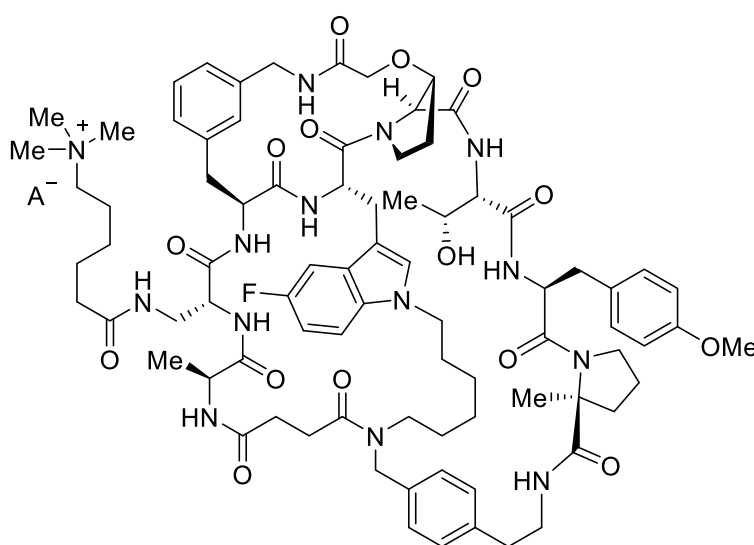


conditions related to PCSK9 activity desirably comprising oral administration of an identified PCSK9 inhibitor. Also provided herein are new salt forms of a PCSK9 inhibitor.

SUMMARY OF THE DISCLOSURE

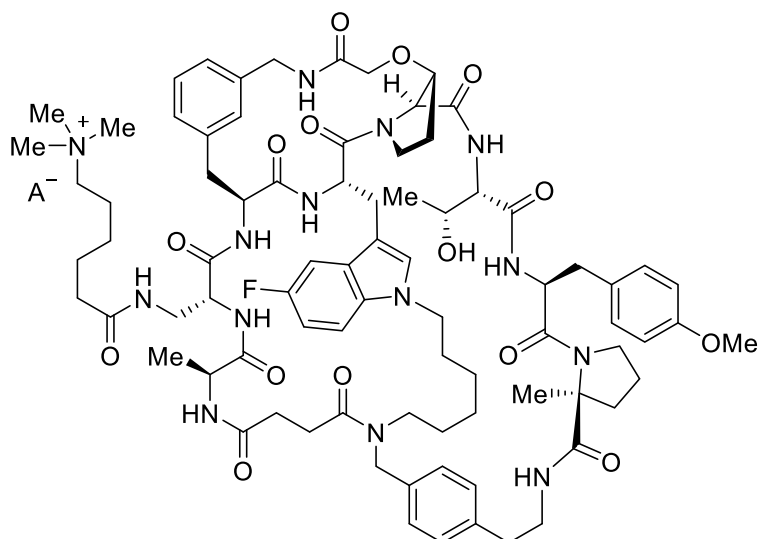
The present disclosure provides a method of treating hypercholesterolemia and other conditions related to PCSK9 activity, e.g. atherosclerosis, atherosclerotic cardiovascular disease, coronary heart disease, metabolic syndrome, acute coronary syndrome, or related cardiovascular disease and cardiometabolic conditions, comprising orally administering to a subject in need an amount of a compound of formula (I)



(I),

wherein A^- is selected from a pharmaceutically acceptable anion, and wherein the amount administered is from about 5 mg to about 300 mg of the compound of formula (I).

In one aspect, there is provided use of a composition in the manufacture of a medicament for the treatment of hypercholesterolemia in a subject in need of such treatment, wherein the composition comprises a compound of formula (I)

