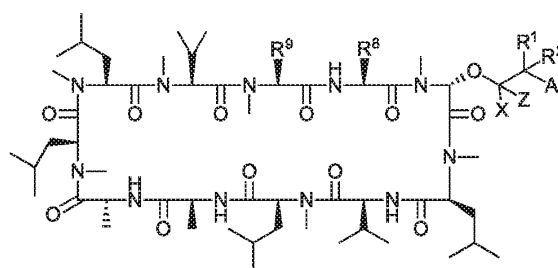


Claims

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 independently selected from H, alkyl, and substituted alkyl, or wherein X and Z are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

A is selected from:

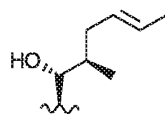
- NR^3R^4 , wherein R^3 and R^4 are independently selected from H, C_1 to C_6 alkyl, or wherein R^3 and R^4 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

and

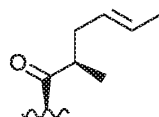
- $N=C(R^5)NR^6R^7$, wherein R^5 , R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

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

R^9 is Formula 1a or 1b



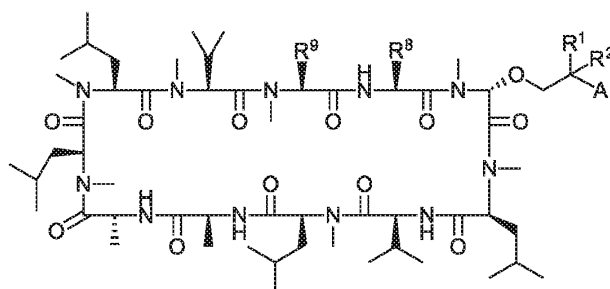
(Formula 1a)



(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, C_1 - C_4 alkyl, or joined together to form an azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, imidazolyl, or phthaloyl residue.

2. A compound according to Formula 4, wherein the compound, or a pharmaceutically acceptable salt thereof is a compound of Formula 1,



(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:

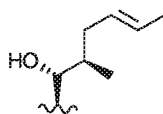
- NR^3R^4 , wherein R^3 and R^4 are independently selected from H, C_1 to C_6 alkyl, or wherein R^3 and R^4 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

and

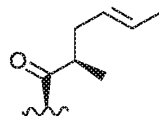
- $N=C(R^5)NR^6R^7$, wherein R^5 , R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

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

R^9 is Formula 1a or 1b



(Formula 1a)

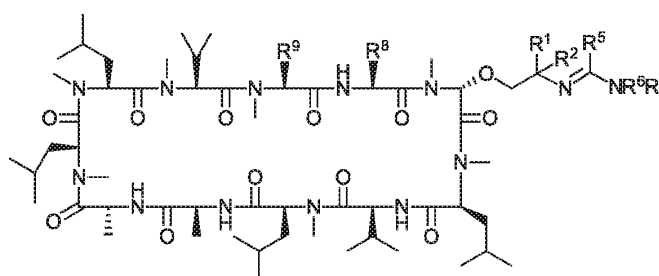


(Formula 1b)

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, C_1 - C_4 alkyl, or joined together to form an azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, imidazolyl, or phthaloyl residue.

3. The compound according to claim 1 or 2, wherein R^1 and R^2 are both hydrogen.
4. The compound according to claim 1 or 2, wherein at least one of R^1 or R^2 is C_1 to C_6 alkyl.
5. The compound according to claim 1 or 2, wherein R^1 and R^2 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring.
6. The compound according to any one of the preceding claims wherein R^8 is ethyl.
7. The compound according to any one of claims 1 to 5, wherein R^8 is selected from 1-hydroxyethyl, isopropyl, and n-propyl.

8. The compound according to any one of claims 1 to 5, wherein R⁸ is n-propyl.
9. The compound according to any one of claims 1 to 5, wherein R⁸ is isopropyl.
10. The compound according to any one of claims 1 to 5, wherein R⁸ is 1-hydroxyethyl.
11. The compound according to any one of the preceding claims, wherein R⁹ is Formula 1a.
12. The compound according to any one of the preceding claims, wherein R⁹ is Formula 1b.
13. The compound according to any one of the preceding claims, wherein A is NR³R⁴.
14. The compound according to claim 13 wherein R³ and R⁴ are both -CH₃.
15. The compound according to claim 13, wherein R³ and R⁴ are joined together to form a morpholinyl residue.
16. The compound according to any one of claims 13 to 15, wherein R⁸ is 1-hydroxyethyl, isopropyl or n-propyl.
17. The compound according to any one of claims 1 to 12, wherein A is -N=C(R⁵)NR⁶R⁷.
18. The compound according to claim 17, wherein R⁵, R⁶ and R⁷ are independently selected from H, C₁ to C₆ alkyl or optionally, substituted C₁ to C₆ alkyl.
19. The compound according to claim 18, wherein R⁵ is H or CH₃ and wherein R⁶ and R⁷ are CH₃.
20. The compound according to claims 17 to 19, wherein R⁸ is ethyl.
21. The compound according to claim 1, or claims 3 to 20, wherein X is C₁ to C₆ alkyl (e.g. methyl), and Z is H.
22. The compound according to claim 1 or 2, wherein the compound, or a pharmaceutically acceptable salt thereof is of Formula 3:



