(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) $-NH-C(O)-[(CH_2)_{y12}-O-]_2-(CH_2)_{y13}R^{14B}$ wherein:

y_{12} and y_{13} are not both 2 and are independently 2 to 4; and

R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

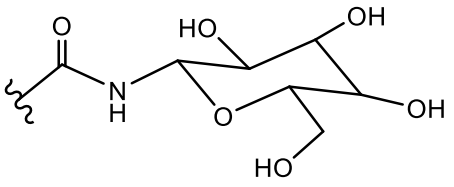
(vii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is $-O-(CH_2)_{zb}-N^+(CH_3)_3$, wherein zb is 3 or 4; and

(viii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) $–O-(CH_2)_2-N^+(CH_3)_3$;

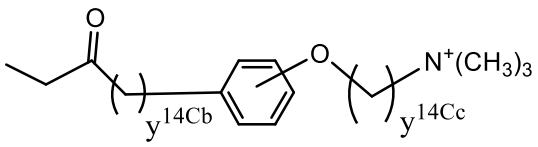
(aii) $-N^+(CH_3)_2R^{14ca}$, wherein R^{14ca} is $–CH_3$ or $–(CH_2)_{1-4}-OCH_3$;

(aiii) a moiety of the formula:



; or

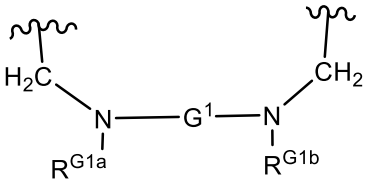
(aiv) a moiety of the formula:



,

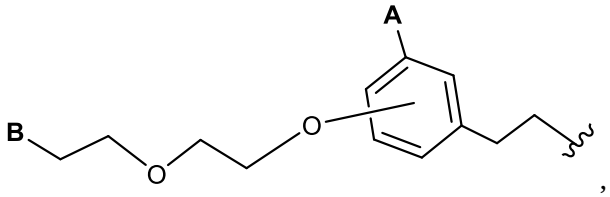
where y^{14Cb} and y^{14Cc} are 1 to 4; or

R^1 and R^2 may be bonded together to form a moiety of the formula:



, wherein:

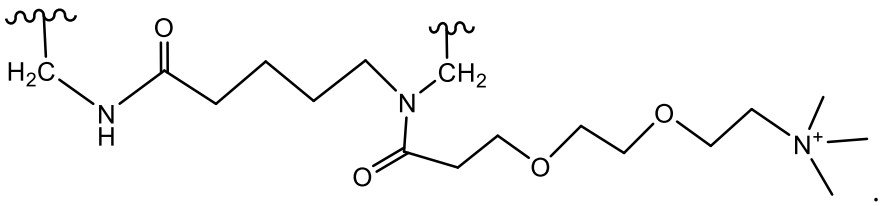
In some examples, it is preferred for **D** to be a moiety of the formula:



,

wherein **A** and **B** are as defined herein.

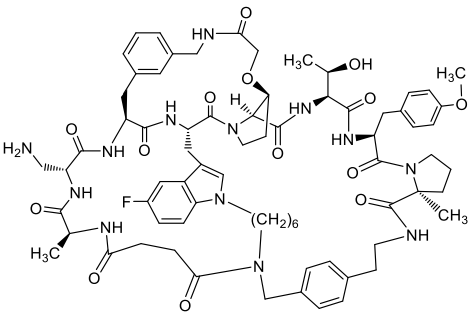
In some examples wherein R^1 and R^2 are joined together, along with the peptide ring to which they are attached forming thereby a cyclic structure, it is preferred for R^1 and R^2 to form a moiety of the structure:



.

In one example the present disclosure provides pharmaceutical compositions comprising a compound of the disclosure, for example, a compound of Formula I, and at least one pharmaceutical excipient, preferably a composition directed to oral administration.

In another aspect the present disclosure provides a compound selected from the group consisting of:



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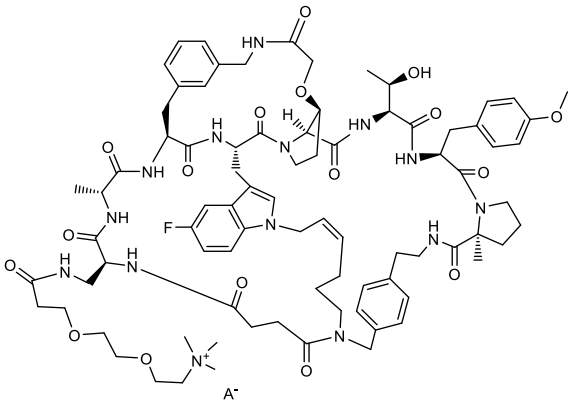

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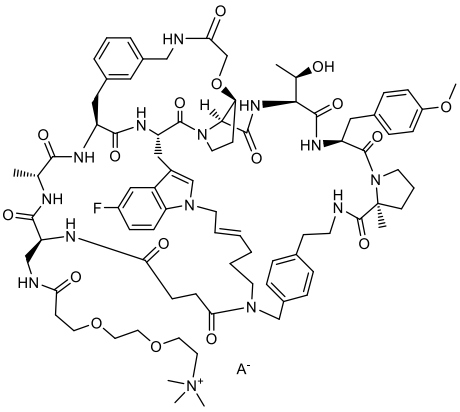

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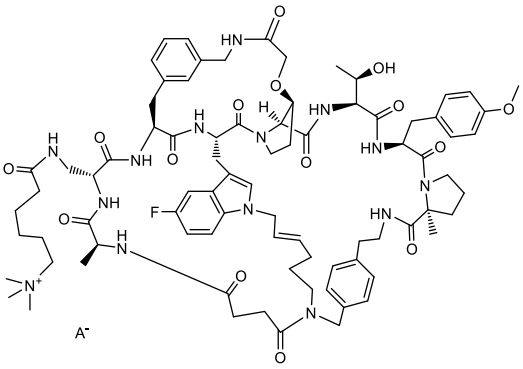

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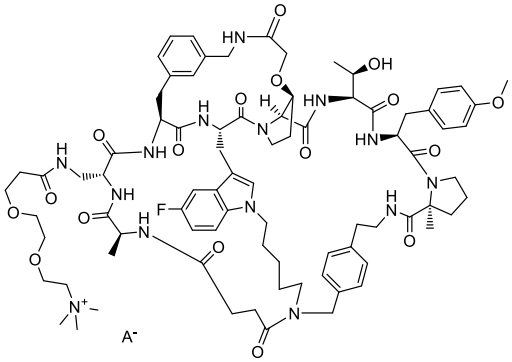

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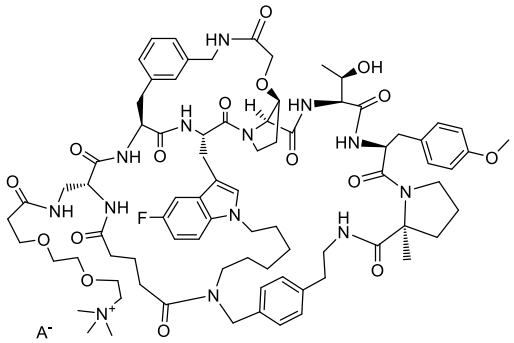

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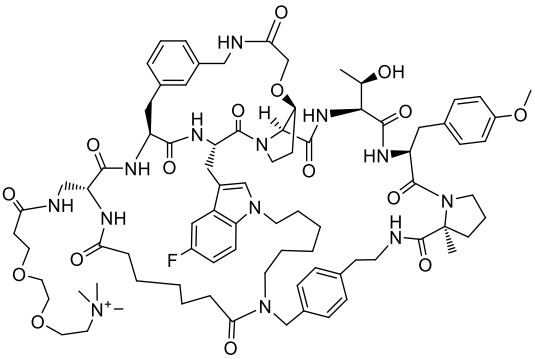

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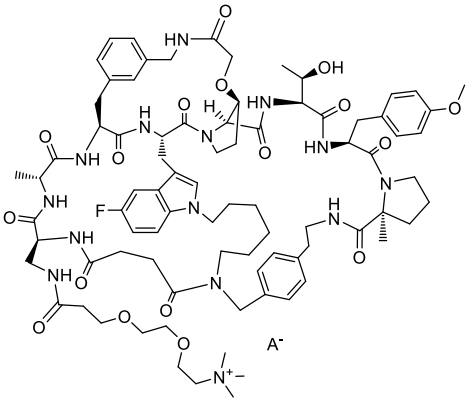

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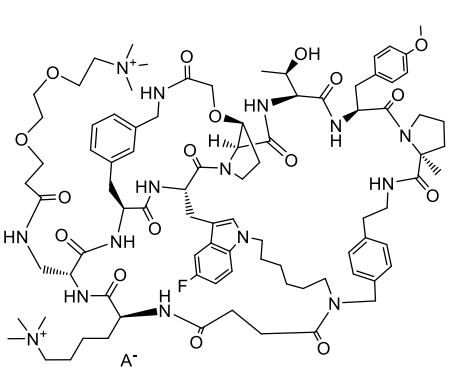

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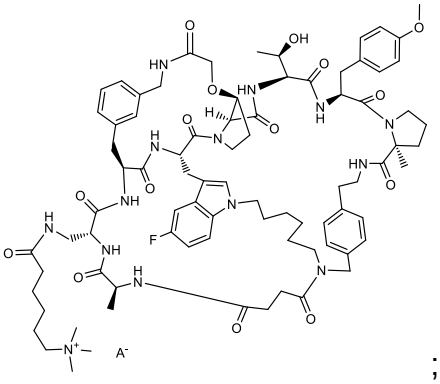

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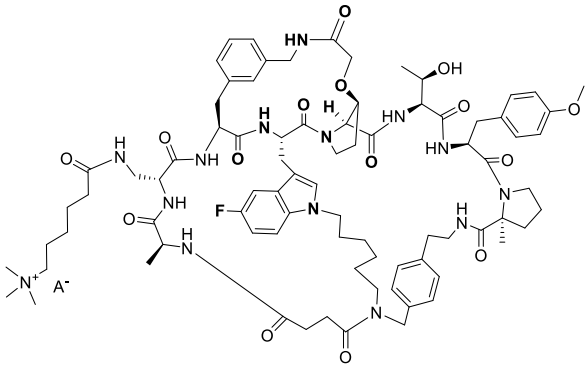

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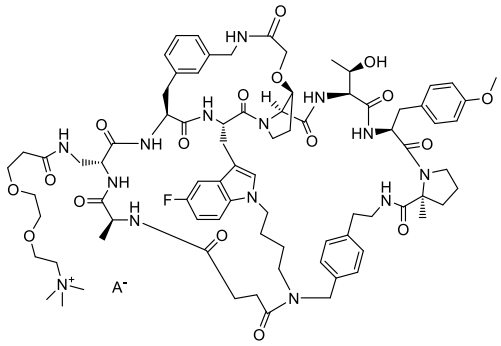

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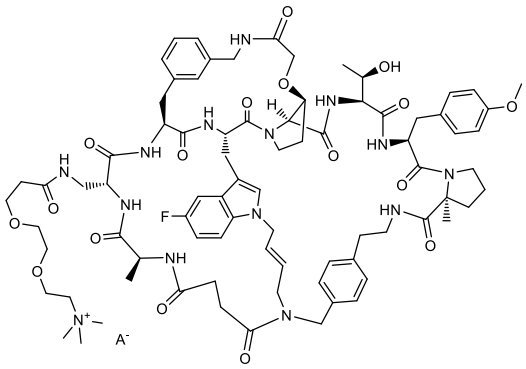

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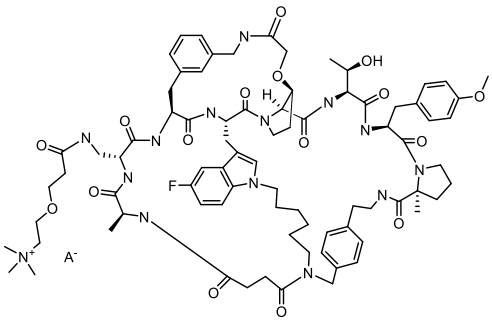

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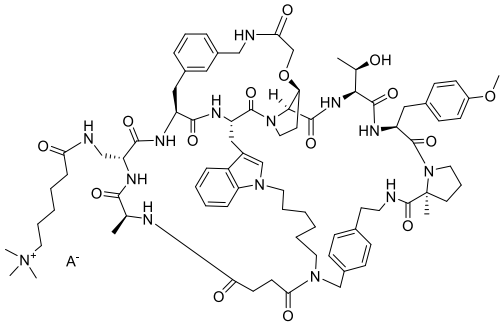

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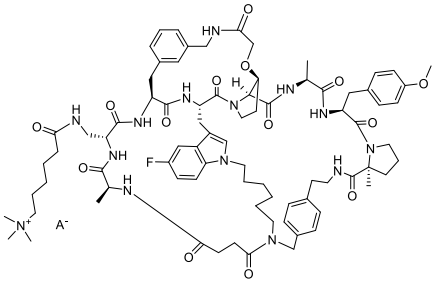

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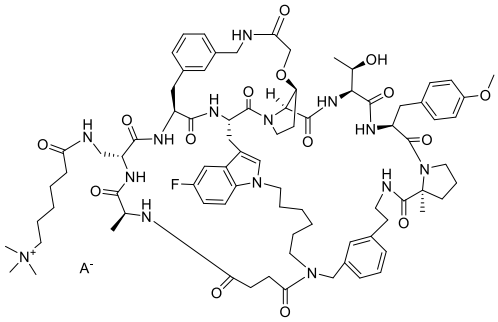

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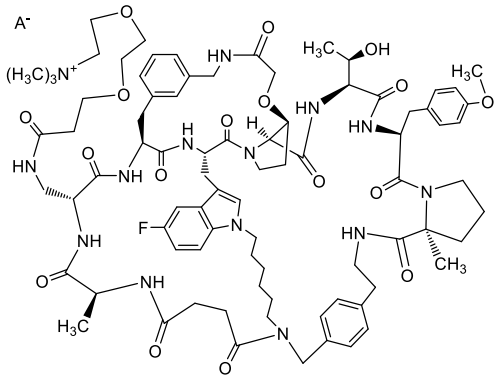

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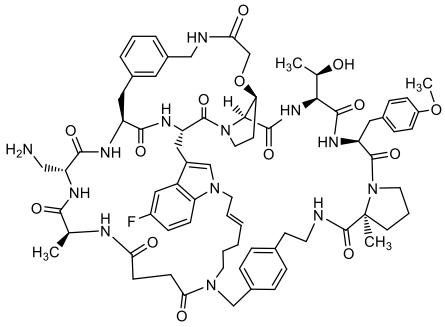