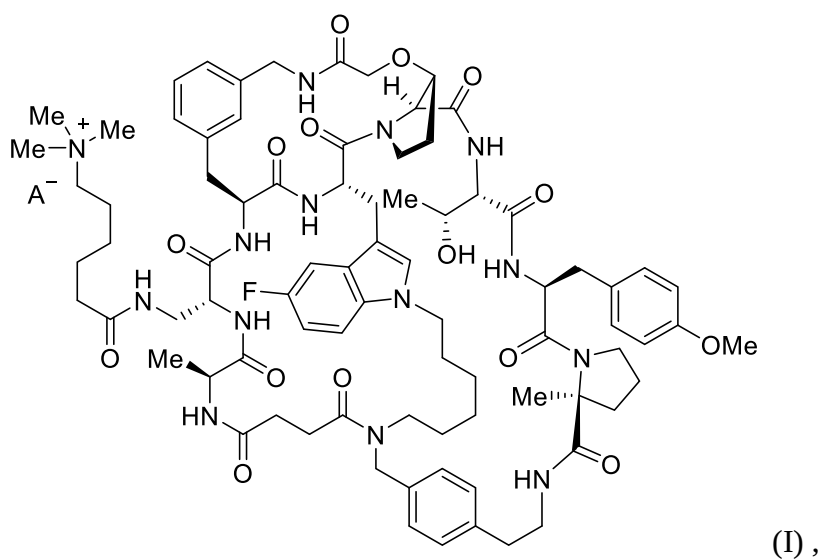


(I),

wherein A^- is selected from a pharmaceutically acceptable anion, and wherein an amount of the compound of formula (I) in the composition is from about 5 mg to about 300 mg.

5 The present disclosure also provides a method of reducing LDL-C in a subject in need thereof comprising orally administering to the subject an amount of a compound of formula (I), wherein A^- is selected from a pharmaceutically acceptable anion, and wherein the amount is from about 5 mg to about 300 mg of the compound of formula (I).

10 In another aspect, there is provided use of a composition in the manufacture of a medicament for reducing LDL-C in a subject in need thereof, wherein the composition comprises a compound of formula (I)

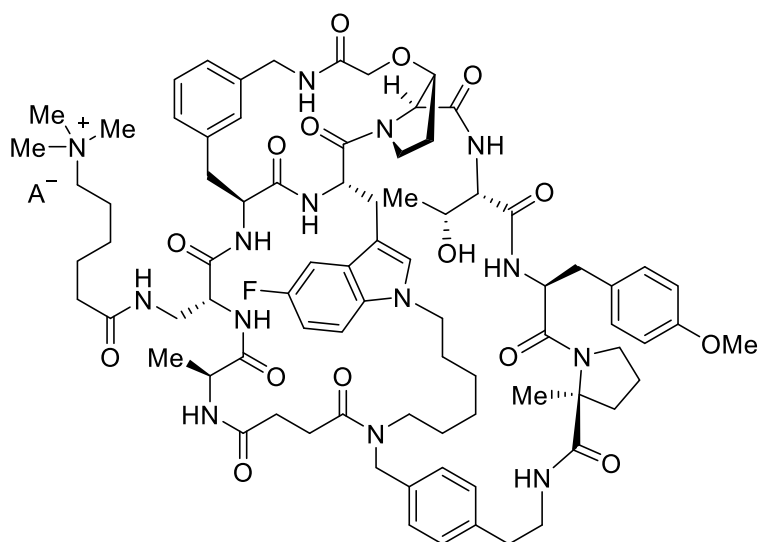


(I),

wherein A^- is a pharmaceutically acceptable anion selected from caprate or acetate, and wherein an amount of the compound of formula (I) in the composition is from about 5 mg to about 300 mg.

The present disclosure provides a method of treating atherosclerotic cardiovascular disease in a subject in need of such treatment comprising orally administering to the subject an amount of a compound of formula (I), wherein A^- is selected from a pharmaceutically acceptable anion, and wherein the amount administered is from about 5 mg to about 300 mg of the compound of formula (I).

In another aspect, there is provided use of a composition in the manufacture of a medicament in the treatment of atherosclerotic cardiovascular disease in a subject in need thereof, wherein the composition comprises a compound of formula (I)

