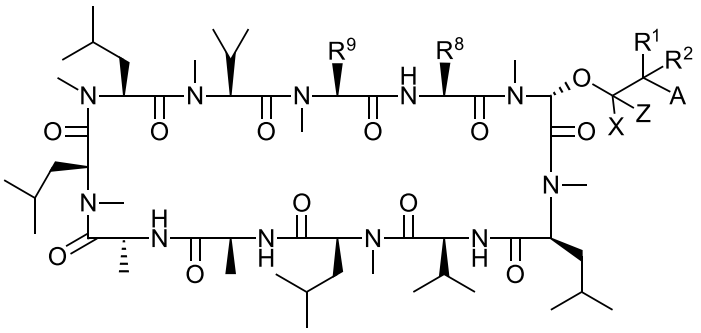
Claims

1. A compound according to Formula 4, or a pharmaceutically acceptable salt thereof,



(Formula 4)

wherein:

R^1 and R^2 are independently selected from H, C_1 to C_6 alkyl or wherein R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

X and Z are both alkyl, or wherein X is alkyl and Z is H, or wherein X and Z are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

A is selected from:

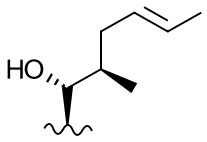
- NR^3R^4, wherein R^3 and R^4 are independently selected from H, C_1 to C_6 alkyl;

and

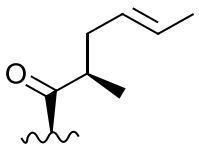
- $N=C(R^5)NR^6R^7$, wherein R^5, R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

R^8 is ethyl, 1-hydroxyethyl, isopropyl, or n-propyl; and

R^9 is Formula 1a or 1b



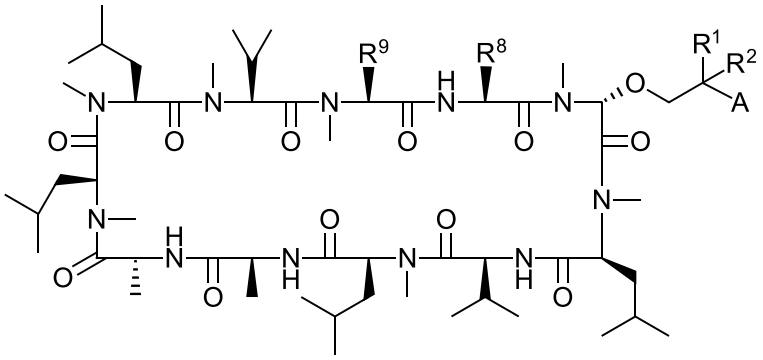
(Formula 1a)



(Formula 1b)

.

2. A compound according to Formula 1 or a pharmaceutically acceptable salt thereof,



(Formula 1)

wherein:

R^1 and R^2 are independently selected from H, C_1 to C_6 alkyl or wherein R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

A is selected from:

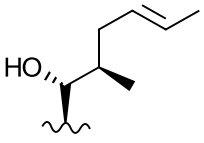
- NR^3R^4, wherein R^3 and R^4 are independently selected from H, C_1 to C_6 alkyl;

and

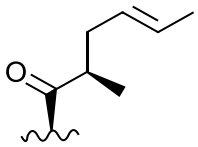
- $N=C(R^5)NR^6R^7$, wherein R^5, R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

R^8 is ethyl, 1-hydroxyethyl, isopropyl, or n-propyl;

R^9 is Formula 1a or 1b



(Formula 1a)



(Formula 1b)

provided that if R^1 and R^2 are both H, or if R^1 is methyl and R^2 is H, and R^8 is selected from ethyl, isopropyl, and n-propyl, R^9 is Formula 1a, and A is NR^3R^4, then R^3 and R^4 are not H or C_1-C_4 alkyl.

