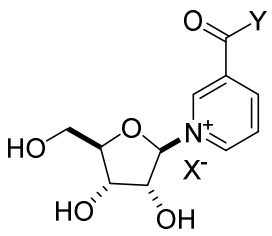
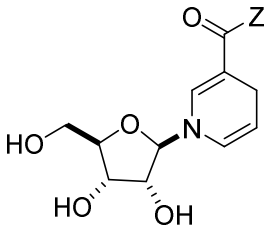
Claims

1. ~~One~~ Use of a therapeutically effective amount of a compound of Formula (V) or ~~more nicotinic riboside compounds in combination with~~Formula (VI):



(V)



(VI)

or pharmaceutically acceptable salts thereof and a therapeutically effective amount of a poly(ADP-ribose) polymerase (PARP) inhibitor ~~for use~~ or pharmaceutically acceptable salts thereof, in the manufacture of a pharmaceutical composition for increasing the level of nicotinamide adenine dinucleotide (NAD^+) in ~~the treatment of a mitochondrial disease, a mitochondria-related disease or condition, or a disease~~a cell type or ~~condition characterized by acute NAD^+ depletion due to DNA damage,~~tissue of a subject wherein:

Y and Z are -OH or $-NH_2$;

X^- is fluoride, chloride, bromide, iodide, nitrate, sulfate, sulfite, phosphate, bicarbonate, carbonate, thiocyanate, formate, acetate, trifluoroacetate, glycolate, lactate, gluconate, ascorbate, benzoate, oxalate, malonate, succinate, citrate, methanesulfonate, ethanesulfonate, propanesulfonate, benzenesulfonate, *p*-toluenesulfonate or trifluoromethanesulfonate; and

the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor is not more than 10% of the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor used in chemotherapy.

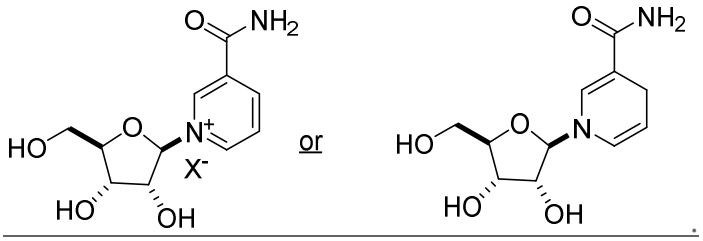
2. The use of claim 1, wherein the poly(ADP-ribose) polymerase (PARP) inhibitor is niraparib, olaparib, rucaparib, talazoparib, veliparib, 4-amino-1,8-naphthalimide, BGB290, CEP9722 or E7016.

3. The use of claim 1 wherein the therapeutically effective amount of the PARP inhibitor is no more than about 10%, about 5%, about 1%, about 0.5% or about 0.1% of the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor used in chemotherapy.

4. The use of claim 3, wherein the PARP inhibitor is olaparib and the therapeutically effective amount of olaparib is no more than about 10 mg, about 5 mg, about 1 mg, about 0.5 mg or about 0.1 mg.

5. The use of claim 1, wherein the therapeutically effective amount of the compound is about 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg or 500 mg.

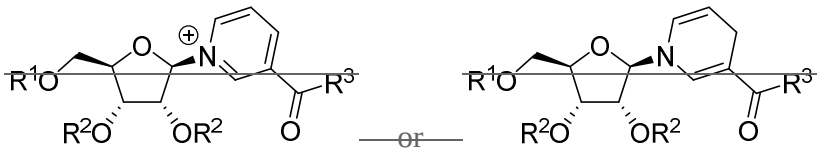
6. The use of claim 1, wherein the compound is



.