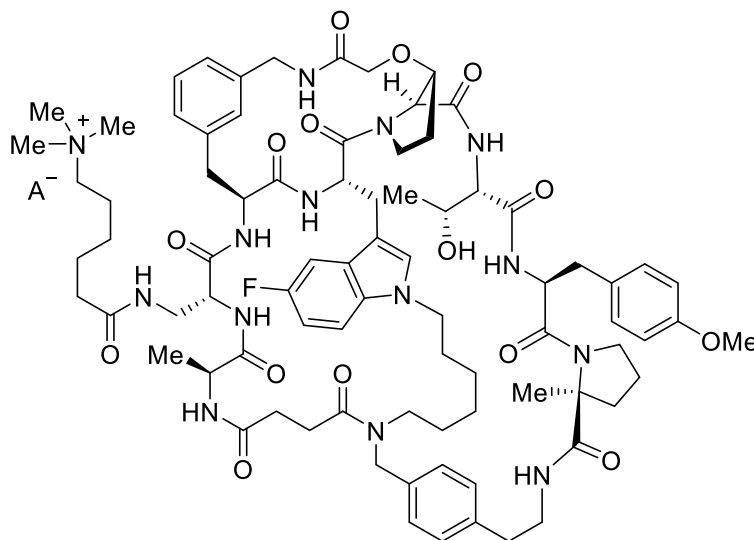


(I) ,

wherein A^- is a pharmaceutically acceptable anion selected from caprate or acetate, and wherein an amount of the compound of formula (I) in the composition is from about 5 mg to about 300 mg.

The present disclosure also provides a method of inhibiting PCSK9 activity in a subject in need thereof comprising orally administering to the subject an amount of a compound of formula (I), wherein A^- is selected from a pharmaceutically acceptable anion, and wherein the amount is from about 5 mg to about 300 mg of the compound of formula (I).

5 In another aspect, there is provided use of a composition in the manufacture of a medicament for inhibiting PCSK9 activity in a subject in need of such treatment, wherein the composition comprises a compound of formula (I)



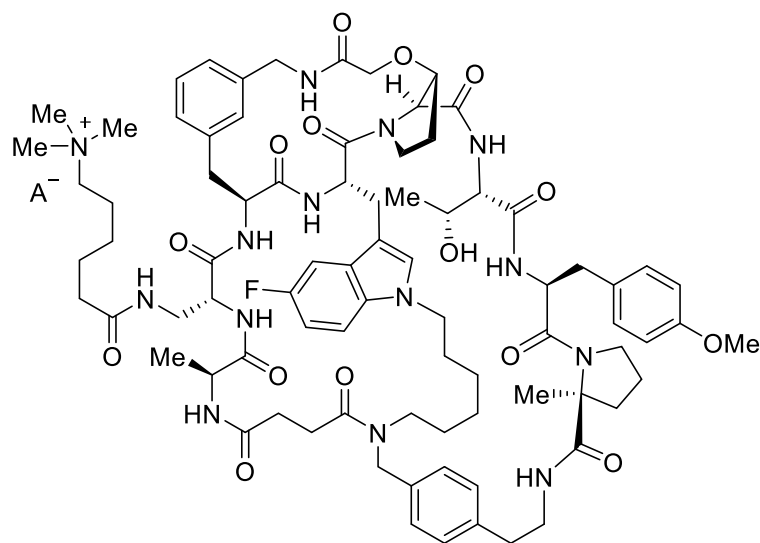
(I) ,

10 wherein A^- is a pharmaceutically acceptable anion selected from caprate or acetate, and wherein an amount of the compound of formula (I) in the composition is from about 5 mg to about 300 mg.

The present disclosure is also directed to particular salts of the compound of formula (I).

15 The present disclosure is also directed to pharmaceutical compositions comprising a compound of formula (I), including particular salts of the compound of formula (I), and a permeation enhancer.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula (I)



(I),

5 wherein A⁻ is a pharmaceutically acceptable anion, and a permeation enhancer.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 shows the pharmacokinetics of single doses of Compound 1, a compound of formula (I), in varying doses from about 10 to about 300 mg.

10 FIG. 2 shows a summary of the statistics of plasma pharmacokinetics following administration of single oral doses of 10 to 300 mg of Compound 1 to healthy male participants.

FIG. 3 shows the % change from baseline LDL-C for formulations of the compound of formula (I), as well as known anti-PCSK9 monoclonal antibodies and an anti-PCSK9 siRNA active, and placebo.

FIG. 4 shows the reduction of plasma levels of free PCSK9, compared to baseline, after single doses of Compound 1.