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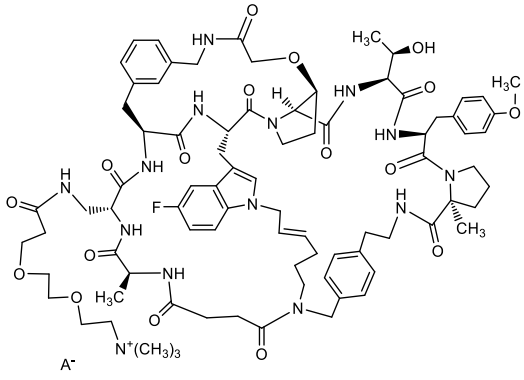

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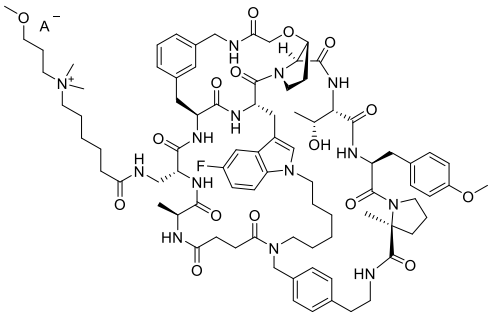
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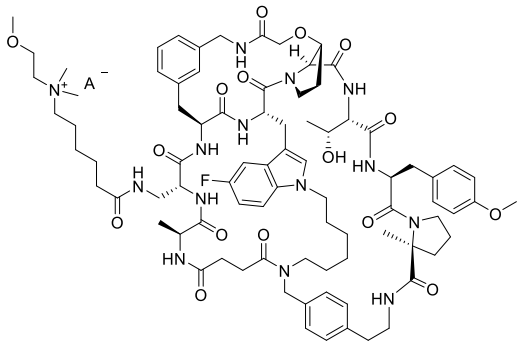
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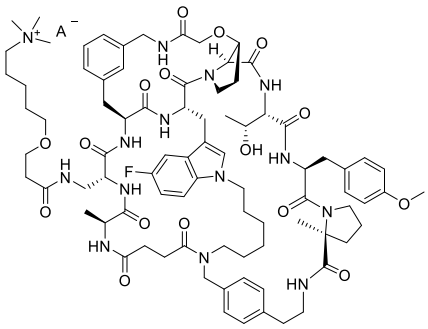
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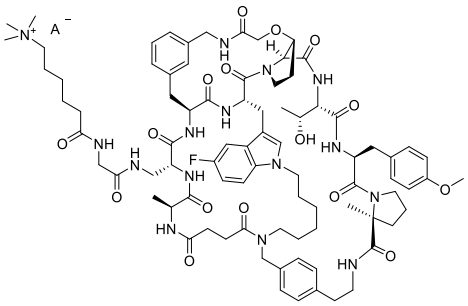
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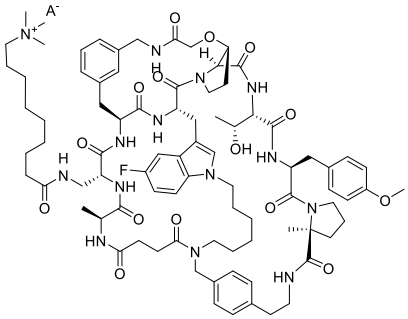
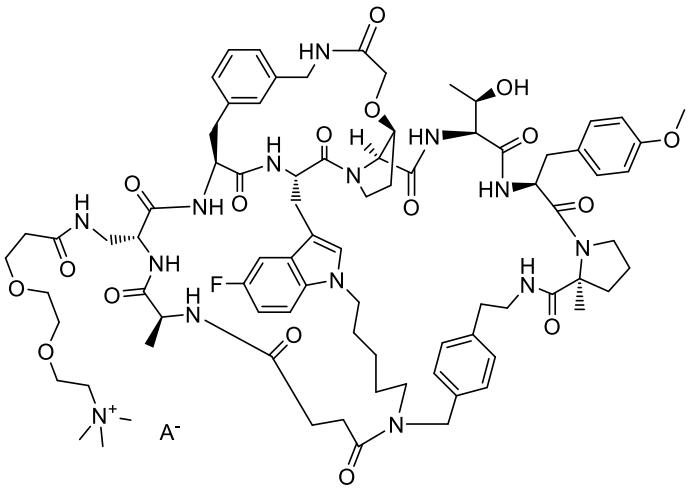

,

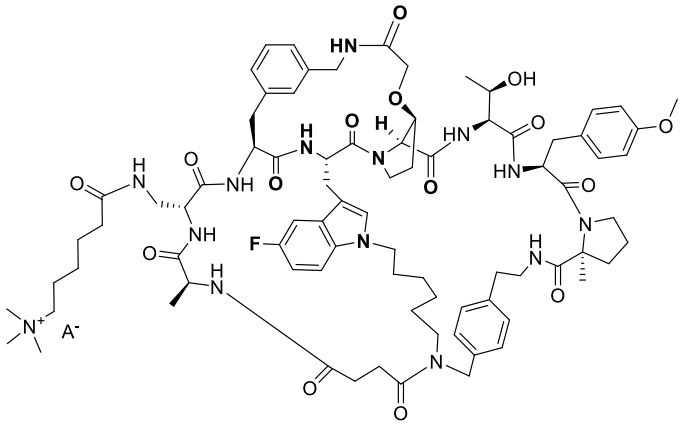
wherein A^- is a pharmaceutically acceptable anion.

In another aspect the present disclosure provides a compound having the structure:



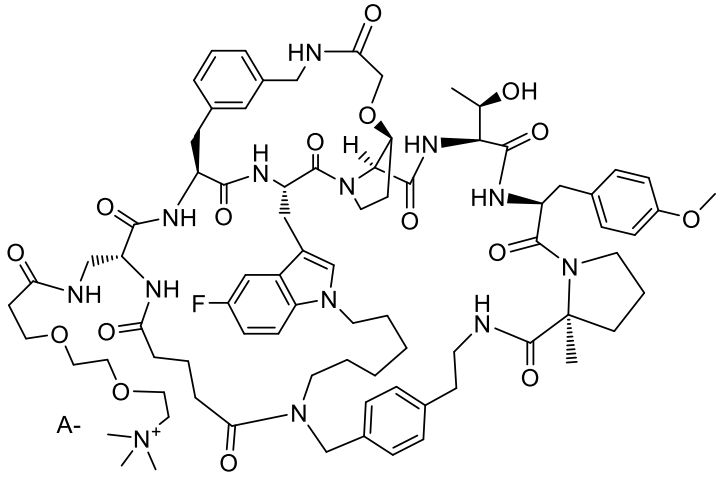
wherein A^- is a pharmaceutically acceptable anion.

In another aspect the present disclosure provides a compound having the structure:



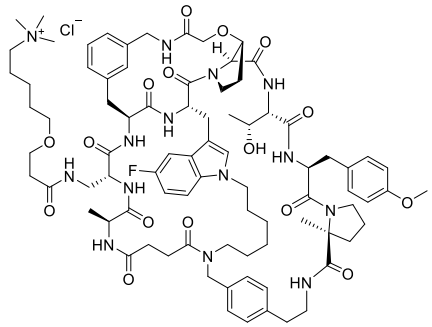
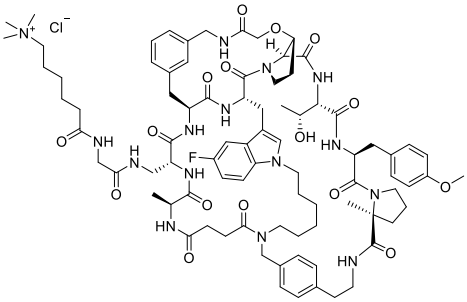
wherein A^- is a pharmaceutically acceptable anion.

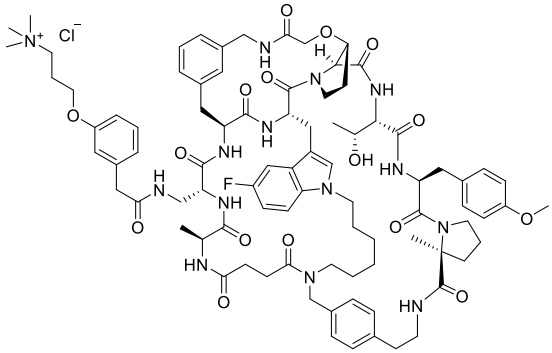
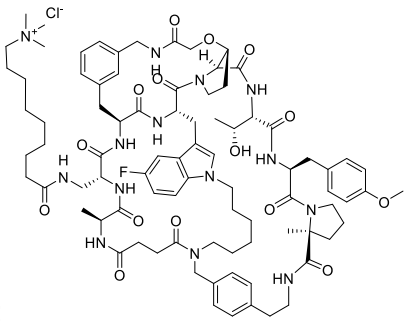
In another aspect the present disclosure provides a compound having the structure:



wherein A^- is a pharmaceutically acceptable anion.

In another aspect the present disclosure provides a compound or a pharmaceutically acceptable salt thereof, selected from the group consisting of:


; 
; and


; 
,

or any other pharmaceutically acceptable salt form thereof.

In another aspect the present disclosure provides a composition comprising at least one compound as defined herein, or a pharmaceutically acceptable salt thereof or freebase form thereof, and at least one pharmaceutically acceptable excipient.

In another aspect the present disclosure provides a composition comprising the compound as defined herein, and at least one pharmaceutically acceptable excipient.

In one example the present disclosure provides a method of antagonizing PCSK9 in the provision of therapy for disease states related to PCSK9 activity, for example, atherosclerosis, hypercholesterolemia, coronary heart disease, metabolic syndrome, acute coronary syndrome, or related cardiovascular disease and cardiometabolic conditions, by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I, or a salt thereof, preferably in the form of a pharmaceutical composition.

In another aspect the present disclosure provides use of a composition as defined herein in the manufacture of a medicament for the treatment of hypercholesterolemia. In another aspect the present disclosure provides use of a compound as defined herein in the manufacture of a medicament for the treatment of hypercholesterolemia.

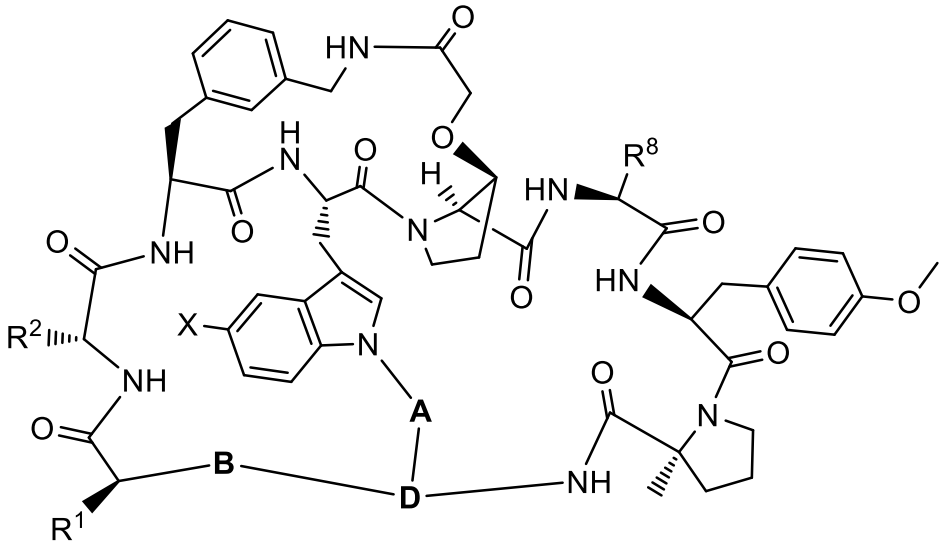
In another aspect the present disclosure provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a composition as defined herein for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

In the description that follows conventional structural representation is employed and includes conventional stereochemical notation for certain asymmetric carbon centers.

What is Claimed is:

1) A compound of Formula I:



Formula I,

wherein:

X is H, F, Cl or Br;

R^1 is selected from:

(a) -H; or

(b) $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) $-NH-C(O)-[(CH_2)_{y12}-O-]_2-(CH_2)_{y13}R^{14B}$ wherein:

y12 and y13 are not both 2 and are independently 2 to 4; and

R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

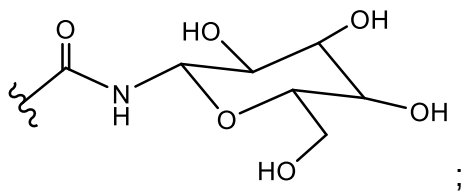
(vii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is -O-$(CH2)_{3-4}$-$N^+(CH_3)_3$; and

(viii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) –O-$(CH2)_2$-$N^+(CH_3)_3$;

(aii) -$N^+(CH_3)_3$; or

(aiii) a moiety of the formula:



;

R^2 is selected from:

(a) -H; and

(b) -$(CH_2)_z$-R^{14A}, wherein: z is 1-6, and R^{14A} is selected from:

(i) -H;

(ii) –NH_2;

(iii) -N^+H_3;

(iv) -$N^+(H_3C)_3$;

(v) -NH-C(O)-[$(CH_2)_2$-O-]$_2$-$(CH_2)_2R^{14B}$ wherein R^{14B} is: -NH_2; -N^+H_3; -$N(CH_3)_2$; or -$N^+(CH_3)_3$;

(vi) -NH-C(O)-[$(CH_2)_{y12}$-O-]$_2$-$(CH_2)_{y13}R^{14B}$ wherein:

y12 and y13 are not both 2 and are independently 2 to 4; and

R^{14B} is: -NH_2; -N^+H_3; -$N(CH_3)_2$; or -$N^+(CH_3)_3$;

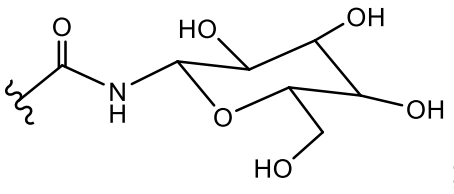
(vii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is -O-$(CH2)_{3-4}$-$N^+(CH_3)_3$; and

(viii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) –O-$(CH_2)_2$-$N^+(CH_3)_3$;

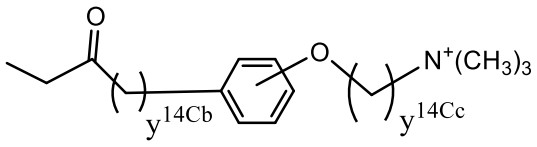
(aii) $-N^{+}(CH_3)_2R^{14ca}$, wherein R^{14ca} is $–CH_3$ or $–(CH_2)_{1-4}-OCH_3$;