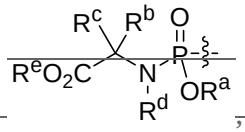
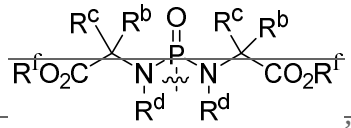
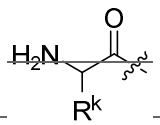
7. The ~~the dose of the PARP inhibitor is significantly lower than the recommended dose of the PARP inhibitor as an anticancer agent; and~~

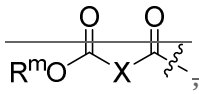
~~the one or more nicotinic riboside compounds comprise one or more of nicotinamide riboside (NR), reduced NR (NRH), nicotinic acid riboside (NAR), reduced NAR (NARH) and pharmaceutically acceptable salts and stereoisomers thereof, or/and one or more derivatives thereof of Formula I or II:~~



~~I~~ ~~II~~

~~wherein:~~

~~R^1 is hydrogen,~~  ,  ,  ~~or~~

 , ~~wherein:~~

~~R^a is hydrogen, linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 1-naphthyl or 2-naphthyl, wherein the phenyl is optionally substituted with F,~~

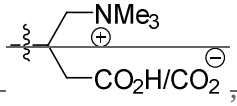
~~Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or $-O$-(linear or branched C_1-C_4 alkyl);~~

~~R^b and R^c at each occurrence independently are hydrogen, linear or branched C_1-C_5 alkyl, $-CH_2$-phenyl, $-CH_2$-3-indole or $-CH_2$-5-imidazole, wherein the alkyl is optionally substituted with $-OH$, $-OR^j$, $-SH$, $-SR^j$, $-NH_2$, $-NHR^j$, $-N(R^j)_2$, $-NHC(=O)R^j$, $-NHC(=NH)NH_2$, $-C(=O)NH_2$, $-CO_2H$ or $-C(=O)OR^j$, and the phenyl is optionally substituted with $-OH$ or $-OR^j$, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl;~~

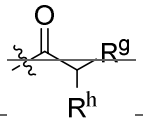
~~R^d at each occurrence independently is hydrogen, methyl or linear or branched C_2-C_4 alkyl;~~

~~R^e and R^f at each occurrence independently are hydrogen, linear or branched C_1-C_8 alkyl, C_3-C_6 cycloalkyl, $-CH_2$-(C_3-C_6 cycloalkyl), phenyl or $-CH_2$-phenyl, wherein the phenyl is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or $-O$-(linear or branched C_1-C_4 alkyl);~~

~~R^k is hydrogen, linear or branched C_1-C_6 alkyl, $-CH_2$-phenyl, $-CH_2$-3-indole or $-CH_2$-5-imidazole, wherein the alkyl is optionally substituted with $-OH$, $-OR^j$, $-SH$, $-SR^j$, $-NH_2$, $-NHR^j$, $-N(R^j)_2$, $-NHC(=O)R^j$, $-NHC(=NH)NH_2$, $-C(=O)NH_2$, $-CO_2H$ or $-C(=O)OR^j$, and the phenyl is optionally substituted with $-OH$ or $-OR^j$, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl;~~

~~R^m is hydrogen, linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, $-CH_2$-phenyl or~~  ~~, wherein the phenyl is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or $-O$-(linear or branched C_1-C_4 alkyl); and~~

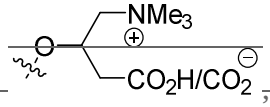
~~X is cis or trans $-HC=CH-$ or $-(CH_2)_n-$ optionally substituted with $-OH$ or $-OR^j$, wherein R^j is linear or branched C_1-C_4 alkyl and n is 1, 2, 3, 4, 5 or 6;~~

~~R^2 at each occurrence independently is hydrogen or~~  ~~, wherein:~~

R^g is hydrogen, linear or branched C_1-C_5 alkyl, $-CH_2$-phenyl, $-CH_2$-3-indole or $-CH_2$-5-imidazole, wherein the alkyl is optionally substituted with $-OH$, $-OR^j$, $-SH$, $-SR^j$, $-NH_2$, $-NHR^j$, $-N(R^j)_2$, $-NHC(=O)R^j$, $-NHC(=NH)NH_2$, $-C(=O)NH_2$, $-CO_2H$ or $-C(=O)OR^j$, and the phenyl is optionally substituted with $-OH$ or $-OR^j$, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl; and