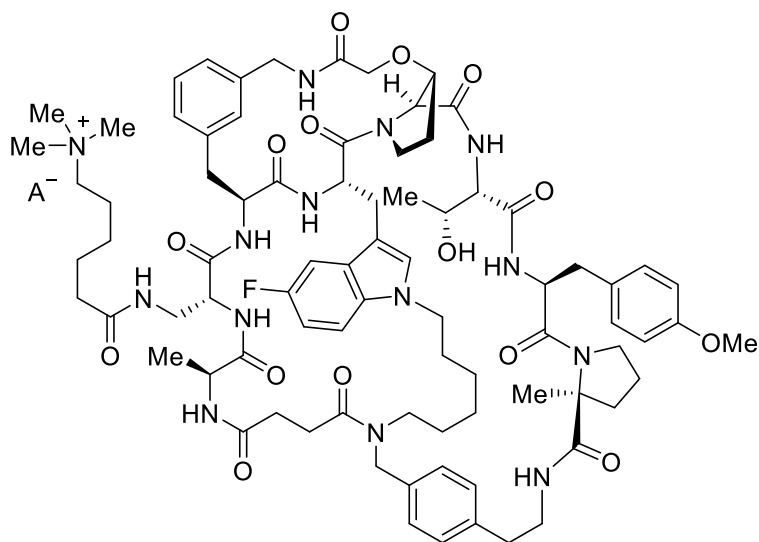
FIG. 5 depicts the stability differences between Compound 1, Compound 2 and Compound 3.

DETAILED DESCRIPTION OF THE INVENTION

This disclosure relates to methods of treating hypercholesterolemia and other conditions related to PCSK9 activity, e.g. atherosclerosis, atherosclerotic cardiovascular disease, coronary heart disease, metabolic syndrome, acute coronary syndrome, or related
5 cardiovascular disease and cardiometabolic conditions. According to the methods of the disclosure, a compound of formula (I)

WE CLAIM:

1. Use of a composition in the manufacture of a medicament for the treatment of hypercholesterolemia in a subject in need of such treatment, wherein the composition comprises a compound of formula (I)



(I),

wherein A⁻ is selected from a pharmaceutically acceptable anion, and wherein an amount of the compound of formula (I) in the composition is from about 5 mg to about 300 mg.

2. The use according to claim 1, wherein the amount of the compound of formula (I) in the composition is from about 10 mg to about 30 mg of the compound of formula (I).

3. The use according to claim 1, wherein the amount of the compound of formula (I) in the composition is 10 mg, 12.5 mg, 15 mg, 17.5 mg, 18 mg or 20 mg.

4. The use according to claim 1, wherein the amount of the compound of formula (I) in the composition is 10 mg or 20 mg.

5. The use according to any of claims 1-4, wherein the compound of formula (I) is to be administered in an oral dosage form which further comprises a permeation enhancer.

6. The use according to claim 5, wherein the permeation enhancer is sodium caprate.

5 7. The use according to claim 5 or 6, wherein the oral dosage form comprises 180 mg of the permeation enhancer.

8. The use according to any of claims 1-7, wherein the compound of formula (I) is to be administered in a single oral dosage form which is to be administered
10 once daily for at least 14 days.

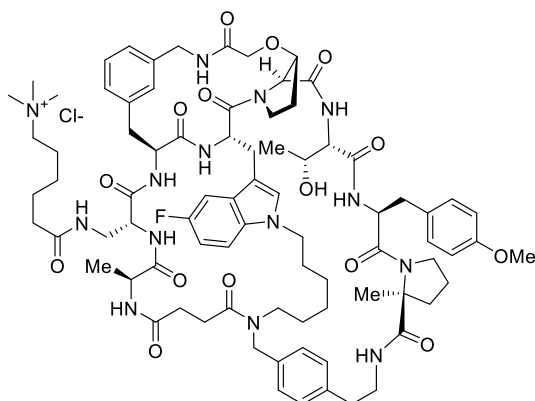
9. The use according to any of claims 1-8, wherein the subject is currently or was previously treated with statin therapy.

15 10. The use according to claim 1, wherein a level of LDL-cholesterol of the subject after treating is reduced from a baseline level of LDL-cholesterol before treating.

11. The use according to claim 10, wherein the level of LDL-cholesterol of the subject after treating is reduced by more than 50% from the baseline level of LDL-
20 cholesterol before treating.