(Formula 3)

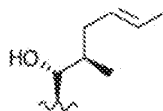
wherein:

R¹ and R² are independently selected from H, C₁ to C₆ alkyl, or wherein R¹ and R² are joined together to form a C₃ to C₆ cycloalkyl or heterocycloalkyl ring;

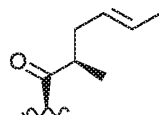
wherein R⁵, R⁶ and R⁷ are independently selected from H, C₁ to C₆ alkyl, and optionally wherein R⁶ and R⁷ are joined together to form a C₃ to C₆ cycloalkyl or heterocycloalkyl ring;

R⁸ is ethyl, 1-hydroxyethyl, isopropyl, or n-propyl; and

R⁹ is Formula 1a or 1b



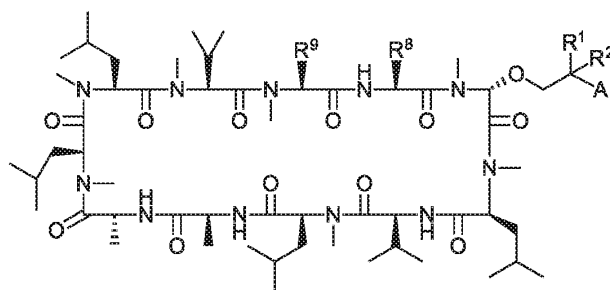
(Formula 1a)



(Formula 1b)

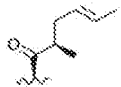
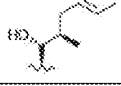
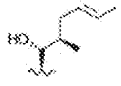
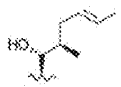
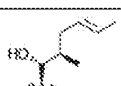
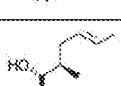
23. The compound according to claim 22 wherein R¹ and R² are both hydrogen.
24. The compound according to claim 22, wherein at least one of R¹ or R² is C₁ to C₆ alkyl.
25. The compound according to claim 22, wherein R¹ and R² are joined together to form a C₃ to C₆ cycloalkyl or heterocycloalkyl ring.

26. The compound according to any one of claims 22 to 25, wherein R⁹ is ethyl.
27. The compound according to any one of claims 22 to 25, wherein R⁸ is isopropyl.
28. The compound according to any one of claims 22 to 25, wherein R⁸ is n-propyl.
29. The compound according to any one of claims 22 to 25, wherein R⁸ is 1-hydroxyethyl.
30. The compound according to any one of claims 22 to 29 wherein R⁵, R⁶ and R⁷ are independently selected from H, C₁ to C₆ alkyl, and optionally, substituted C₁ to C₆ alkyl.
31. The compound according to claim 30 and wherein R⁵ is H or CH₃ and wherein R⁶ and R⁷ are CH₃.
32. 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:

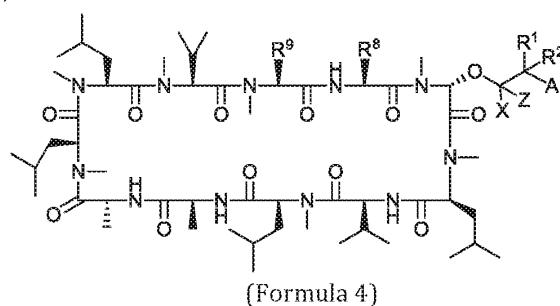


(Formula 1)

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	

Compound	R ¹	R ²	A	R ⁸	R ⁹
6	H	H		-CH(CH ₃) ₂	
9	H	H	-N=C(CH ₃)N(CH ₃) ₂	-CH ₂ CH ₃	
10	H	H	-N=C(H)N(CH ₃) ₂	-CH ₂ CH ₃	
11	CH ₃	CH ₃	-N(CH ₃) ₂	-CH ₂ CH ₃	
12	-CH ₂ -	-CH ₂ -	-N(CH ₃) ₂	-CH ₂ CH ₃	
13	-CH ₂ -	-CH ₂ -	N=C(CH ₃)N(CH ₃) ₂	-CH ₂ CH ₃	