R^h is hydrogen, methyl or $-NH_2$;

or R^g and R^h together with the carbon atom to which they are connected form a C_3-C_6 cycloalkyl or phenyl ring, wherein the phenyl ring is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or $-O$-(linear or branched C_1-C_4 alkyl); and

R^3 is $-NH_2$, $-NHR^n$, $-N(R^n)_2$, $-OH$, $-OR^o$ or 

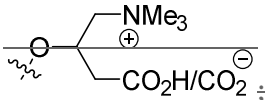
, wherein:

R^n at each occurrence independently is linear or branched C_1-C_6 alkyl or allyl, wherein the alkyl is optionally substituted with $-OH$ or $-O$-(linear or branched C_1-C_3 alkyl), or both occurrences of R^n and the nitrogen atom to which they are connected form a 3- to 6-membered heterocyclic ring; and

R^o is linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl or $-CH_2$-phenyl, wherein the phenyl is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or $-O$-(linear or branched C_1-C_4 alkyl);

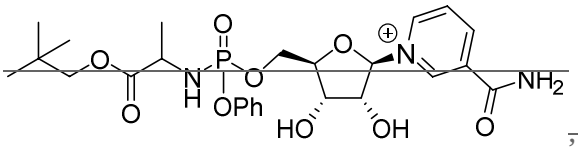
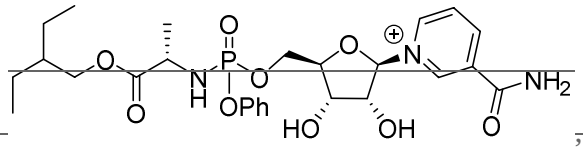
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph or stereoisomer thereof;

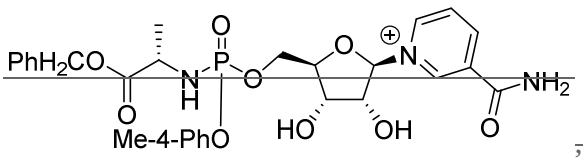
with the proviso that:

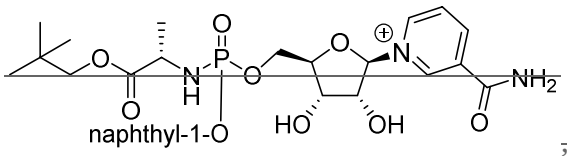
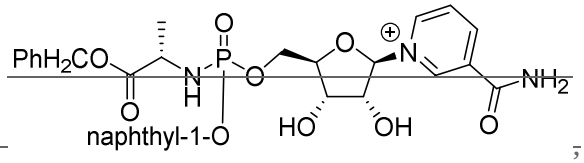
1) R^1 and both occurrences of R^2 all are not hydrogen except when R^3 is 

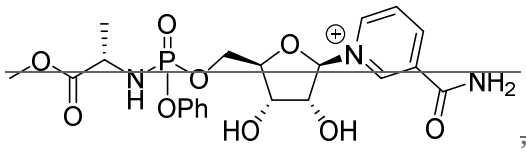
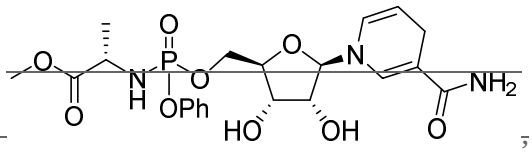
; and

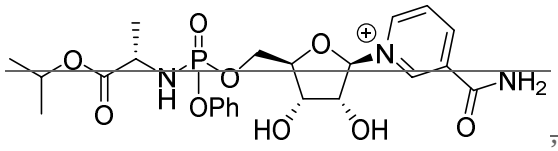
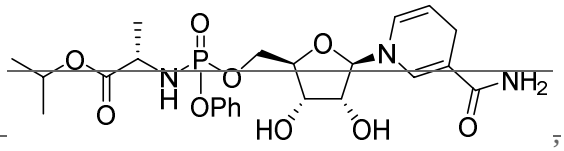
2) the compound of Formula I or II is not:

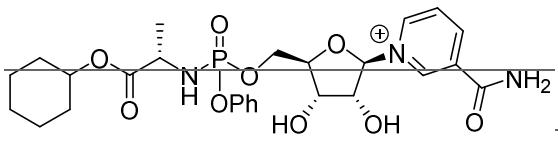
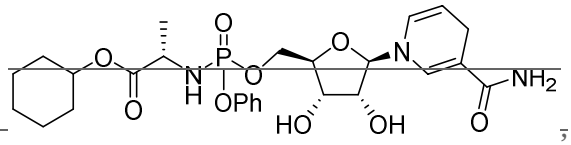
 ,  ,

 ,

 ,  ,

 ,  ,

 ,  ,

 , ~~or~~  ,

~~or a salt or stereoisomer thereof.~~use of claim 6, wherein the

~~2. The one or more compounds in combination with the PARP inhibitor for use according to claim 1, wherein the mitochondrial disease is selected from mitochondrial myopathies; Kearns-Sayre syndrome (KSS); Pearson syndrome; Leigh syndrome; neuropathy, ataxia, retinitis pigmentosa and ptosis (NARP); mitochondrial DNA depletion syndrome (Alper's disease); mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome; mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome; myoclonic epilepsy with ragged red fibers (MERRF); chronic progressive external ophthalmoplegia (CPEO); Leber's hereditary optic neuropathy (LHON); and diabetes mellitus and deafness.~~

~~3. The one or more compounds in combination with the PARP inhibitor for use according to claim 1, wherein the mitochondria-related disease or condition is a neurodegenerative disorder,~~

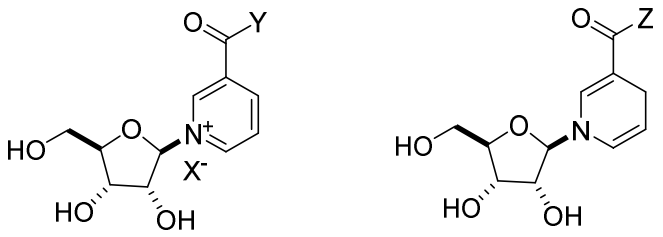
~~a neuronal activation disorder, a muscle disorder, a beta oxidation disorder, a metabolic disorder, an inflammatory disorder, a vascular disorder, a kidney disorder, a liver disorder, or male or female infertility.~~

~~4. The one or more compounds in combination with the PARP inhibitor for use according to claim 3, wherein the mitochondria-related disease or condition is an inflammatory disorder selected from neuroinflammation, gastrointestinal disorders, peritonitis, pancreatitis, glomerulonephritis, liver disorders, multiple organ dysfunction syndrome, metabolic disorders, cardiac disorders, vascular disorders, reperfusion injury, airway disorders, arthritis, skin disorders, Sjögren syndrome, eye disorders, systemic lupus erythematosus, hypertension and dysmenorrhea.~~

~~5. The one or more compounds in combination with the PARP inhibitor for use according to claim 1, wherein the disease or condition characterized by acute NAD^+ depletion due to DNA damage is selected from exposure to radiation, radiation or chemotherapy-induced disorders, burn injuries, chemical exposure with manifestation of exfoliative dermatitis, exposure to chemical warfare agents, Stevens-Johnson syndrome, acute respiratory distress syndrome, inhalational lung injury due to smoke or chemical toxins, trauma-related crush injuries, peripheral nerve injuries, spinal cord injuries, and contusion to internal organs.~~

~~6. The one or more compounds in combination with the~~ PARP inhibitor ~~for use according to any one of claims 1 to 5, wherein the one or more nicotinic riboside compounds comprise one or more of nicotinamide riboside (NR), reduced NR (NRH), nicotinic acid riboside (NAR), reduced NAR (NARH) and~~is olaparib and the therapeutically effective amount of olaparib is no more than about 10 mg, about 5 mg, about 1 mg, about 0.5 mg or about 0.1 mg.