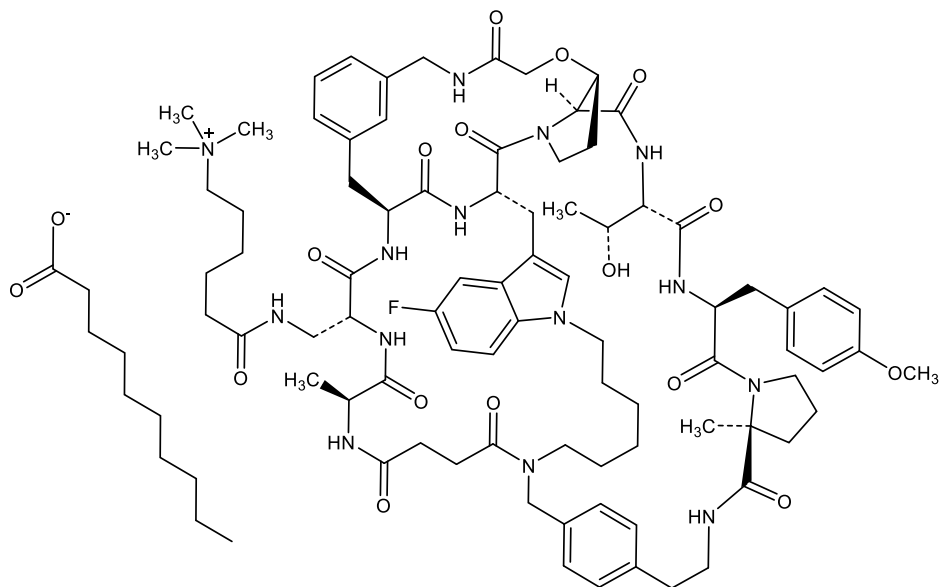
12. The use according to any of claims 1-11, wherein the subject is a human.

13. The use according to any of claims 1-12, wherein the compound of formula (I) is selected from



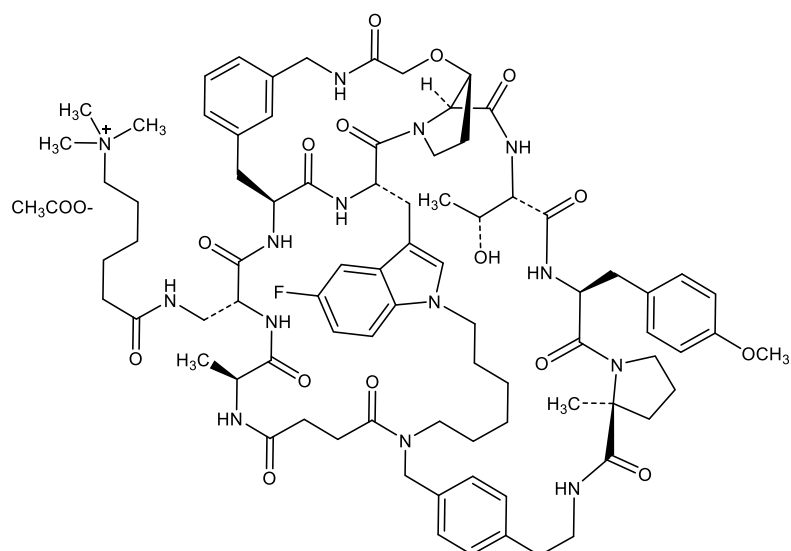
Compound 1;

5



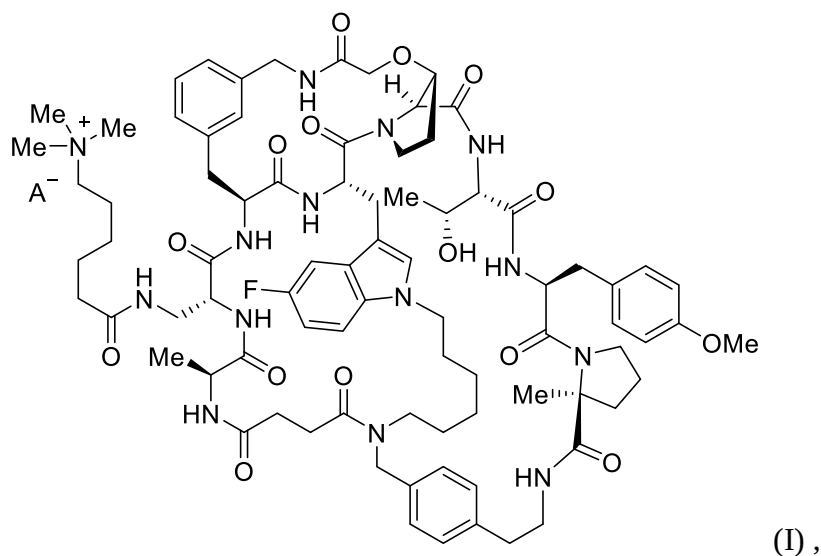
Compound 2;