(aiii) a moiety of the formula:



; or

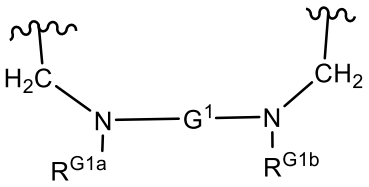
(aiv) a moiety of the formula:



,

where y^{14Cb} and y^{14Cc} are 1 to 4; or

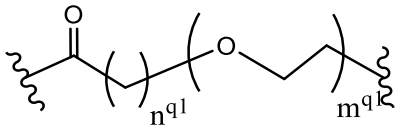
R^1 and R^2 may be bonded together to form a moiety of the formula:



, wherein:

G^1, R^{G1a} and R^{G1b} are defined as follows:

(a) G^1 is a linker moiety of the formula:



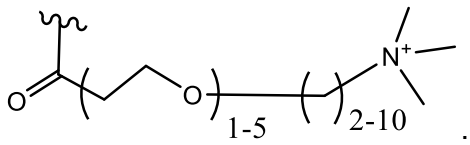
,

wherein n^{q1} is 1 to 6, m^{q1} is 0, 1 or 2 and together the value of n^{q1} and m^{q1} are selected such that the length of the linker moiety they define does not exceed a total of 8 carbon and/or oxygen atoms comprising the chain including the carbon atom in the chain that forms the carbonyl moiety;

R^{G1a} is selected from: (i) –H; and (ii) alkyl of up to 4 carbon atoms; and

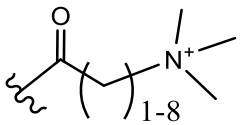
R^{G1b} is selected from:

(i) a moiety of the formula:



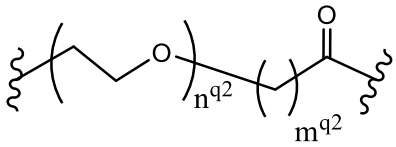
; and

(ii) a moiety of the formula:



; or

(b) G^1 is a linker moiety of the formula:

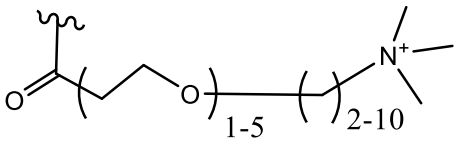


,

wherein n^{q2} is 0, 1 or 2, m^{q2} is 1 to 6, and together the value of n^{q2} and m^{q2} are selected such that the length of the linker moiety they define does not exceed a total of 8 carbon and/or oxygen atoms comprising the chain including the carbon atom in the chain that forms the carbonyl moiety;

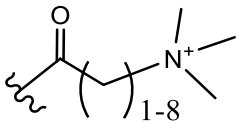
R^{G1a} is selected from:

(i) a moiety of the formula:



; and

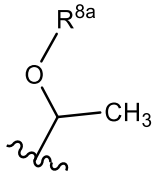
(ii) a moiety of the formula:



; and

R^{G1b} is selected from: (i) –H; and (ii) alkyl of up to 4 carbon atoms;

R^8 is $–CH_3$ or a moiety of the formula:

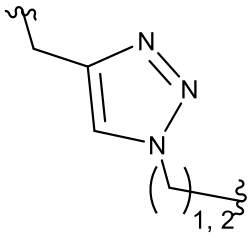


,

wherein R^{8a} is –H, or a linear, branched or cyclic alkyl of up to four carbon atoms;

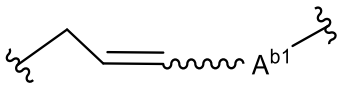
A is selected from:

(a) a moiety of the formula:



;

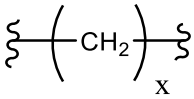
(b) $-CH_2-(CH_2)_y-CH_2-$, wherein y is 1 to 6;

(c) a moiety of the formula: 

,

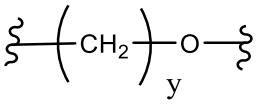
wherein A^{b1} is:

(i) a moiety of the formula:



wherein x is 1 to 6; or

(ii) a moiety of the formula:



wherein y is 1 to 5;

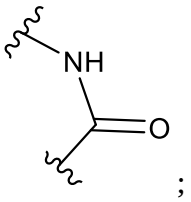
(d) a moiety of the formula: $-CH_2-(CH_2)_m-O-(CH_2)_n-$, wherein m = 1 to 5, and n= 0 or 1 to 4;

B is:

(a) a bond;

(b) $-(CH_2)_{1-2}-$; or

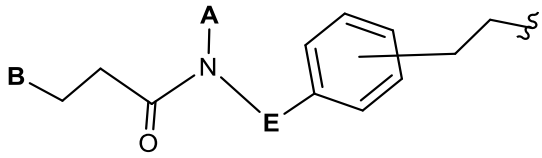
(c) a moiety of the formula:



;

D is:

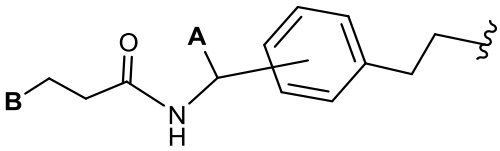
(a) a moiety of the Formula:



,

wherein **E** is $-CH_2-$ or $-(CH_2)_{2-4}-O-$, and **A** and **B** are as defined above;

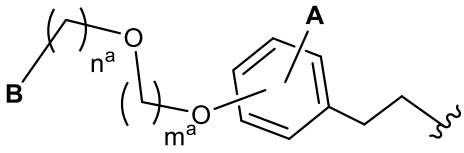
(b) a moiety of the formula:



,

wherein **A** and **B** are as defined above;

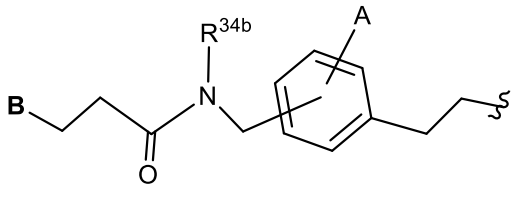
(c) a moiety of the formula:



,

wherein n^a is 1, 2, or 3, m^a is 2, 3, or 4, and $n^a + m^a$ is ≥ 3, and wherein **A** and **B** are as defined above;

(d) a moiety of the formula:



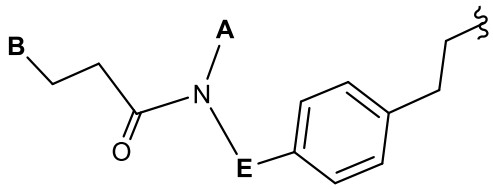
,

wherein, R^{34b} is –H or a liner, branched or cyclic alkyl of up to four carbon atoms, and **A** and **B** are as defined above,

or a pharmaceutically acceptable salt of any thereof.

2. A compound according to Claim 1 of **Formula I,** wherein X is F, or a pharmaceutically acceptable salt of any thereof.

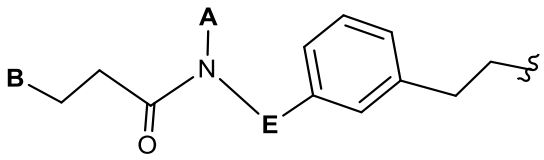
3. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

wherein, **E** is $-CH_2-$ or $-(CH_2)_2-O-$, or a pharmaceutically acceptable salt thereof.

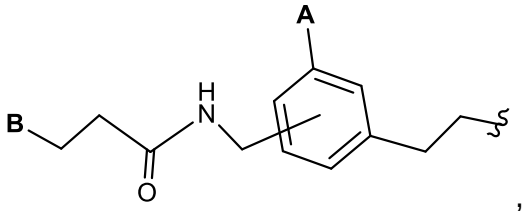
4. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

wherein, **E** is $-CH_2-$ or $-(CH_2)_2-O-$, or a pharmaceutically acceptable salt thereof.

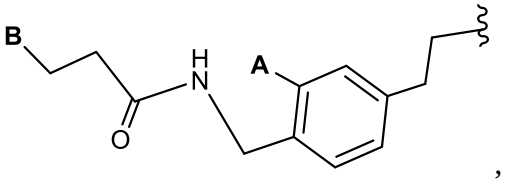
5. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

or a pharmaceutically acceptable salt thereof.

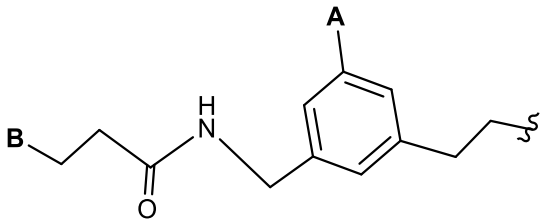
6. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

or a pharmaceutically acceptable salt thereof.

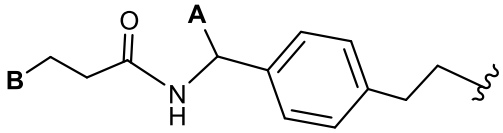
7. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

or a pharmaceutically acceptable salt thereof.

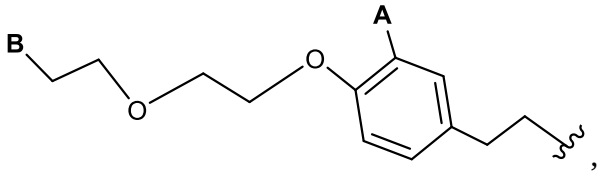
8. A compound of Claim 2 wherein **D** is a moiety of the formula:



,

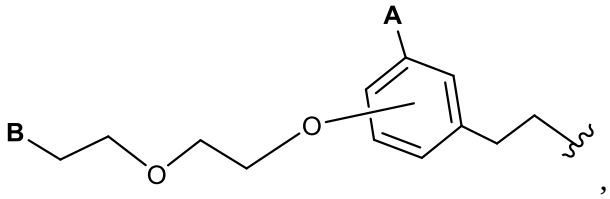
or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 2 wherein **D** is a moiety of the formula:



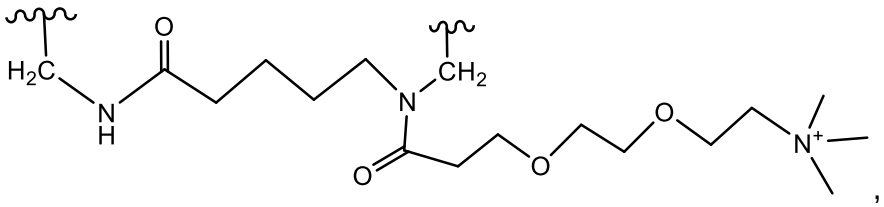
or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 2 wherein **D** is a moiety of the formula:



or a pharmaceutically acceptable salt thereof.

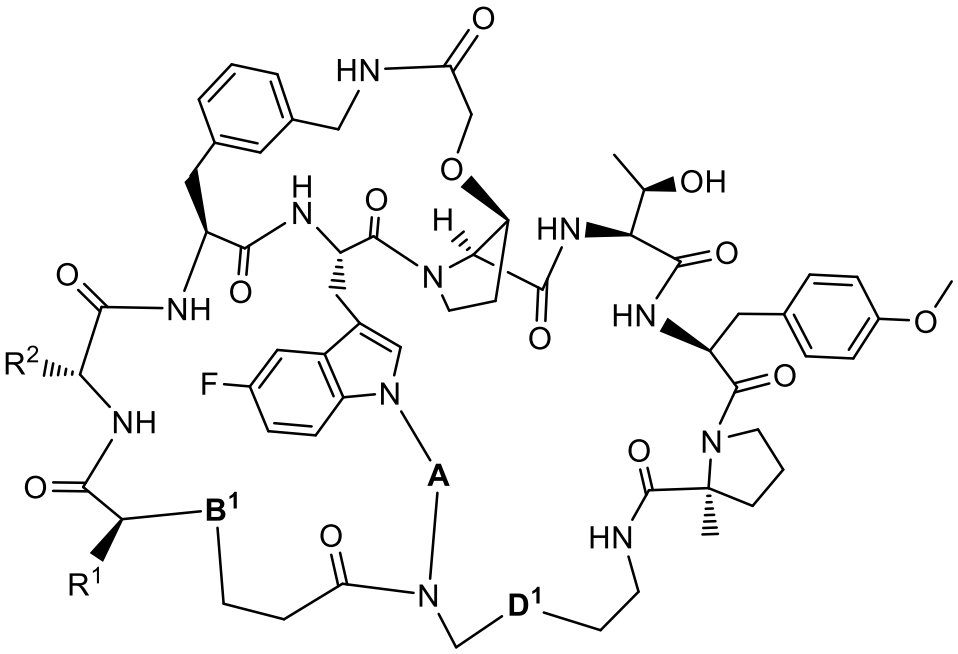
11. A compound of Claim 2 wherein **R^1** and **R^2** are joined together with a moiety of the formula:



such that together with the cyclopeptide to which R^1 and R^2 are attached they form a cyclic structure,

or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 2 having the structure of **Formula IIB,** or a pharmaceutically acceptable salt thereof:

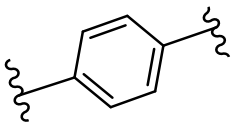


Formula IIB,

B¹ is –((CH₂)₀₋₂)-; and

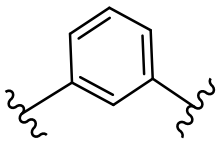
D¹ is:

(a) a moiety of the formula:



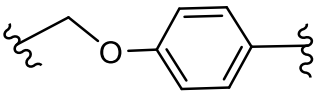
;

(b) a moiety of the formula:



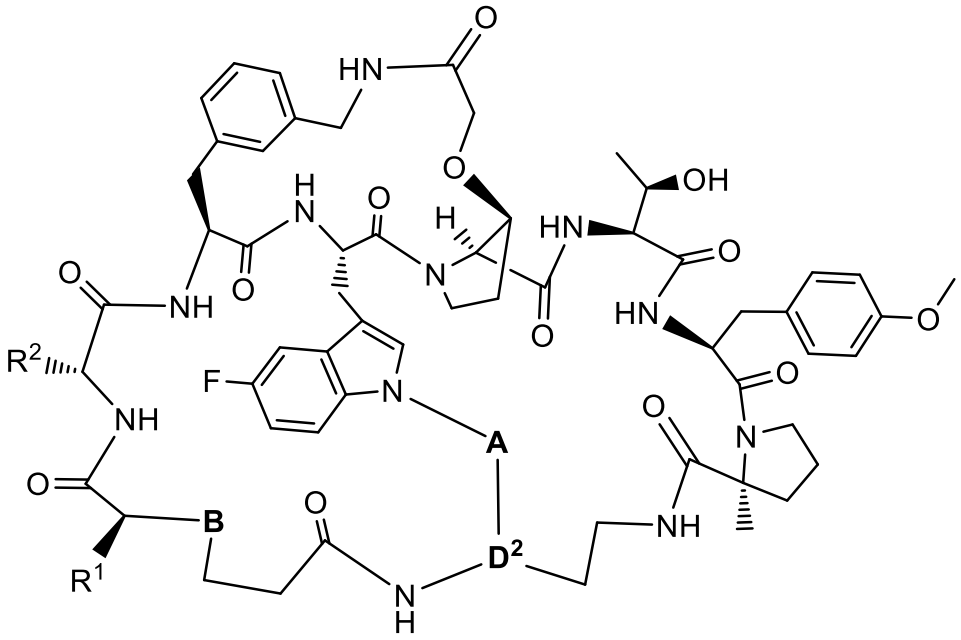
; or

(c) a moiety of the formula:



.

