: administering to the human an effective dose of a composition comprising at least one lipopeptide of any one of claims 1 to 23 to treat the eosinophilic respiratory condition, disorder or disease~~.

30. The ~~method~~use of claim 29, wherein the eosinophilic respiratory condition, disorder or disease is a viral respiratory disease.

31. The ~~method~~use of claim 29, wherein the eosinophilic respiratory condition, disorder or disease is severe acute respiratory syndrome.

32. The ~~method~~use of claim 29, wherein the severe acute respiratory syndrome is caused by a coronavirus.

33. The ~~method~~use of any one of claims 25 to 32, wherein the human is largely resistant to medical and surgical interventions for treating the condition, disorder or disease.

34. The ~~method~~use of any one of claims 25 to 32, wherein the human exhibits or has resistance to steroid treatments.

35. The ~~method~~use of any one of claims 25 to 32, wherein the human has steroid treatment resistant asthma.

36. The ~~method~~use of any one of claims 25 to 35, wherein ~~the administration of~~ the composition ~~to the human~~ reduces or delays the need to provide the human with assisted respiration.

37. Use of a salmonid oil composition or a composition comprising at least one lipopeptide of any one of claims 1 to 23, in the manufacture of a medicament ~~A method~~ for reducing eosinophil effector function in a human in need thereof~~, comprising administering to the human a salmonid oil composition or a composition comprising at least one lipopeptide any one of claims 1 to 23 to reduce eosinophil effector function~~.

38. The ~~method~~use of any one of claims 25 to 37, wherein the composition further comprises caproic acid, caprylic acid, capric acid, lauric acid, behenic acid, lignoceric acid, myrstoleic acid, heptadecenoic acid, elaidic acid, gadoleic acid, erucic acid, brassidic acid, nervonic acid, gamma linolenic acid, columbinic acid, stearidonic acid, mead acid, or dihomo gamma linolenic acid, or any combination thereof.

39. The ~~method~~use of any one of claims 25 to 38, wherein the composition further comprises ligustilide, germacrene, thymol, eugenol, carvacrol, linalool, citronellol, terpineol, bisbalol, santalol, thujone, pinacamphone, italidone, linalyl acetate, geranyl acetate, citronellyl formate, helenalin, elecampane, furocoumarin, chavicol, sitosterol, stigmasterol, or 3-butyliden-4,5-dihydrophthalide, or any combination thereof.

40. The ~~method~~use of any one of claims 25 to 39, wherein the composition further comprises iturin A, hoiamides, heronamides, laxaphycin, apramides, dragonamides, gageotetrins, lyngbyabellins, cyclodycidins, parguerine, pumilacidin, sulforeido lipopeptides, fengycins, mebamamides, penicimutamides, sulfoglycolipids, halovir, kahalalide, or tuftsin, or any salt thereof, or any combination of the foregoing.

41. The ~~method~~use of any one of claims 25 to 40, wherein the composition is to be administered as a syrup, chewable, capsule or soft gel, or the composition is formulated for aerosol administration.

42. An article of manufacture, comprising:

a container comprising a composition comprising at least one lipopeptide of any one of claims 1 to 23; and

a label containing instructions for use of such composition.

43. The article of manufacture of claim 42, wherein the composition is provided in a dosage form.

44. The article of manufacture of claim 42 or 43, wherein the dosage form is a syrup, chewable, capsule or soft gel.

45. The article of manufacture of claim 42 or 43, wherein the container is an aerosol container.

46. A kit, comprising:

a dosage form of a composition comprising a composition comprising at least one lipopeptide of any one of claims 1 to 23; and

a package insert containing instructions for use of such composition.

47. The kit of claim 46, wherein the dosage form is a syrup, chewable, capsule or soft gel, or the dosage form is in aerosol form.

48. A salmonid oil composition or a composition comprising at least one lipopeptide of any one of claims 1 to 23, for use in therapy.