or



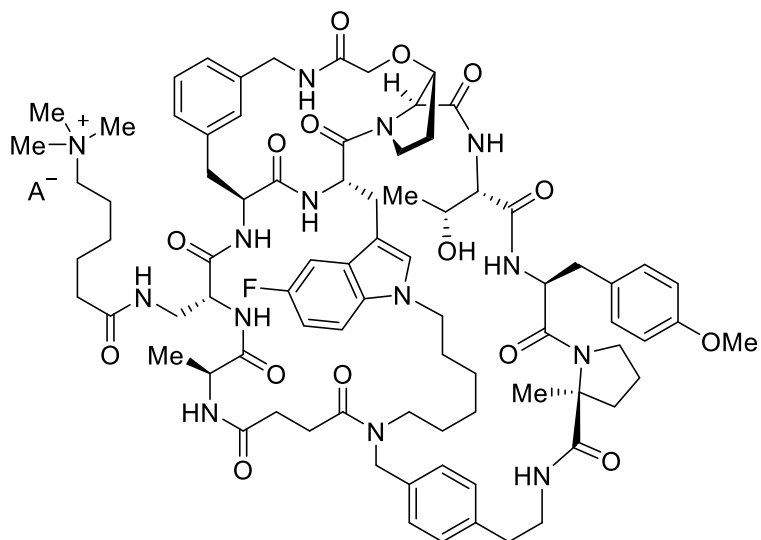
Compound 3.

14. Use of a composition in the manufacture of a medicament for reducing
 5 LDL-C in a subject in need thereof, wherein the composition comprises a compound of
 formula (I)



- wherein A⁻ is a pharmaceutically acceptable anion selected from caprate or acetate, and
 wherein an amount of the compound of formula (I) in the composition is from about 5 mg to
 10 about 300 mg.

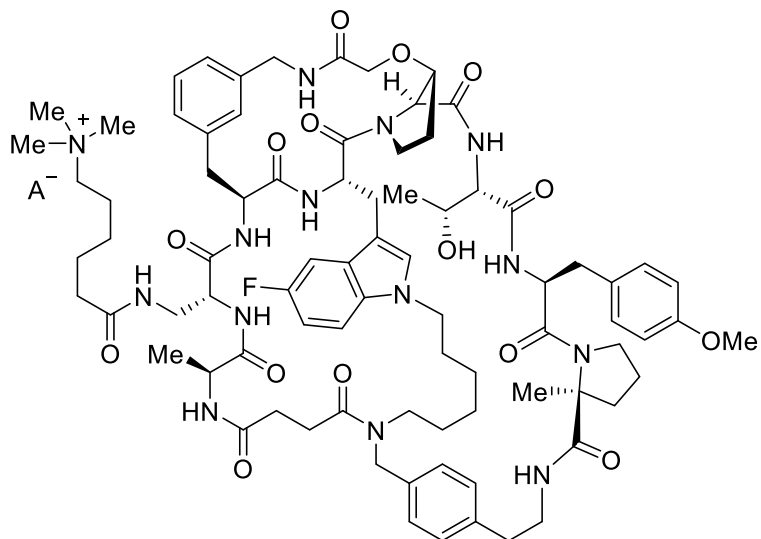
15. Use of a composition in the manufacture of a medicament in the
 treatment of atherosclerotic cardiovascular disease in a subject in need thereof, wherein the
 composition comprises a compound of formula (I)



(I),

wherein A^- is a pharmaceutically acceptable anion selected from caprate or acetate, and
 wherein an amount of the compound of formula (I) in the composition is from about 5 mg to
 5 about 300 mg.