13. A compound of Claim 2 having the structure of **Formula IIC**, or a pharmaceutically acceptable salt thereof:



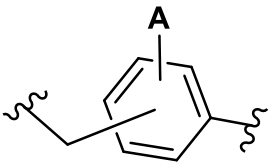
,

Formula IIC,

wherein

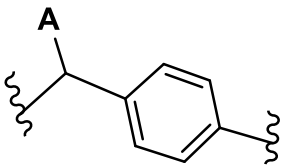
D² is:

(a) a moiety of the formula:



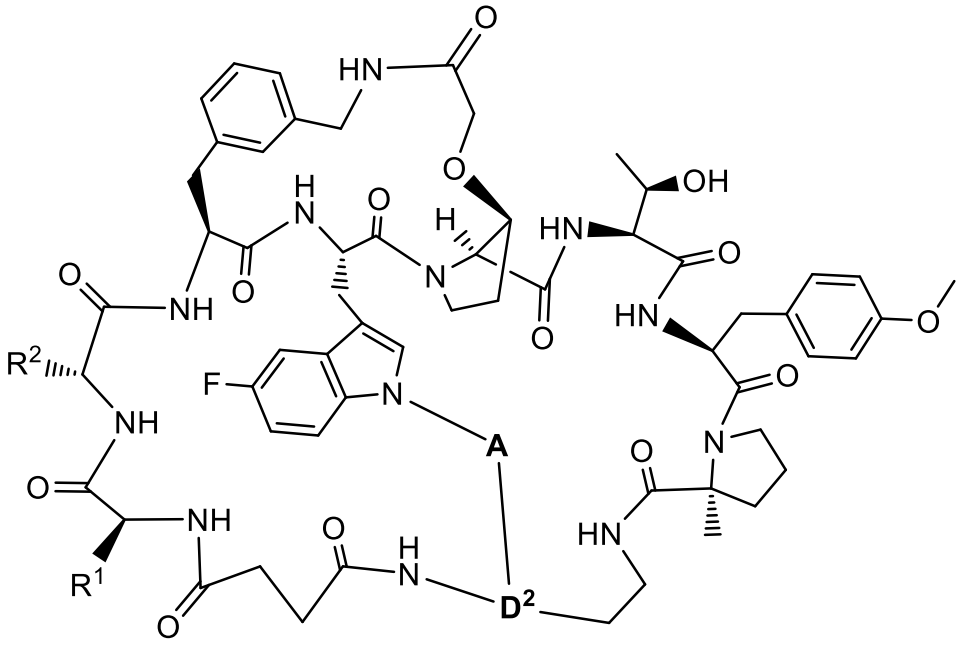
or

(b) a moiety of the formula:



.

14. A Compound of Claim 2 having the structure of Formula IID, or a pharmaceutically acceptable salt thereof:



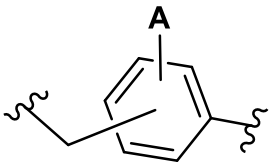
,

Formula IID

wherein

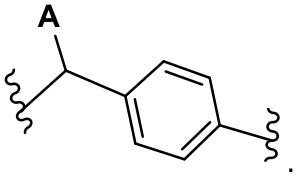
D² is:

(a) a moiety of the formula:



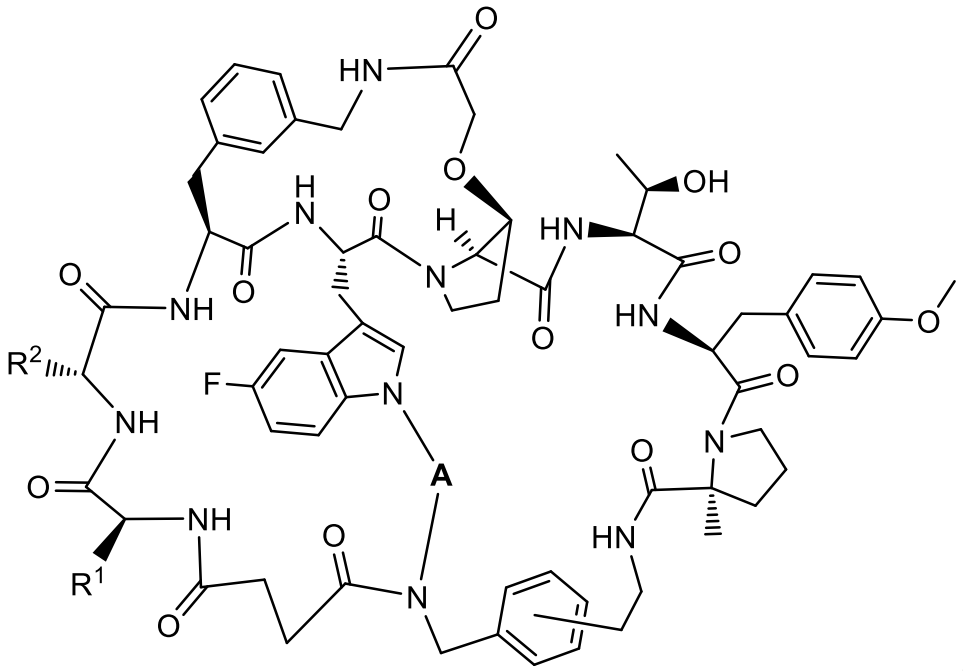
; or

(b) a moiety of the formula:



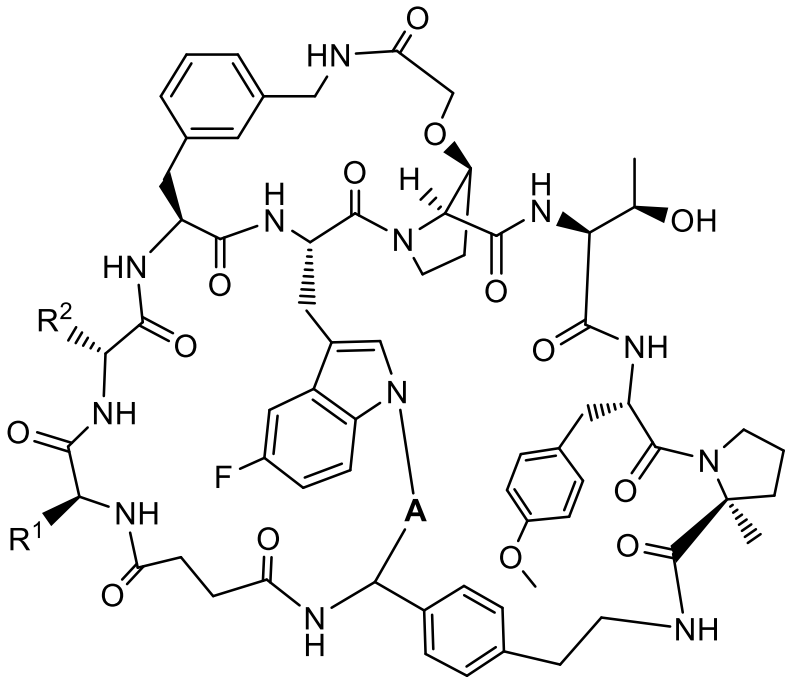
.

15. A compound of Claim 2 having the structure of **Formula IIE**, or a pharmaceutically acceptable salt thereof:



Formula IIE.

16. A compound of Claim 2 having the structure of Formula **IIF**, or a pharmaceutically acceptable salt thereof:

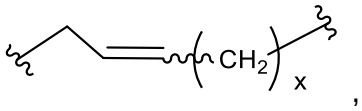


Formula IIF.

17. A compound of any of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein **A** is:

(a) $-(CH_2)_6$;

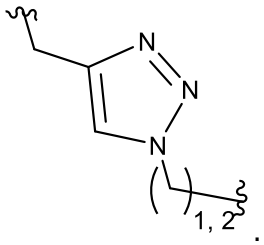
(b) a moiety of the formula:



,

wherein x is 1 to 3; or

(c) a moiety of the formula:



.

18. A compound of any of Claims 1 to 10 and 12 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is:

$-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is:

(a) -H;

(b) $-NH_2$;

(c) $-N^+H_3$;

(d) $-N^+(H_3C)_3$;

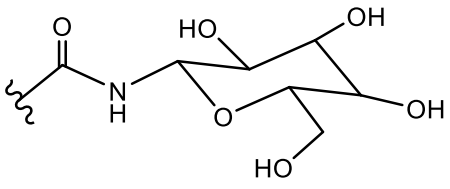
(e) $-NH-C(O)-[(CH_2)_{2-4}-O-]_{2-4}-(CH_2)_{2-4}R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(f) $-NH-C(O)-[(CH_2)_y]R^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) $-O-(CH_2)_{2-4}-N^+(CH_3)_3$;

(aii) $-N^{+}(CH_3)_3$; or

(aiii) a moiety of the formula:



.

19. A compound of any of Claims 1 to 10 and 12 to 16, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:

(a) -H;

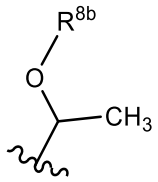
(b) $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is:

(i) -H;

(ii) $-N^{+}H_3$; or

(iii) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2-N^{+}(CH_3)_3$.

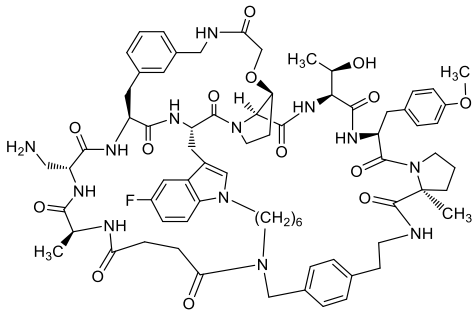
20. A compound of any of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^8 is a moiety of the formula:



,

wherein R^{8b} is –H, $-CH_3$, or $–C(CH_3)_3$.

21 A compound of claim 1, which is selected from the group consisting of:



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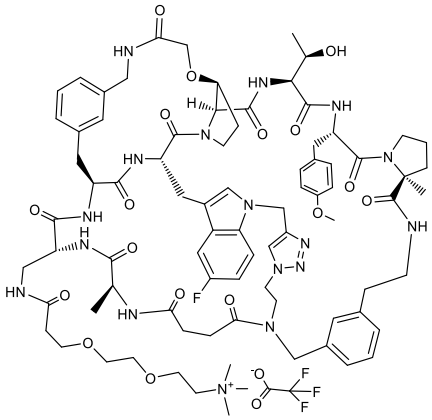

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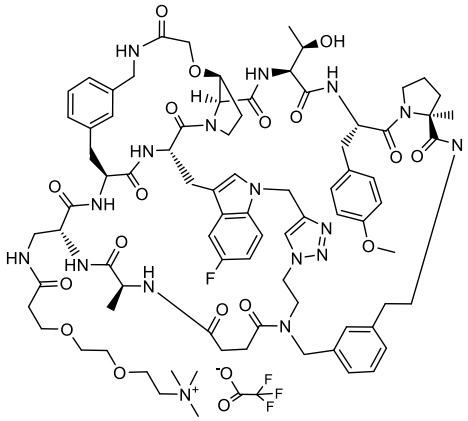

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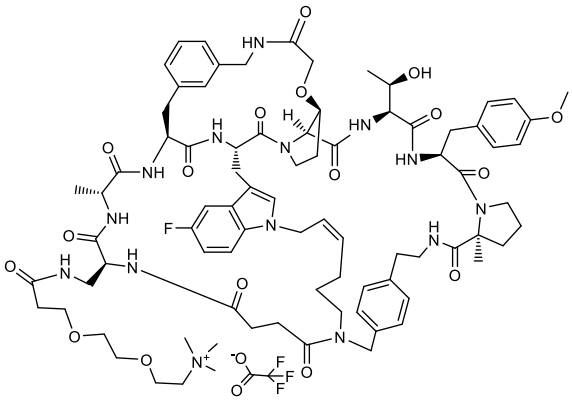

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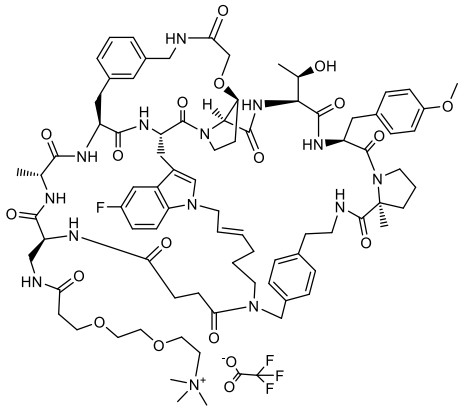

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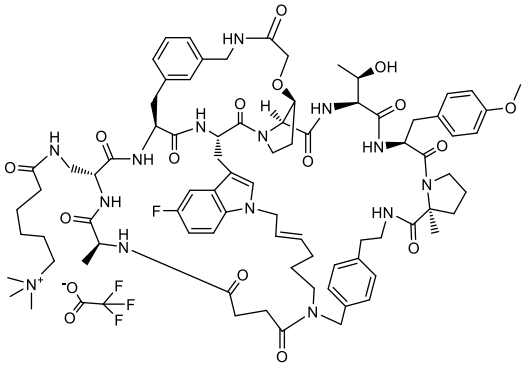