3. The compound according to claim 1 or 2, wherein:
a. R^1 and R^2 are both hydrogen; or

b. at least one of R^1 or R^2 is C_1 to C_6 alkyl; or wherein

c. R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring.

4. The compound according to any one of the preceding claims wherein R^8 is ethyl.

5. The compound according to any one of claims 1 to 3, wherein R^8 is selected from 1-hydroxyethyl, isopropyl, and n-propyl.

6. The compound according to any one of the preceding claims, wherein R^9 is Formula 1a.

7. The compound according to any one of the preceding claims, wherein A is NR^3R^4.

8. The compound according to claim 7 wherein R^3 and R^4 are both $-CH_3$.

9. The compound according to claim 7 or 8, wherein R^8 is 1-hydroxyethyl, isopropyl or n-propyl.

10. The compound according to any one of claims 1 to 6, wherein A is $-N=C(R^5)NR^6R^7$.

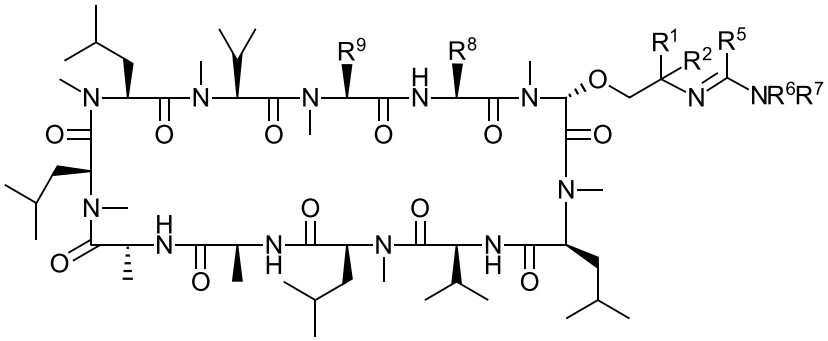
11. The compound according to claim 10, wherein R^5, R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl or optionally, substituted C_1 to C_6 alkyl.

12. The compound according to claim 11, wherein R^5 is H or CH_3 and wherein R^6 and R^7 are CH_3.

13. The compound according to claim 10 or 11, wherein R^8 is ethyl.

14. The compound according to any one of claims 1 to 13, wherein the Compound is of Formula 4 and wherein X is C_1 to C_6 alkyl (e.g. methyl), and Z is H.

15. The compound according to claim 2, wherein the compound, or a pharmaceutically acceptable salt thereof is of Formula 3:



(Formula 3)

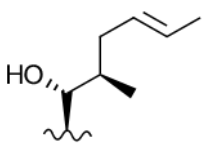
wherein:

R^1 and R^2 are independently selected from H, C_1 to C_6 alkyl, or wherein R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

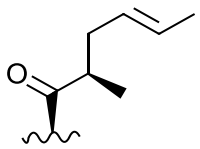
wherein R^5, R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

R^8 is ethyl, 1-hydroxyethyl, isopropyl, or n-propyl; and

R^9 is Formula 1a or 1b



(Formula 1a)



(Formula 1b)

16. The compound according to claim 15 wherein:

a. R^1 and R^2 are both hydrogen; or

b. wherein at least one of R^1 or R^2 is C_1 to C_6 alkyl; or wherein

c. R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring.

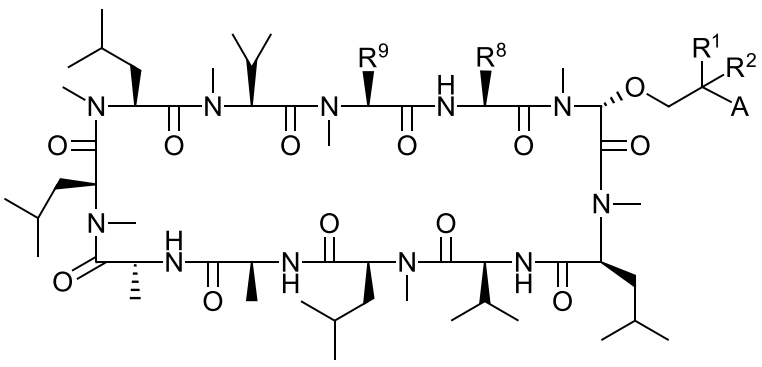
17. The compound according to claim 15 or 16, wherein R^8 is ethyl.