16. Use of a composition in the manufacture of a medicament for
 inhibiting PCSK9 activity in a subject in need of such treatment, wherein the composition
 comprises a compound of formula (I)

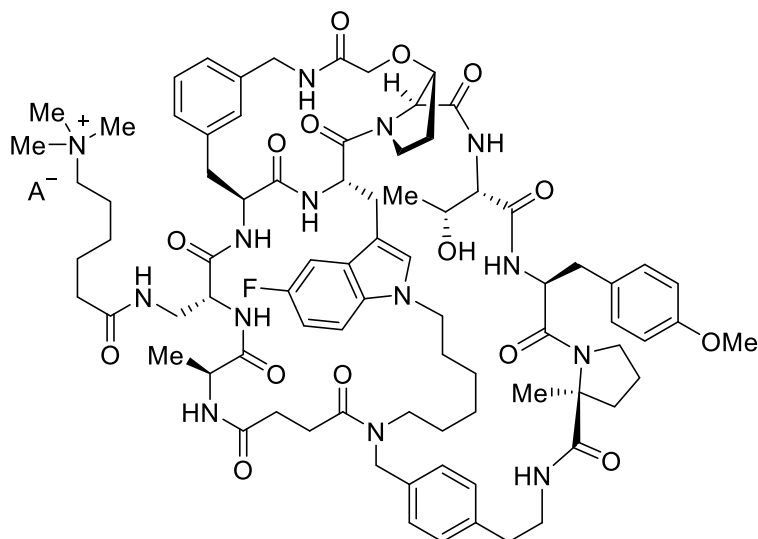


(I),

wherein A^- is a pharmaceutically acceptable anion selected from caprate or acetate, and
 wherein an amount of the compound of formula (I) in the composition is from about 5 mg to
 about 300 mg.

17. The use according to any of Claims 1 to 16, wherein the subject in need fasts approximately 30 minutes before the administration of a compound of formula (I).

5 18. A pharmaceutical composition comprising a compound of formula (I)



(I),

wherein A⁻ is a pharmaceutically acceptable anion, and a permeation enhancer.

10 19. The pharmaceutical composition of claim 18, wherein the permeation enhancer is sodium caprate.

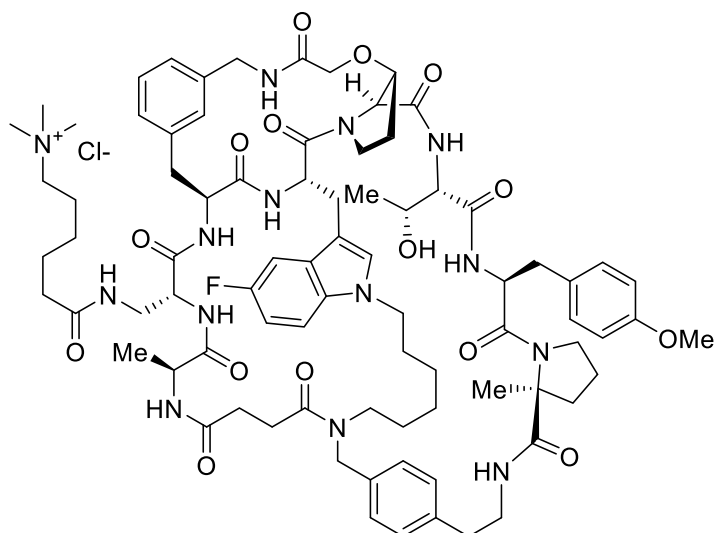
20. The pharmaceutical composition of claims 18 or 19, further comprising a diluent selected from a polyethylene glycol, microcrystalline cellulose, mannitol, starch,
15 dicalcium phosphate, calcium carbonate, sodium carbonate, lactose or combinations thereof.

21. The pharmaceutical composition of claim 20, wherein the diluent is selected from microcrystalline cellulose, lactose or macrogol (PEG 4000).