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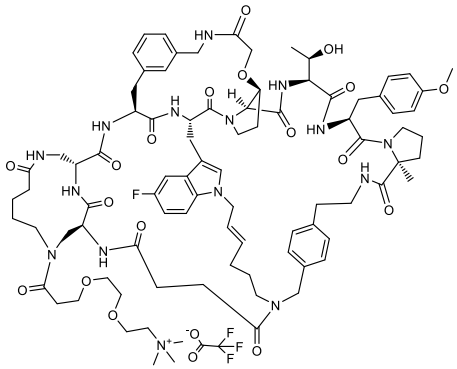

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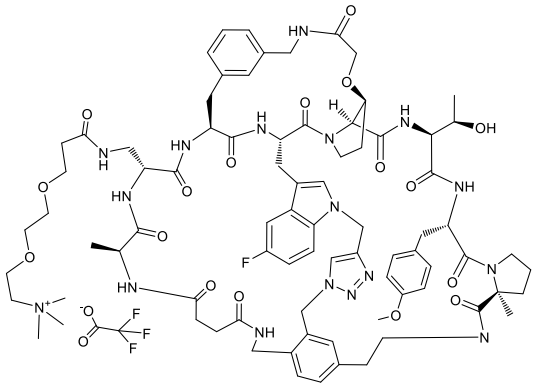

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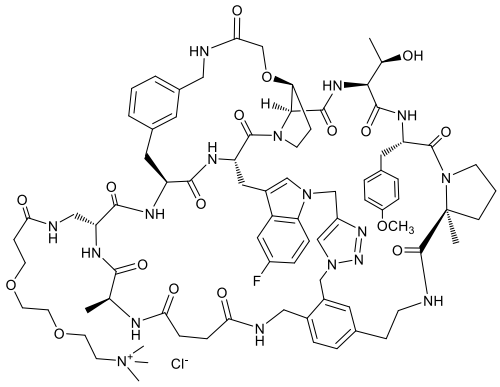

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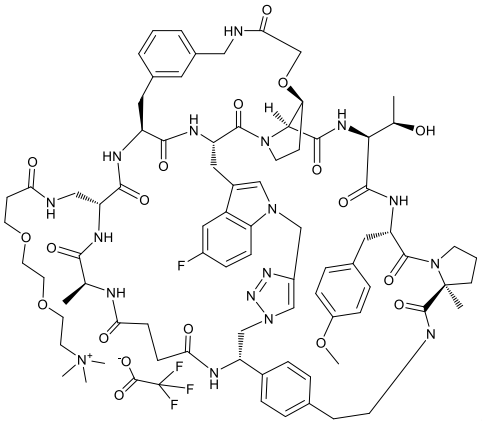

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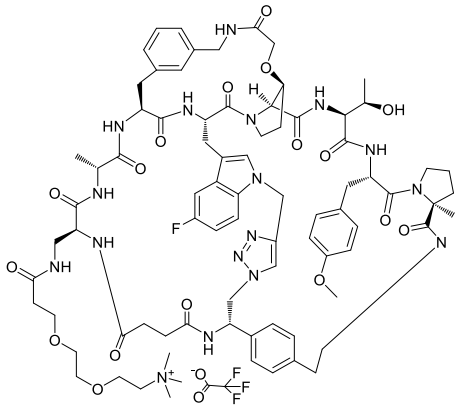

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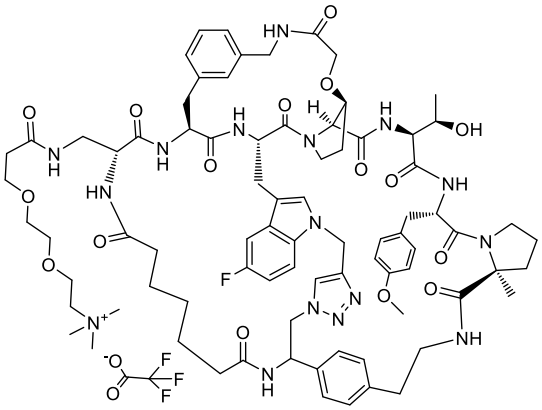

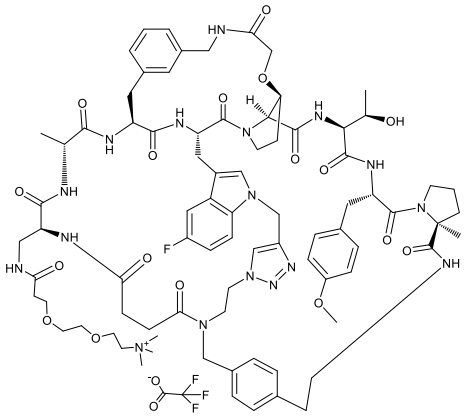

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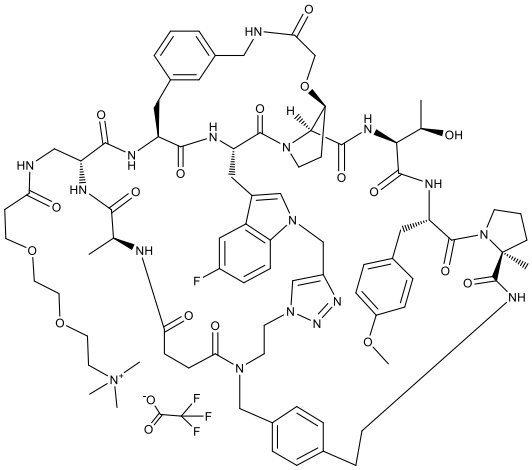

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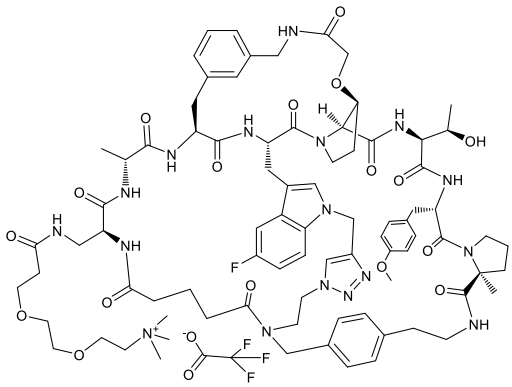

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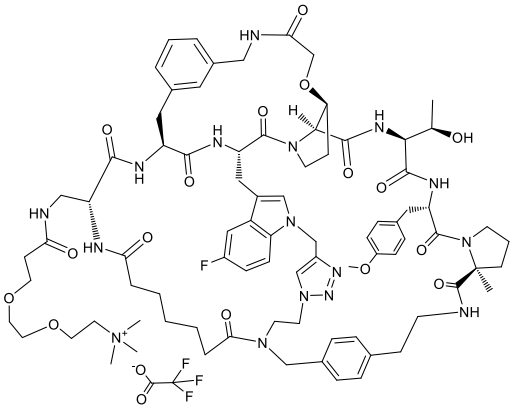

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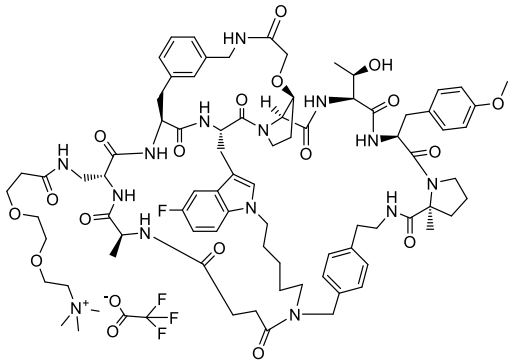

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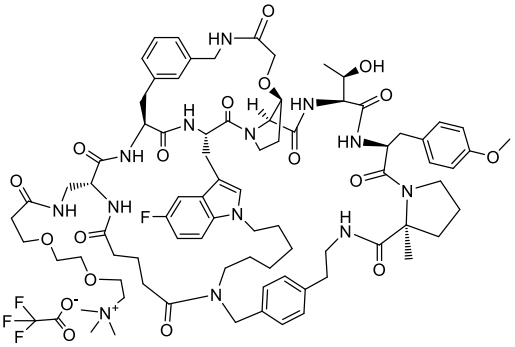

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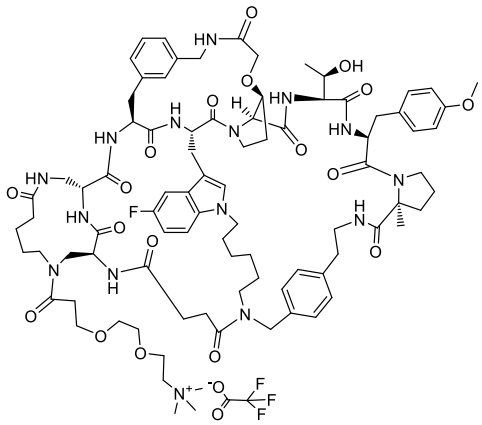

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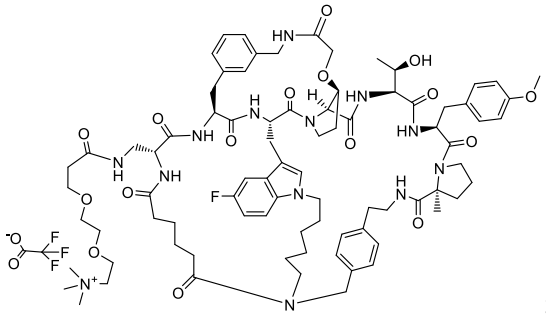

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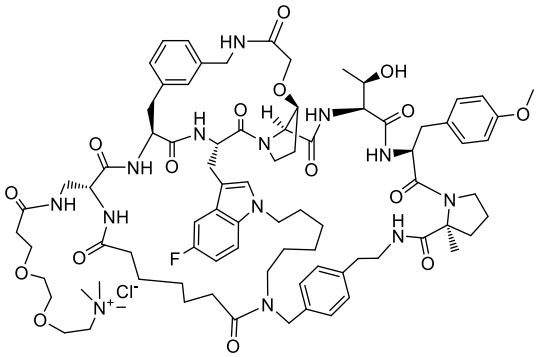

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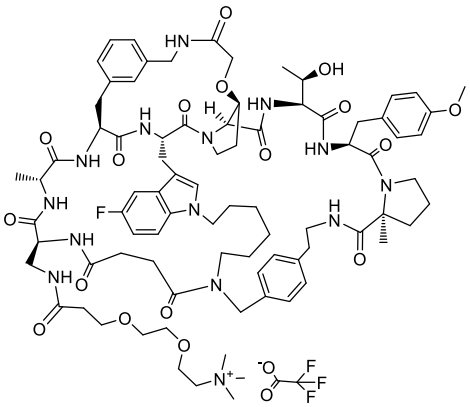

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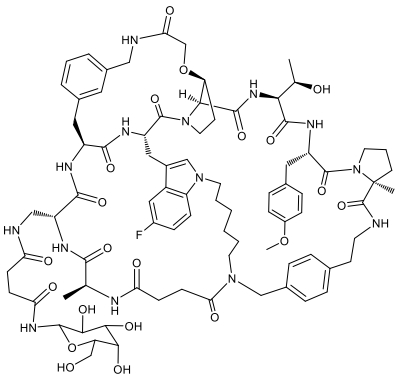

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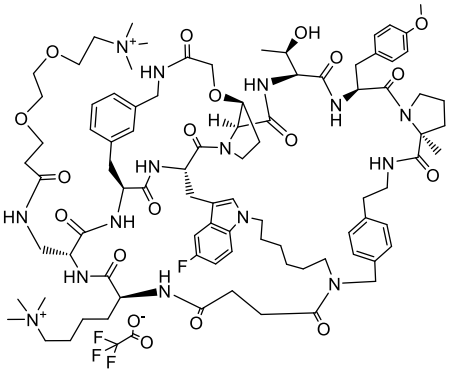

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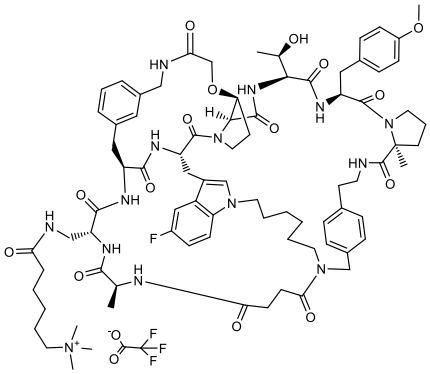

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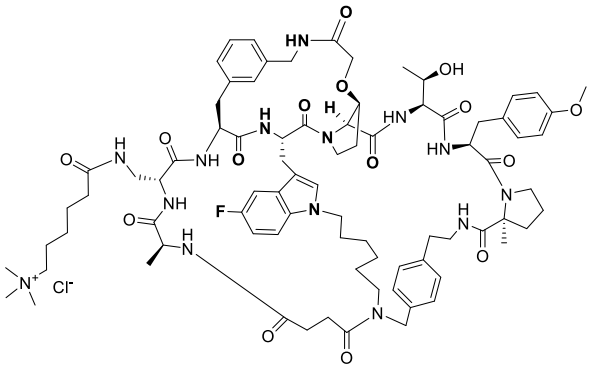

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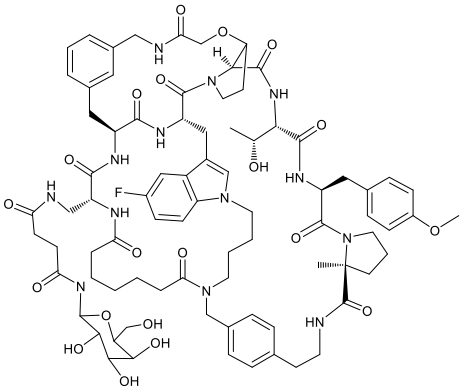

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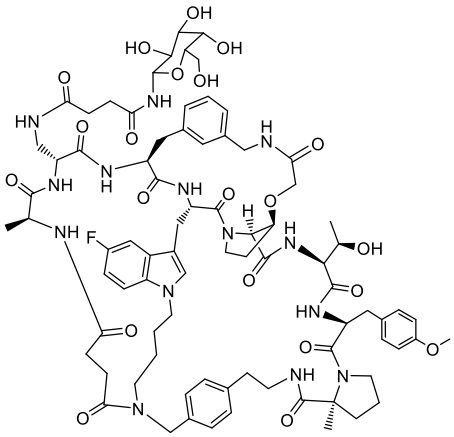

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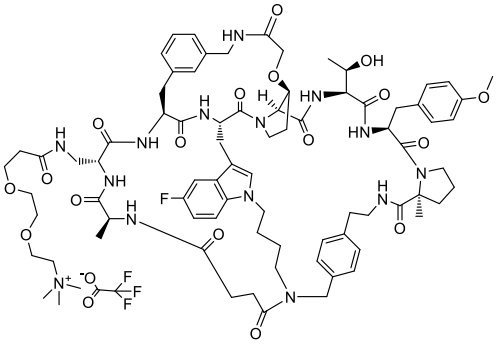