18. The compound according to claim 15 or 16, wherein R^8 is isopropyl, n-propyl, or 1-hydroxyethyl.

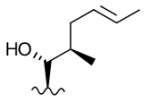
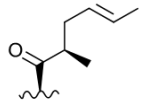
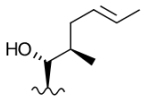
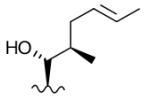
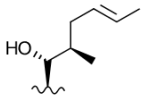
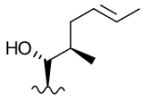
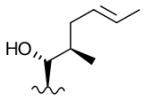
19. The compound according to any one of claims 15 to 18 wherein R^5, R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally, substituted C_1 to C_6 alkyl.

20. The compound according to claim 19 and wherein R^5 is H or CH_3 and wherein R^6 and R^7 are CH_3.

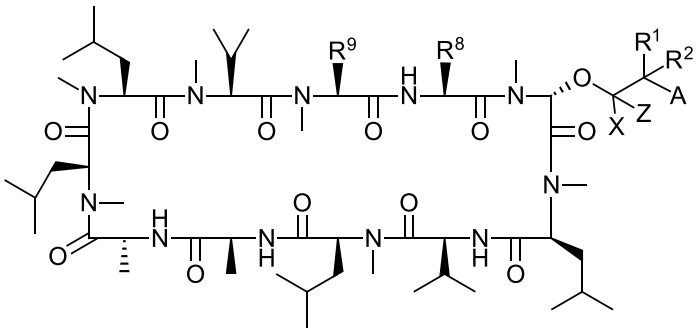
21. The compound according to claim 1 or 2, wherein the compound, or pharmaceutically acceptable salt thereof is selected from the group consisting of the following compounds of Formula I or pharmaceutically acceptable salts thereof:



(Formula 1)

Compound	R^1	R^2	A	R^8	R^9
2	H	H	$-N(CH_3)_2$	$-CH(OH)CH_3$	
5	H	H	$-N(CH_3)_2$	$-CH(CH_3)_2$	
9	H	H	$-N=C(CH_3)N(CH_3)_2$	$-CH_2CH_3$	
10	H	H	$-N=C(H)N(CH_3)_2$	$-CH_2CH_3$	
11	CH_3	CH_3	$-N(CH_3)_2$	$-CH_2CH_3$	
12	$-CH_2-$	$-CH_2-$	$-N(CH_3)_2$	$-CH_2CH_3$	
13	$-CH_2-$	$-CH_2-$	$-N=C(CH_3)N(CH_3)_2$	$-CH_2CH_3$	

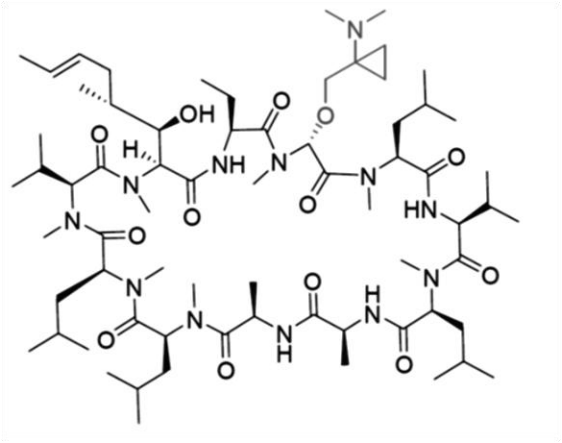
or is selected from a compound of Formula 4 or a pharmaceutically acceptable salt thereof,