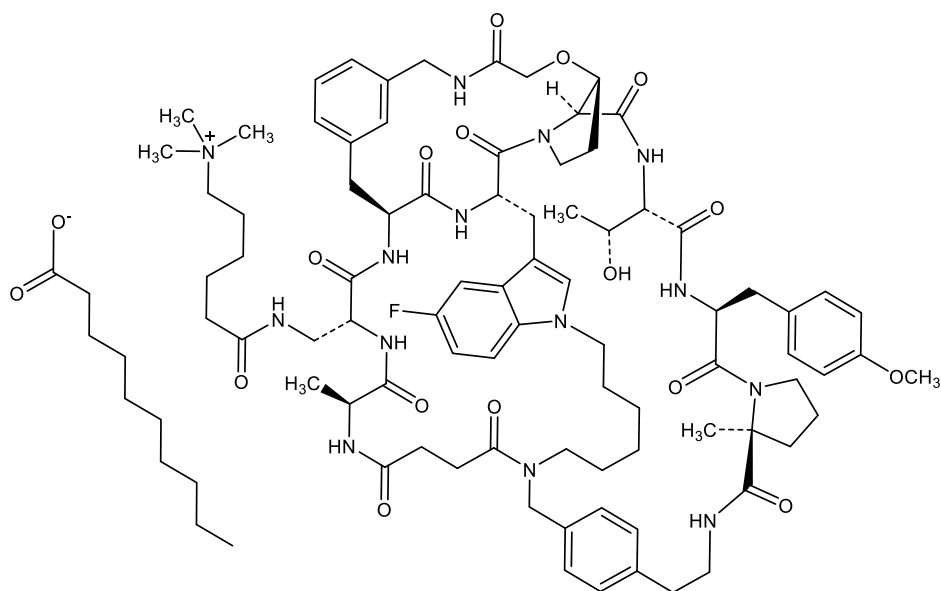
20 22. The pharmaceutical composition of any of claims 18-21 wherein the pharmaceutical composition is in the form of a tablet.

23. The pharmaceutical composition of any of claims 18-21, wherein the pharmaceutical composition is in the form of a capsule.

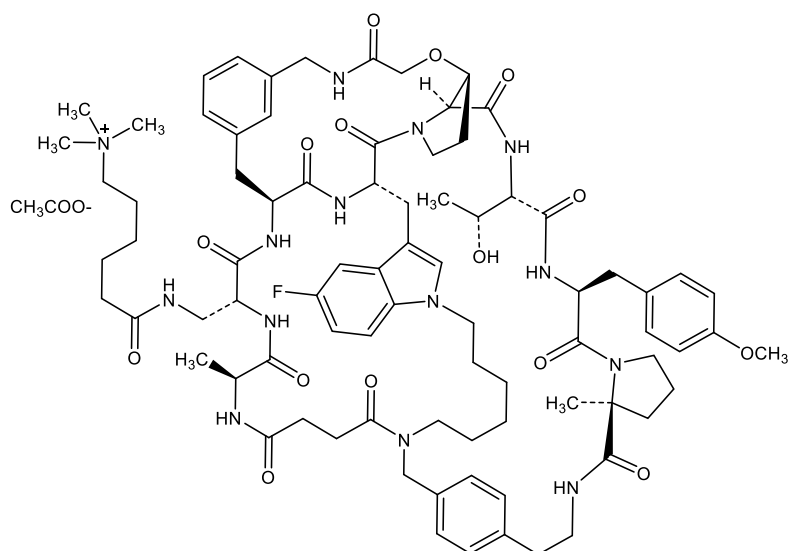
24. The pharmaceutical composition of any of claims 18-23, wherein the
5 compound of formula (I) is selected from



Compound 1;



Compound 2; or



Compound 3.

25. The pharmaceutical composition of any of claims 18-24, wherein the
 5 pharmaceutical composition comprises a) about 1 % to 7 % by weight relative to the total weight of the pharmaceutical composition of a compound of formula (I); b) about 1 % to 75% by weight relative to the total weight of the pharmaceutical composition of a permeation enhancer; c) at least one diluent; and d) optionally a glidant and/or a lubricant.

10 26. The pharmaceutical composition of any of claims 18-24, wherein the pharmaceutical composition comprises a) about 2% to 6% by weight relative to the total weight of the pharmaceutical composition of a compound of formula (I); b) about 18 % to 74% by weight relative to the total weight of the pharmaceutical composition of a permeation enhancer, where the permeation enhancer is sodium caprate; c) at least one diluent selected
 15 from PEG4000, microcrystalline cellulose and lactose; d) 0% to about 3% by weight relative to the total weight of the pharmaceutical composition of a glidant, where the glidant is silicon dioxide; e) 0% to about 2% by weight relative to the total weight of the pharmaceutical composition of a lubricant where the lubricant is magnesium stearate and f) optionally at least one disintegrant.