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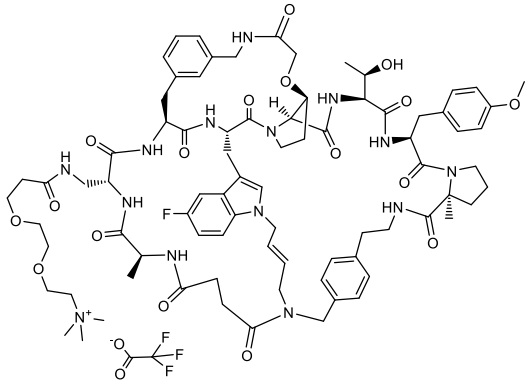

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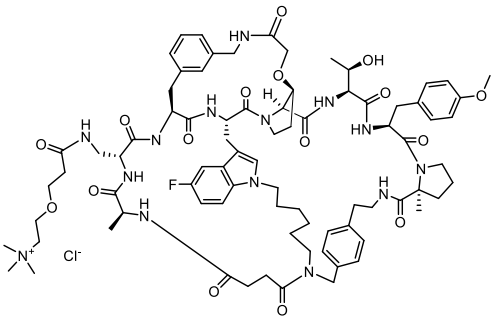

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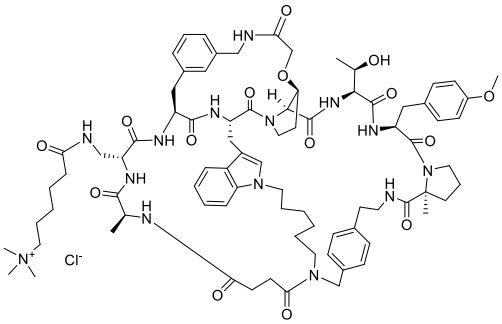

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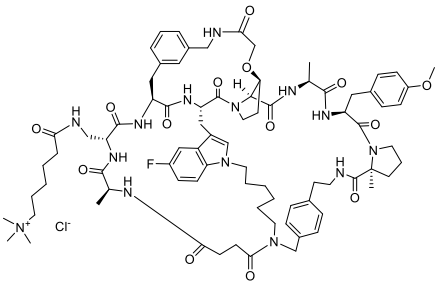

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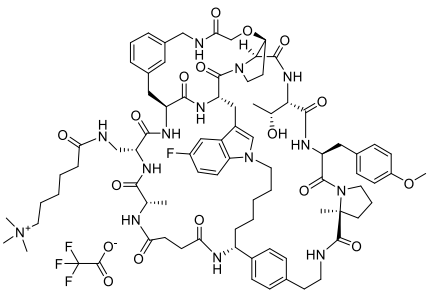

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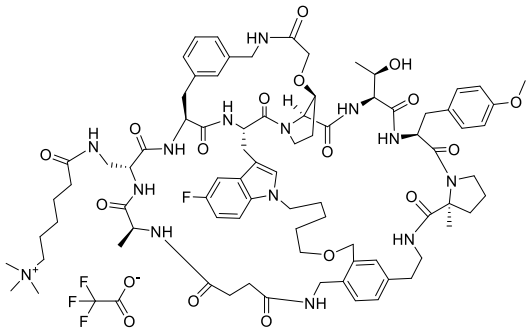

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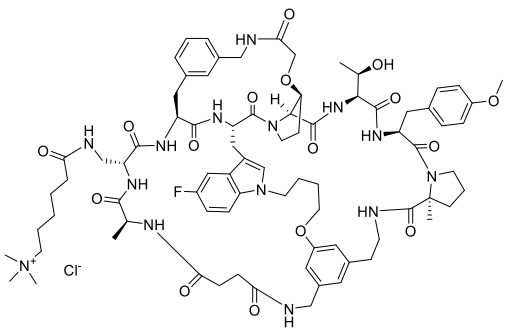

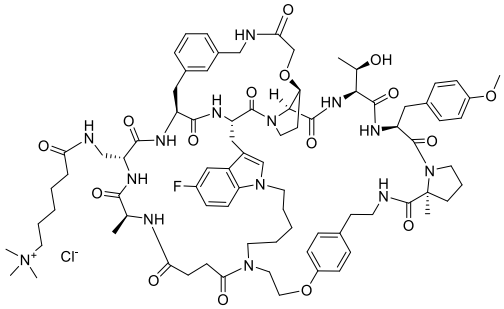

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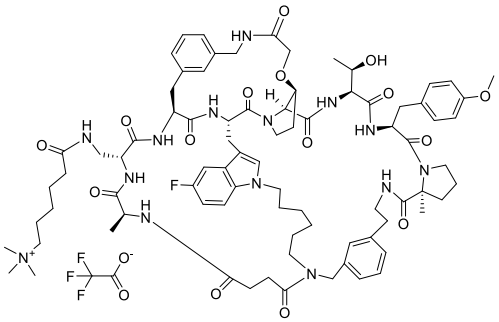

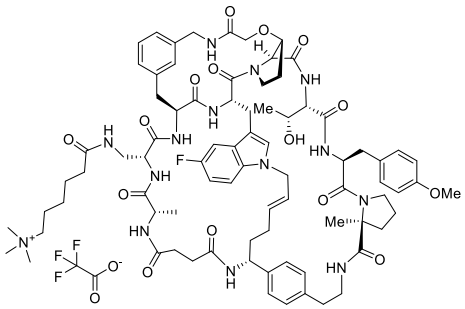

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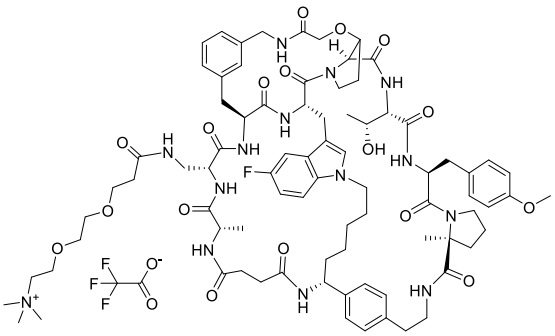

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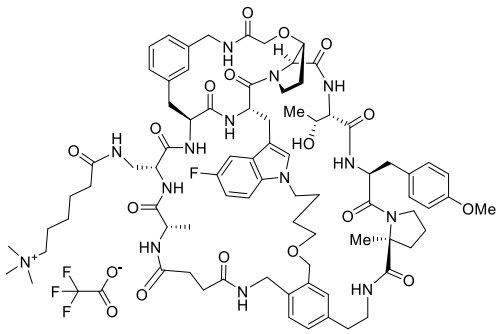

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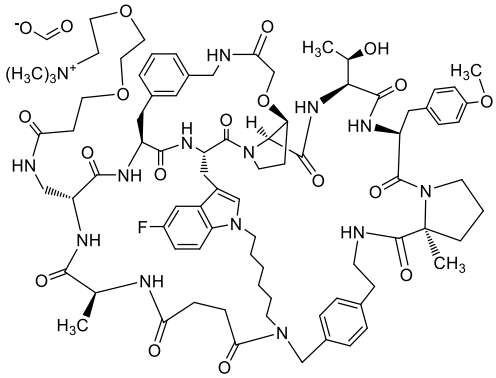

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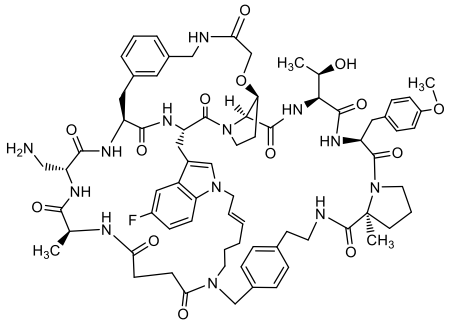

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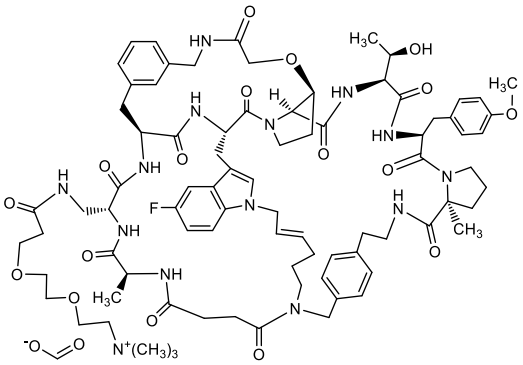

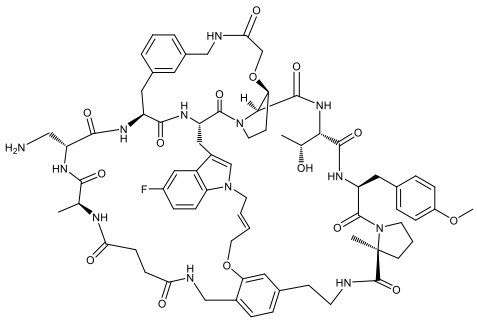

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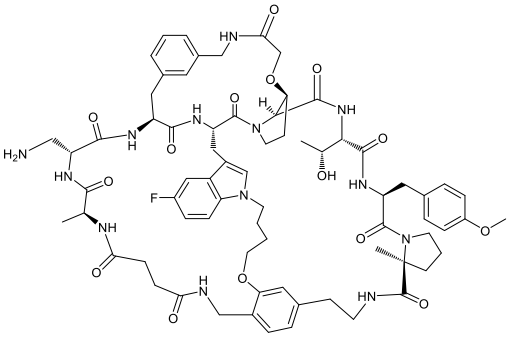

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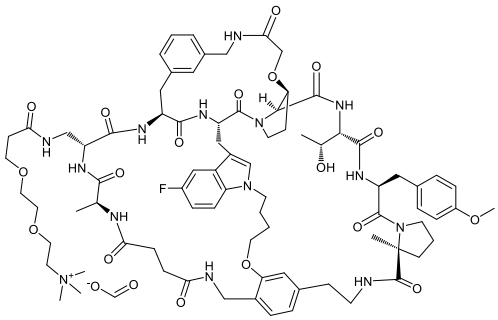

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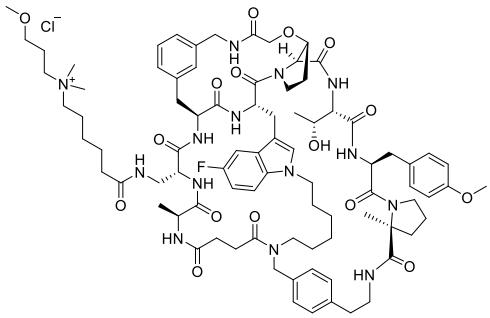

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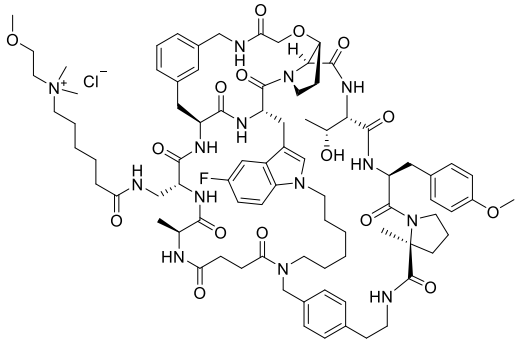
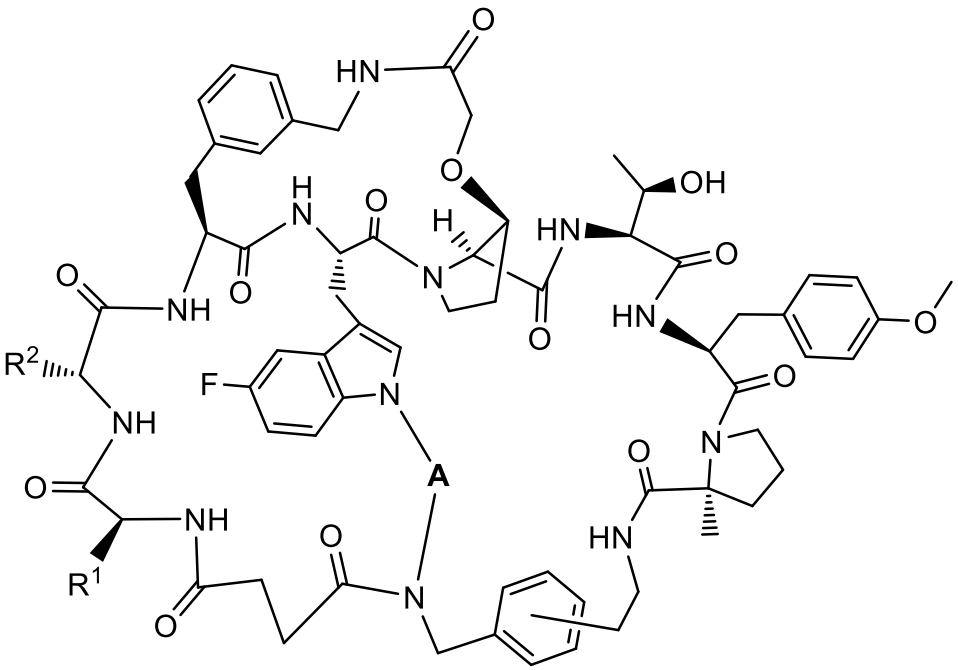


,

or any other pharmaceutically acceptable salt form thereof.

22. A composition comprising at least one compound of any of claims 1 to 21, or a pharmaceutically acceptable salt thereof or freebase form thereof, and at least one pharmaceutically acceptable excipient.