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

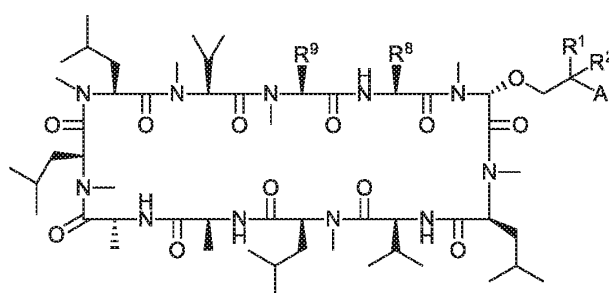


wherein R⁹ is Formula 1a, R⁸ is ethyl, X is H, and Z is methyl, R¹ and R² are both H, and A is -N(CH₃)₂.

33. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32 in the manufacture of a medicament for the prevention and/or treatment of a disease or condition, e.g. a disease or condition of the kidney.
34. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32 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; e.g. a cyclophilin-mediated disease or condition of the kidney.

35. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32, in the manufacture of a medicament for the prevention and/or treatment of a disease or condition associated with cell injury or cell death, e.g. cell injury or cell death in an organ.
36. The use according to claim 35, wherein the disease or condition associated with cell injury or cell death is organ injury or organ failure.
37. The use according to claim 35 to 36 wherein the organ is selected from the group consisting of kidney, liver, heart, lung, pancreas, intestine, cornea, skin, brain and nerve tissue.
38. The use according to any one of claims 33 to 37, wherein the disease or condition is ischemia-reperfusion injury.
39. The use according to claim 38, wherein the ischemia-reperfusion injury is renal ischemia-reperfusion injury.
40. The use according to any one of claims 33 to 39, wherein the disease or condition is acute kidney injury.
41. The use of a compound of Formula 1, or a pharmaceutically acceptable salt thereof,



(Formula 1)

in the manufacture of a medicament for the prevention or treatment of organ failure; optionally the failure of the kidney, liver, heart, lung, pancreas,

intestine, cornea, skin, brain or nerve tissue; or for the prevention or treatment of renal ischemia-reperfusion injury, or acute kidney injury, wherein:

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

A is selected from:

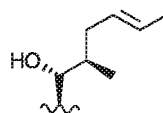
- NR^3R^4 , wherein R^3 and R^4 are independently selected from H, C_1 to C_6 alkyl, or wherein R^3 and R^4 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

and

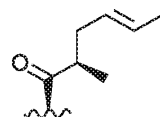
- $N=C(R^5)NR^6R^7$, wherein R^5 , R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl, and optionally wherein R^6 and R^7 are joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

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 and R^8 is selected from ethyl and R^9 is Formula 1a and A is selected from NR^3R^4 , then R^3 and R^4 are not selected from H, C_1 to C_4 alkyl, or joined together to form a C_3 to C_6 cycloalkyl or heterocycloalkyl ring;

or wherein the compound is selected from Compounds 2 to 15 of Table 1.

42. The use according to claim 40 or 41, wherein the acute kidney injury is associated with, or a consequence of kidney transplantation.

43. The use according to any one of claims 33 to 42, wherein the medicament is administered to an organ transplant recipient or a donor, optionally wherein the medicament is administered to an organ donor and/or to an organ recipient prior to, during, and/or after transplantation of an organ from said organ donor to said organ recipient.
44. The use according to any one of claims 33 to 43, wherein the medicament is adapted for oral administration, or is adapted for administration by intravenous injection or infusion.
45. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32, or a compound as defined in claim 41 in the manufacture of a medicament for preserving an organ and/or protecting an organ from organ injury, the use comprising administering the compound to an organ donor prior to the removal of said organ from said donor and/or to an organ recipient prior to, during or after the transplantation of said organ.
46. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32 or a compound as defined in claim 41, for preserving an organ and/or protecting an organ from organ injury, the use comprising administering the compound to an organ donor prior to removal of said organ from said donor, and/or to an organ.
47. A method of preserving or protecting an organ from organ injury, wherein the method comprises a step of administering a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 32, or a compound as defined in claim 41 to an organ donor prior to the removal of said organ from said donor, and/or to an organ.
48. The use or method according to any one of claims 43 to 47, wherein the organ is selected from the group consisting of kidney, liver, heart, lung, pancreas, intestine, cornea, skin, brain and nerve tissue.
49. The use or method according to any one of claims 43 to 48, wherein the donor is a live donor, or wherein the donor is a clinically dead donor.

50. The use or method according to any one of claims 43 to 49, wherein the compound is administered to the donor and/or recipient by intravenous injection or infusion.