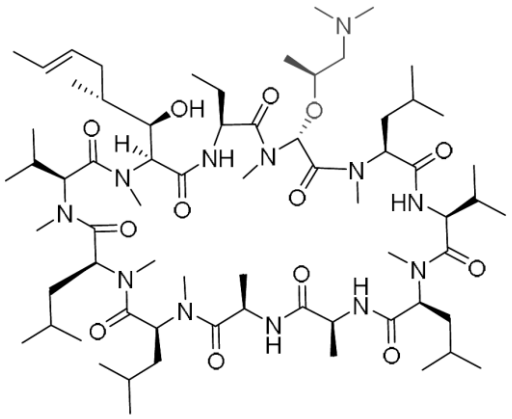


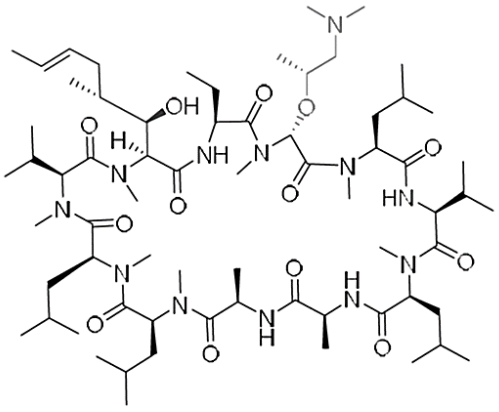
(Formula 4)

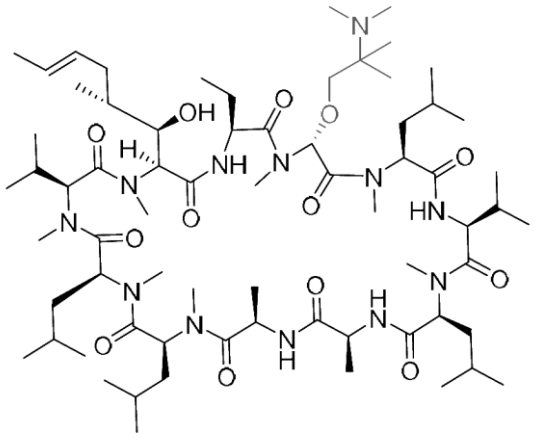
wherein R^9 is Formula 1a, R^8 is ethyl, Z is H, and X is methyl, R^1 and R^2 are both H, and A is $-N(CH_3)_2$.

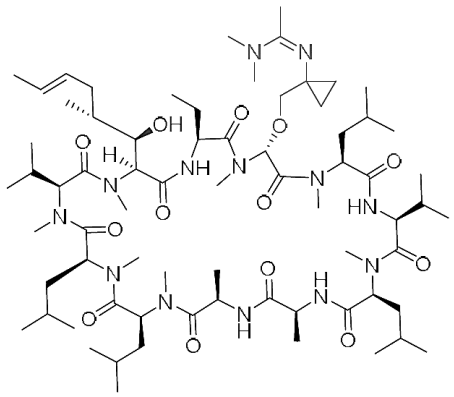
22. The compound of claim 1, wherein the compound, or pharmaceutically acceptable salt thereof is selected from the group consisting of:


,




,


, and



.

23. A compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 22 for use in the prevention and/or treatment of a disease or condition.

24. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 22 in the manufacture of a medicament for the prevention and/or treatment of a cyclophilin-mediated disease or condition, e.g. cyclophilin A and/or D; a disease or condition of the kidney, a cyclophilin-mediated disease or condition of the kidney; a disease or condition associated with cell injury or cell death, e.g. cell injury or cell death in an organ; organ injury or organ failure, wherein the organ is selected from the group consisting of kidney, liver, heart, lung, pancreas, intestine, cornea, skin, brain and nerve tissue; ischemia-reperfusion injury; renal ischemia-reperfusion injury; or acute kidney injury.

25. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.