23. A compound of claim 15, having the structure of **Formula IIE**, or a pharmaceutically acceptable salt thereof,



Formula IIE

wherein

R^1 is selected from:

(a) -H; or

(b) $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) $-NH-C(O)-[(CH_2)_{y12}-O-]_2-(CH_2)_{y13}R^{14B}$ wherein: y12 and y13 are not both 2 and are independently 2 to 4; and R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is $-O-(CH2)_{3-4}-N^+(CH_3)_3$; and

(viii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) $–O-(CH2)_2-N^+(CH_3)_3$;

(aii) $-N^+(CH_3)_3$; or

R^2 is selected from:

(a) -H; and

(b) $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is selected from:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) $-NH-C(O)-[(CH_2)_{y12}-O-]_2-(CH_2)_{y13}R^{14B}$ wherein: y12 and y13 are not both 2 and are independently 2 to 4; and R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is $-O-(CH2)_{3-4}-N^+(CH_3)_3$; and

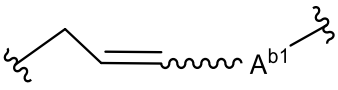
(viii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) $–O-(CH_2)_2-N^+(CH_3)_3$;

(aii) $-N^+(CH_3)_2R^{14ca}$, wherein R^{14ca} is $–CH_3$ or $–(CH_2)_{1-4}-OCH_3$;

A is selected from:

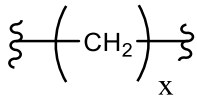
(a) $-CH_2-(CH_2)_y-CH_2-$, wherein y is 1 to 6;

(b) a moiety of the formula: 

,

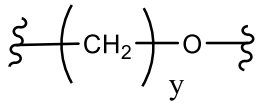
wherein A^{b1} is:

(i) a moiety of the formula:



wherein x is 1 to 6; or

(ii) a moiety of the formula:



wherein y is 1 to 5; and

(c) a moiety of the formula: $-CH_2-(CH_2)_m-O-(CH_2)_n-$, wherein m = 1 to 5, and n= 0 or 1 to 4.

24. A compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) $-NH-C(O)-[(CH_2)_2-O-]_2-(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) $-NH-C(O)-[(CH_2)_{y12}-O-]_2-(CH_2)_{y13}R^{14B}$ wherein: y12 and y13 are not both 2 and are independently 2 to 4; and R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is $-O-(CH2)_{3-4}-N^+(CH_3)_3$; and

(viii) $-NH-C(O)-(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) $–O-(CH2)_2-N^+(CH_3)_3$;

(aii) $-N^+(CH_3)_3$; or

R^2 is $-(CH_2)_z-R^{14A}$, wherein: z is 1-6, and R^{14A} is selected from:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) -NH-C(O)-[$(CH_2)_2$-O-]$_2$-$(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) -NH-C(O)-[$(CH_2)_{y12}$-O-]$_2$-$(CH_2)_{y13}R^{14B}$ wherein: y12 and y13 are not both 2 and are independently 2 to 4; and R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is -O-$(CH2)_{3-4}$-$N^+(CH_3)_3$; and

(viii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) –O-$(CH_2)_2$-$N^+(CH_3)_3$;

(aii) $-N^+(CH_3)_2R^{14ca}$, wherein R^{14ca} is $–CH_3$ or $–(CH_2)_{1-4}$-OCH_3;

A is $-CH_2$-$(CH_2)_y$-CH_2-, wherein y is 1 to 6.

25. A compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein

R^1 is -$(CH_2)_z$-R^{14A}, wherein: z is 1-6, and R^{14A} is:

(i) -H;

R^2 is -$(CH_2)_z$-R^{14A}, wherein: z is 1-6, and R^{14A} is selected from:

(i) -H;

(ii) $–NH_2$;

(iii) $-N^+H_3$;

(iv) $-N^+(H_3C)_3$;

(v) -NH-C(O)-[$(CH_2)_2$-O-]$_2$-$(CH_2)_2R^{14B}$ wherein R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vi) -NH-C(O)-[$(CH_2)_{y12}$-O-]$_2$-$(CH_2)_{y13}R^{14B}$ wherein: y12 and y13 are not both 2 and are independently 2 to 4; and R^{14B} is: $-NH_2$; $-N^+H_3$; $-N(CH_3)_2$; or $-N^+(CH_3)_3$;

(vii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is -O-$(CH2)_{3-4}$-$N^+(CH_3)_3$; and

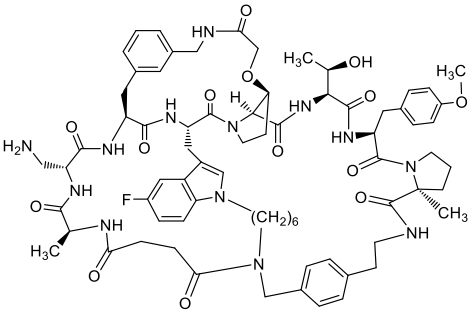
(viii) -NH-C(O)-$(CH_2)_yR^{14C}$, wherein, y= 1 to 6 and R^{14C} is:

(ai) –O-$(CH_2)_2$-$N^+(CH_3)_3$;

(aii) $-N^+(CH_3)_2R^{14ca}$, wherein R^{14ca} is $–CH_3$ or $–(CH_2)_{1-4}$-OCH_3;

A is $-CH_2$-$(CH_2)_y$-CH_2-, wherein y is 1 to 6.

26. A compound selected from the group consisting of:



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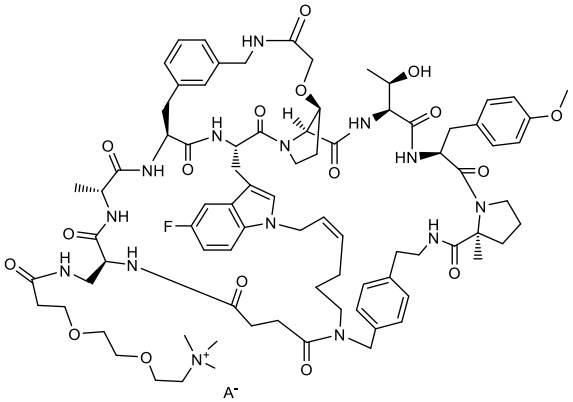

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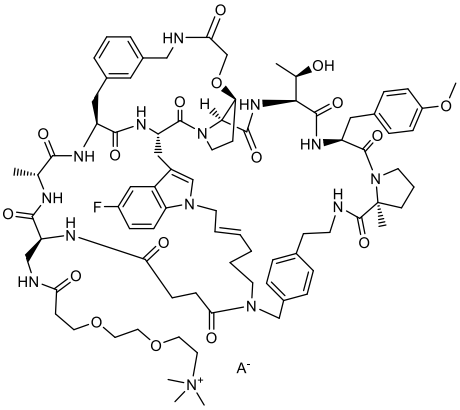

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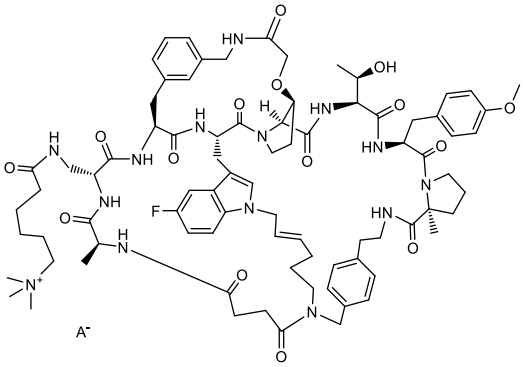

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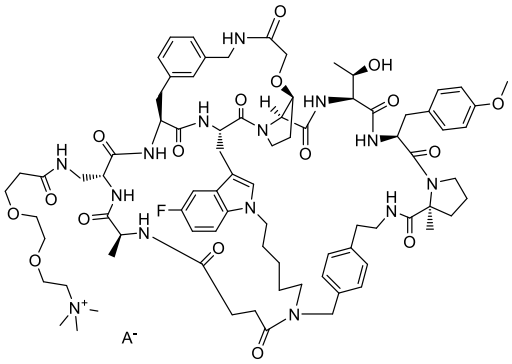

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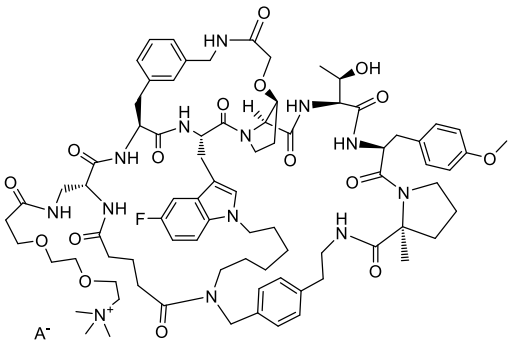

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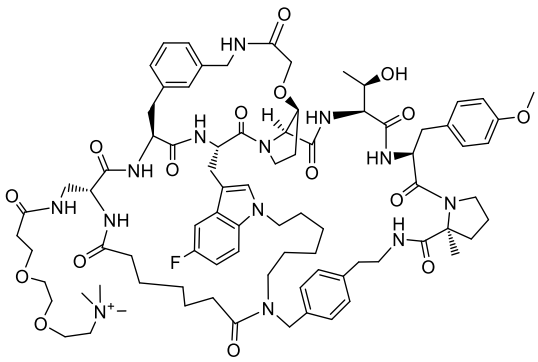

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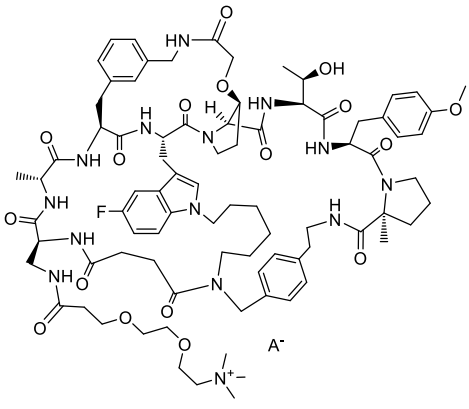

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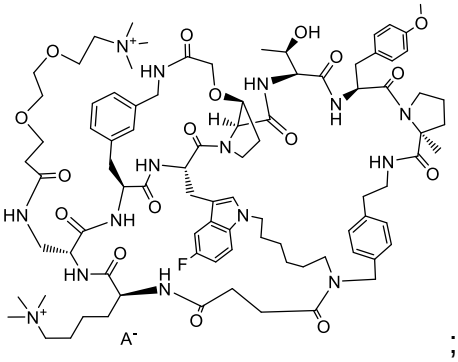

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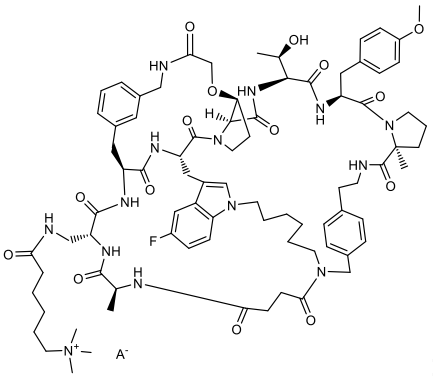

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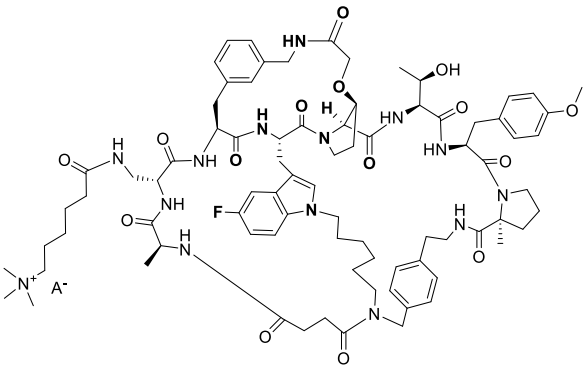

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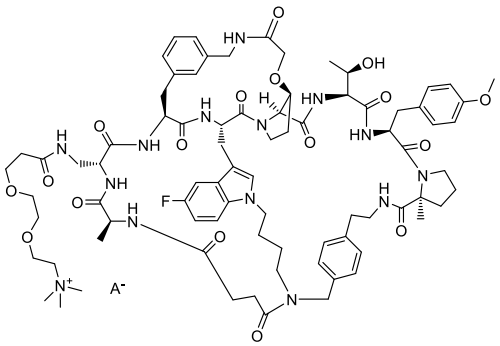

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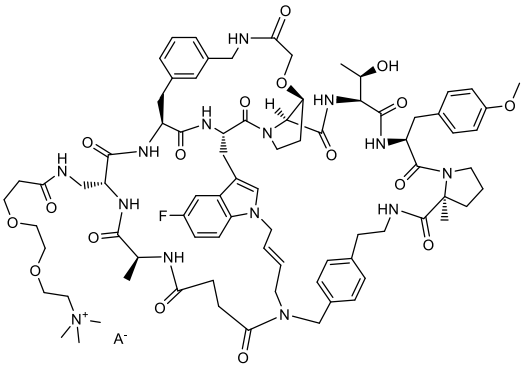

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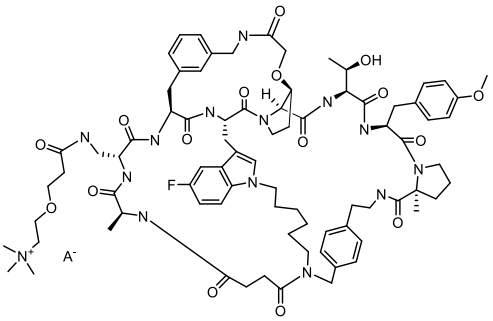

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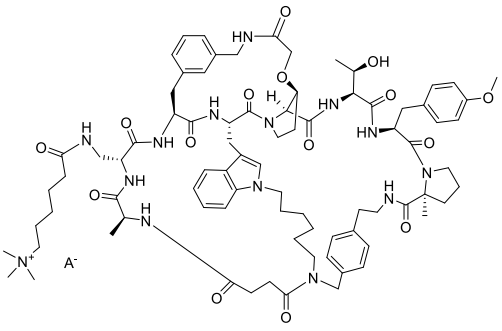

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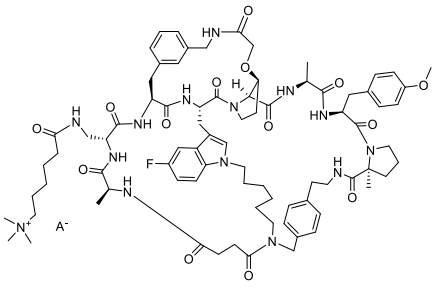

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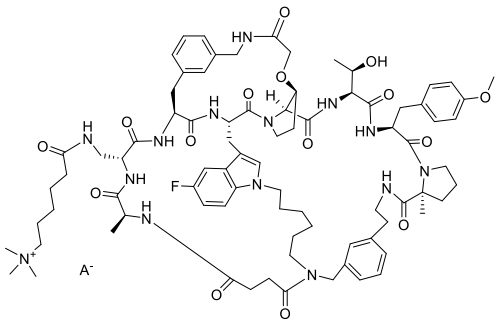

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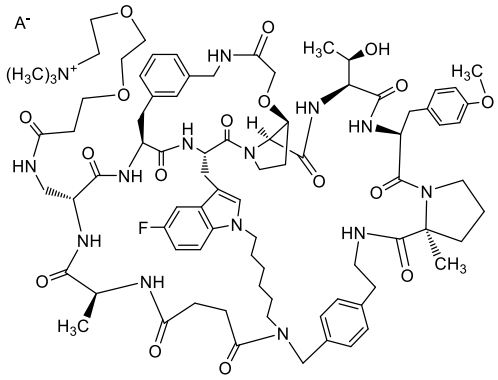