8. A use of a therapeutically effective amount of a compound of Formula (V) or Formula (VI):



(V) (VI)

or pharmaceutically acceptable salts and ~~stereoisomers thereof.~~

a therapeutically effective amount of a poly(ADP-ribose) polymerase (~~7. The one or more compounds in combination with the~~ PARP) inhibitor ~~for use according to any one of claims 1 to 6, wherein the dose of each of the one or more nicotinic riboside compounds independently is from 1 mg ± 10% to 100 mg ± 10%, from 100 mg ± 10% to 500 mg ± 10%, or from 500 mg ± 10% to 1000 mg ± 10% per day.~~

~~8. The one or more compounds in combination with the PARP inhibitor for use according to any one of claims 1 to 7, wherein the PARP inhibitor is selected from niraparib, olaparib, rucaparib, talazoparib, veliparib, 4-amino-1,8-naphthalimide, BGB290, CEP9722, E7016 and~~or pharmaceutically acceptable salts thereof~~.~~ in the manufacture of a pharmaceutical composition for increasing the level of cytoprotection in a cell type or tissue of a subject, wherein:

~~9. The one~~Y and Z are -OH or ~~more compounds in combination with~~ $-NH_2$;

X^- is fluoride, chloride, bromide, iodide, nitrate, sulfate, sulfite, phosphate, bicarbonate, carbonate, thiocyanate, formate, acetate, trifluoroacetate, glycolate, lactate, gluconate, ascorbate, benzoate, oxalate, malonate, succinate, citrate, methanesulfonate, ethanesulfonate, propanesulfonate, benzenesulfonate, *p*-toluenesulfonate or trifluoromethanesulfonate; and

the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor ~~for use according to any one of claims 1 to~~is not more than 10% of the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor used in chemotherapy.

9. The compound of claim 8, wherein the ~~dose~~poly(ADP-ribose) polymerase (PARP) inhibitor is niraparib, olaparib, rucaparib, talazoparib, veliparib, 4-amino-1,8-naphthalimide, BGB290, CEP9722 or E7016.

10. The use of claim 8, wherein the therapeutically effective amount of the PARP inhibitor is no more than about 10%, about 5%, about 1%, about 0.5% or about 0.1% of ~~its recommended dose as an~~

anticancer agent.

10. The one or more compounds in combination with the the therapeutically effective amount of the poly(ADP-ribose) polymerase (PARP) inhibitor used in chemotherapy.

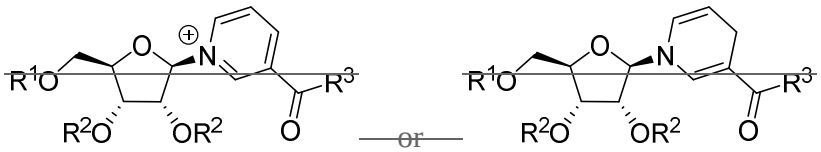
11. forThe use according to any one of claims 1 to 9claim 10, wherein the PARP inhibitor is olaparib, and the dosetherapeutically effective amount of olaparib is no more than about 10 mg, about 5 mg, about 1 mg, about 0.5 mg or about 0.1 mg.

12. per day.

11. Use of one or more nicotinic riboside compounds and a poly(ADP-ribose) polymerase (PARP) inhibitor in the manufacture of a pharmaceutical composition for the treatment of a mitochondrial disease, a mitochondria-related disease or condition, or a disease or condition characterized by acute NAD^+ depletion due to DNA damage, wherein:

the dose of the PARP inhibitor is significantly lower than the recommended dose of the PARP inhibitor as an anticancer agent; and

the one or more nicotinic riboside compounds comprise one or more of nicotinamide riboside (NR), reduced NR (NRH), nicotinic acid riboside (NAR), reduced NAR (NARH) and pharmaceutically acceptable salts and stereoisomers thereof, or/and one or more derivatives thereof of Formula I or II:

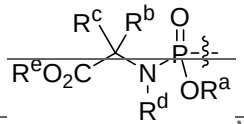


or

I II

wherein:

R^1 is hydrogen,



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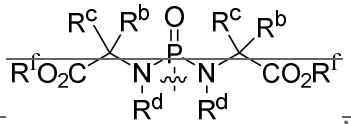

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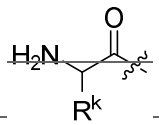

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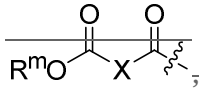