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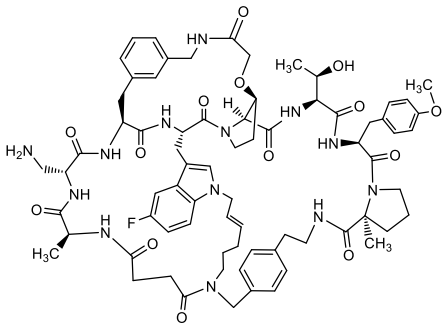

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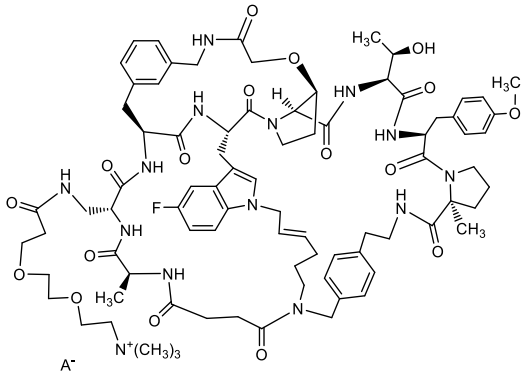

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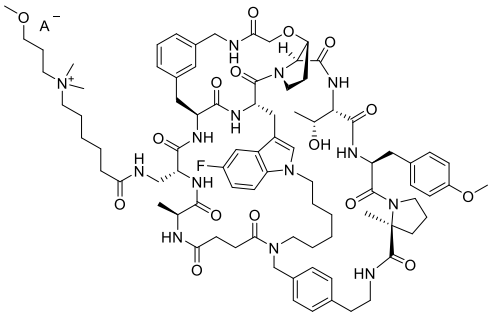

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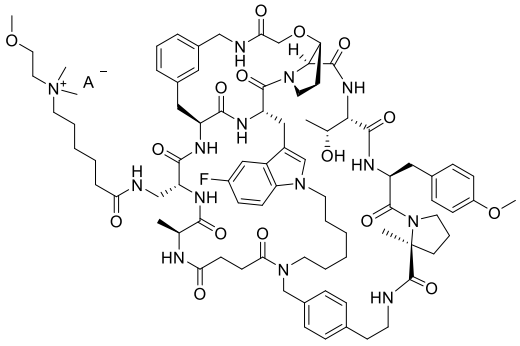

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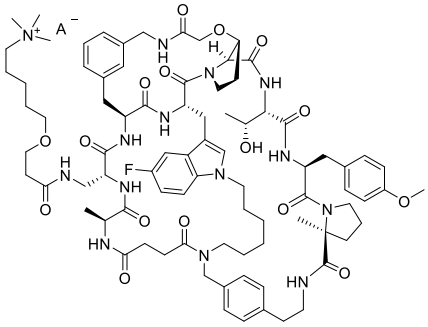

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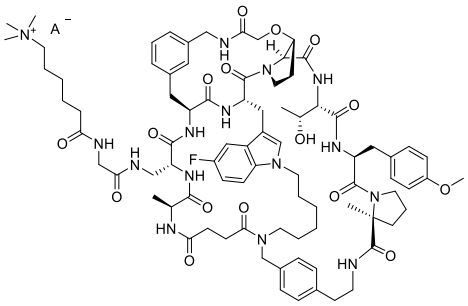

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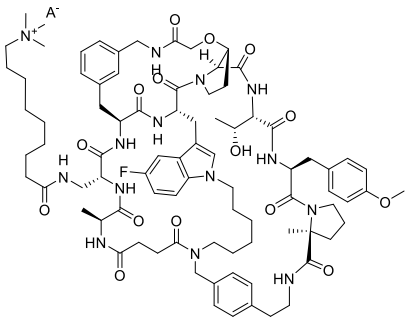
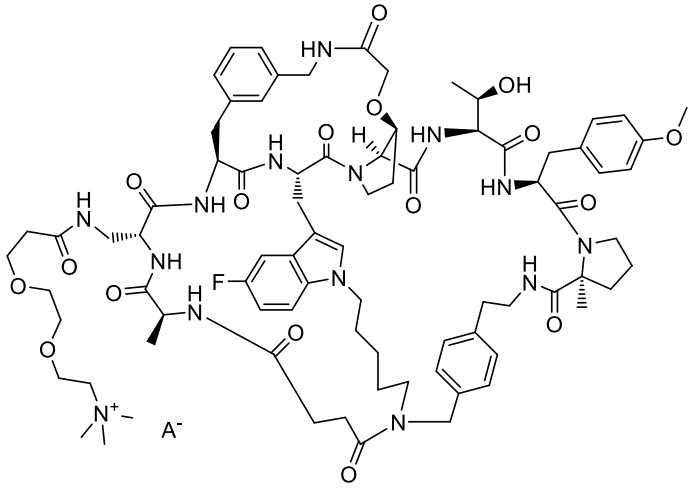


,

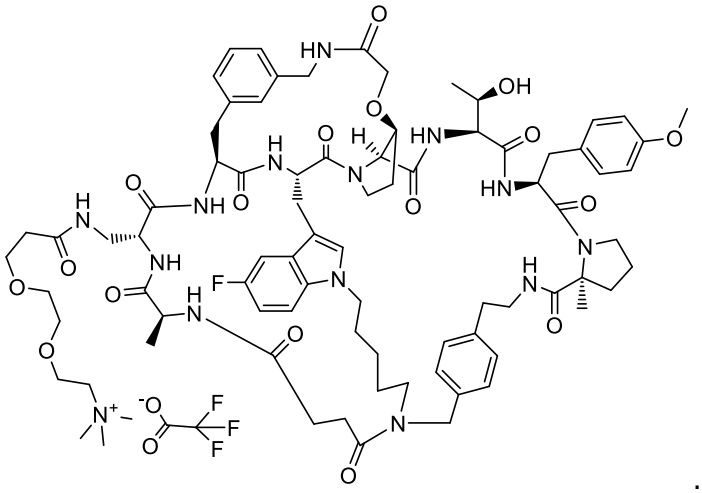
wherein A^- is a pharmaceutically acceptable anion.

27. The compound having the structure:



wherein A^- is a pharmaceutically acceptable anion.

28. A compound of claim 27, wherein the compound is:



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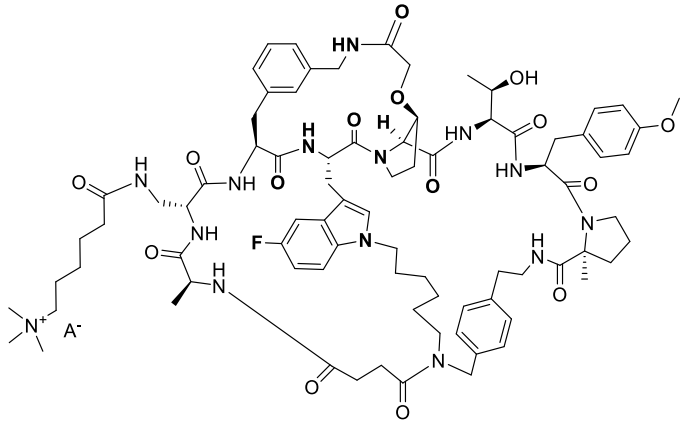
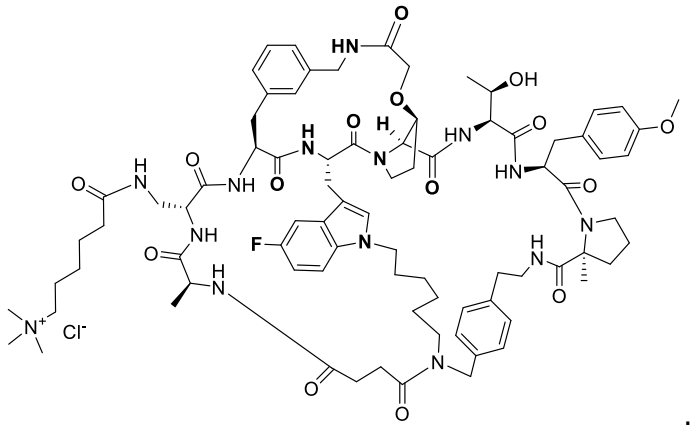
29. The compound having the structure:

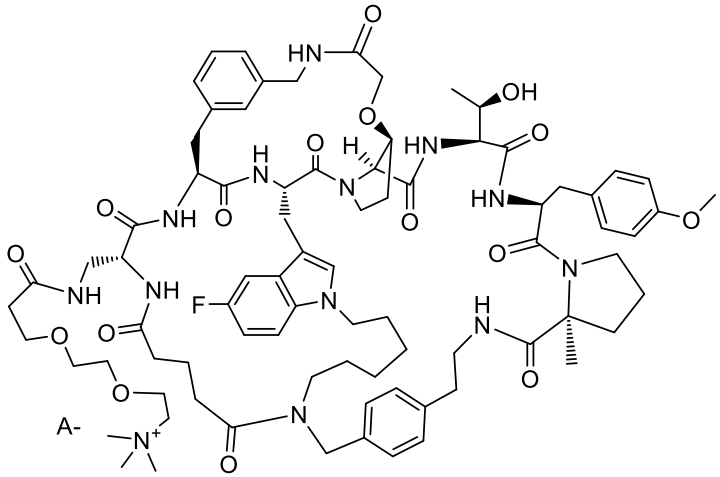


wherein A^- is a pharmaceutically acceptable anion.

30. A compound of claim 29, wherein the compound is:

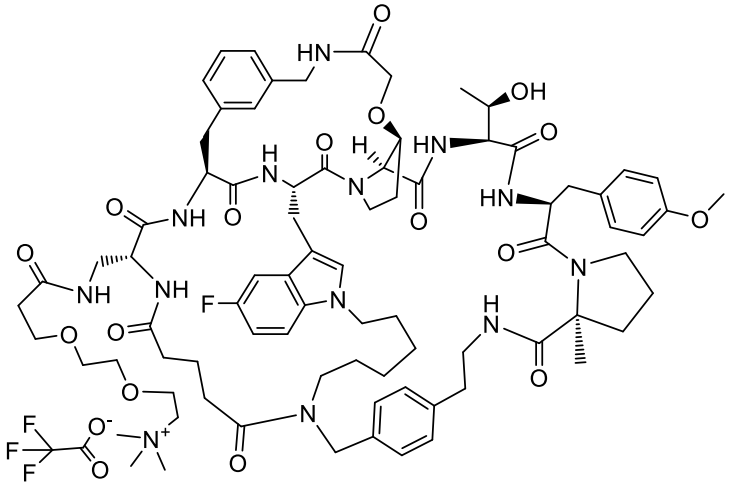


31. The compound having the structure:



wherein A^- is a pharmaceutically acceptable anion.

32. A compound of claim 31, wherein the compound is:



33. A composition comprising the compound of any one of Claims 23 to 32, and at least one pharmaceutically acceptable excipient.

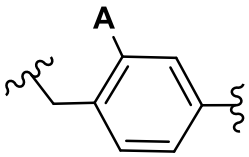
34. Use of a composition of Claim 22 or Claim 33 in the manufacture of a medicament for the treatment of hypercholesterolemia.

35. Use of compound of any of Claims 1 to 21 or Claims 23 to 32 in the manufacture of a medicament for the treatment of hypercholesterolemia.

36. A compound according to any of Claims 1 to 21 or Claims 23 to 32, or a pharmaceutically acceptable salt thereof, or a composition according to Claim 22 or Claim 33 for use in therapy.

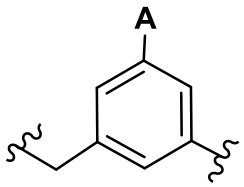
37. A compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{D^2}$ is:

(a) a moiety of the formula:



; or

(b) a moiety of the formula:



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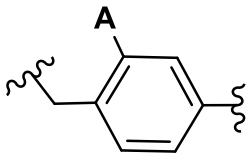
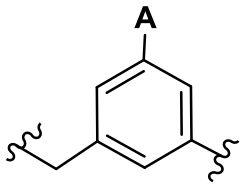
38. A compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein **D²** is:

(a) a moiety of the formula:



; or

(b) a moiety of the formula:



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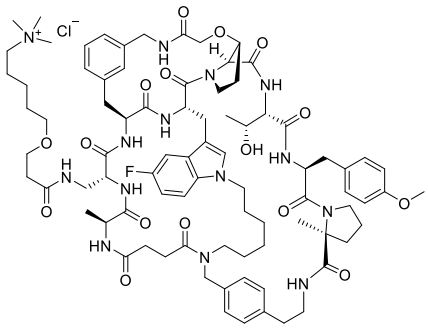
39. A compound or a pharmaceutically acceptable salt thereof, selected from the group consisting of:



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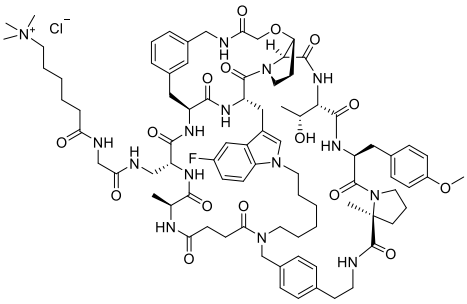
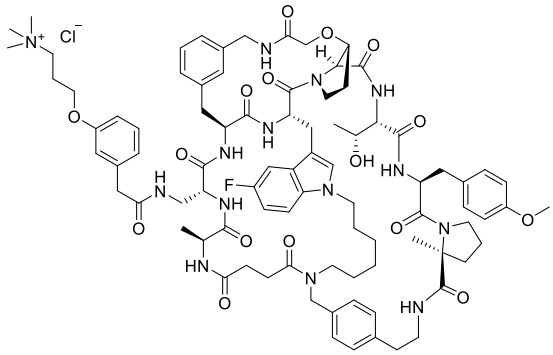


; and



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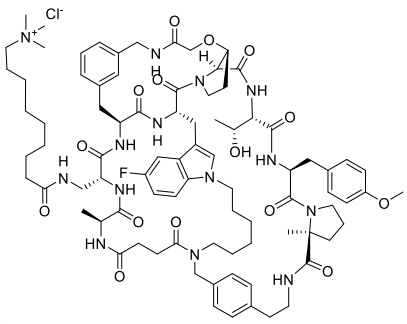

,

or any other pharmaceutically acceptable salt form thereof.