, wherein:

R^a is hydrogen, linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, 1-naphthyl or 2-naphthyl, wherein the phenyl is optionally substituted with F,

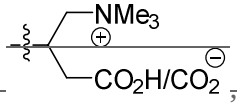
Cl, -NO_2, linear or branched C_1-C_4 alkyl, -CF_3 or -O (linear or branched C_1-C_4 alkyl);

R^b and R^c at each occurrence independently are hydrogen, linear or branched C_1-C_5 alkyl, -CH_2-phenyl, -CH_2-3-indole or -CH_2-5-imidazole, wherein the alkyl is optionally substituted with -OH, -OR^j, -SH, -SR^j, -NH_2, -NHR^j, -$N(R^j)_2$, -$NHC(=O)R^j$, -$NHC(=NH)NH_2$, -$C(=O)NH_2$, -CO_2H or -$C(=O)OR^j$, and the phenyl is optionally substituted with -OH or -OR^j, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl;

R^d at each occurrence independently is hydrogen, methyl or linear or branched C_2-C_4 alkyl;

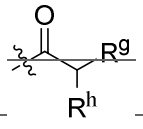
R^e and R^f at each occurrence independently are hydrogen, linear or branched C_1-C_8 alkyl, C_3-C_6 cycloalkyl, -CH_2-(C_3-C_6 cycloalkyl), phenyl or -CH_2-phenyl, wherein the phenyl is optionally substituted with F, Cl, -NO_2, linear or branched C_1-C_4 alkyl, -CF_3 or -O (linear or branched C_1-C_4 alkyl);

R^k is hydrogen, linear or branched C_1-C_6 alkyl, -CH_2-phenyl, -CH_2-3-indole or -CH_2-5-imidazole, wherein the alkyl is optionally substituted with -OH, -OR^j, -SH, -SR^j, -NH_2, -NHR^j, -$N(R^j)_2$, -$NHC(=O)R^j$, -$NHC(=NH)NH_2$, -$C(=O)NH_2$, -CO_2H or -$C(=O)OR^j$, and the phenyl is optionally substituted with -OH or -OR^j, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl;

R^m is hydrogen, linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, -CH_2-phenyl or 

, wherein the phenyl is optionally substituted with F, Cl, -NO_2, linear or branched C_1-C_4 alkyl, -CF_3 or -O-(linear or branched C_1-C_4 alkyl); and

X is cis or trans -HC=CH- or -$(CH_2)_n$- optionally substituted with -OH or -OR^j, wherein R^j is linear or branched C_1-C_4 alkyl and n is 1, 2, 3, 4, 5 or 6;

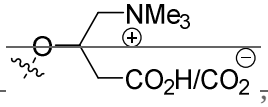
R^2 at each occurrence independently is hydrogen or 

, wherein:

R^g is hydrogen, linear or branched C_1-C_5 alkyl, $-CH_2$-phenyl, $-CH_2$-3-indole or $-CH_2$-5-imidazole, wherein the alkyl is optionally substituted with -OH, $-OR^j$, -SH, $-SR^j$, $-NH_2$, $-NHR^j$, $-N(R^j)_2$, $-NHC(=O)R^j$, $-NHC(=NH)NH_2$, $-C(=O)NH_2$, $-CO_2H$ or $-C(=O)OR^j$, and the phenyl is optionally substituted with -OH or $-OR^j$, wherein R^j at each occurrence independently is linear or branched C_1-C_4 alkyl; and

R^h is hydrogen, methyl or $-NH_2$;

or R^g and R^h together with the carbon atom to which they are connected form a C_3-C_6 cycloalkyl or phenyl ring, wherein the phenyl ring is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or -O-(linear or branched C_1-C_4 alkyl); and

R^3 is $-NH_2$, $-NHR^n$, $-N(R^n)_2$, -OH, $-OR^o$ or 

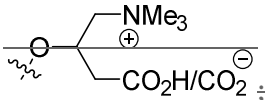
, wherein:

R^n at each occurrence independently is linear or branched C_1-C_6 alkyl or allyl, wherein the alkyl is optionally substituted with -OH or -O-(linear or branched C_1-C_3 alkyl), or both occurrences of R^n and the nitrogen atom to which they are connected form a 3- to 6-membered heterocyclic ring; and

R^o is linear or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl or $-CH_2$-phenyl, wherein the phenyl is optionally substituted with F, Cl, $-NO_2$, linear or branched C_1-C_4 alkyl, $-CF_3$ or -O-(linear or branched C_1-C_4 alkyl);

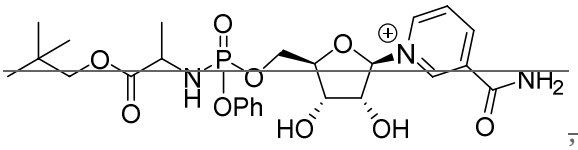
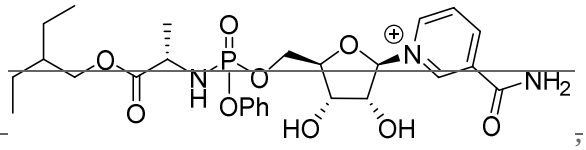
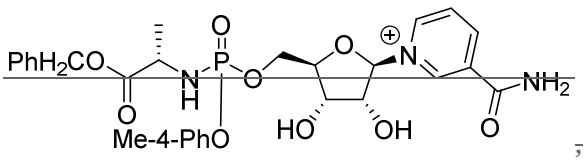
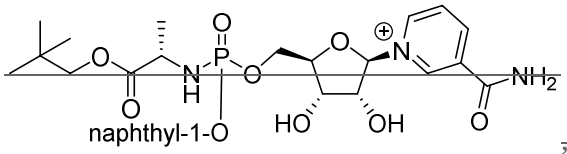
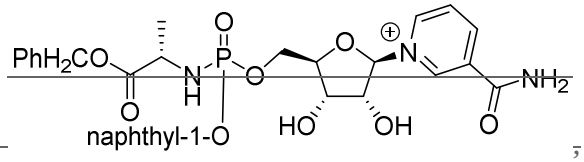
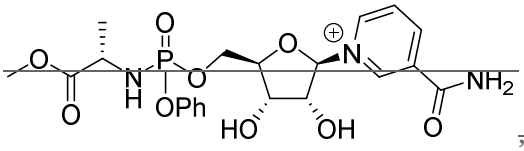
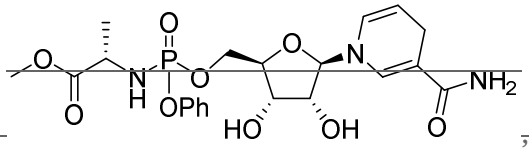
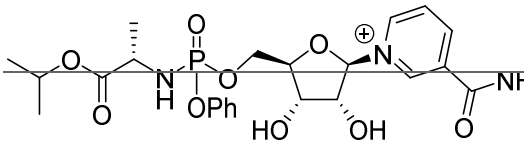
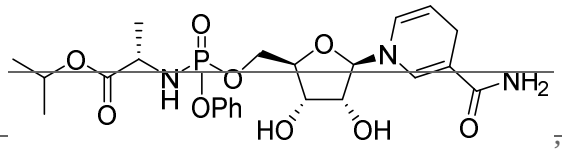
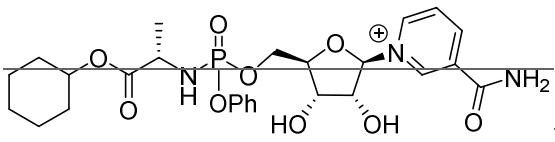
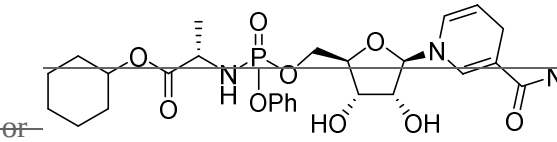
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph or stereoisomer thereof;

with the proviso that:

1) R^1 and both occurrences of R^2 all are not hydrogen except when R^3 is 

; and

2) the compound of Formula I or II is not:

~~or a salt or stereoisomer thereof.~~

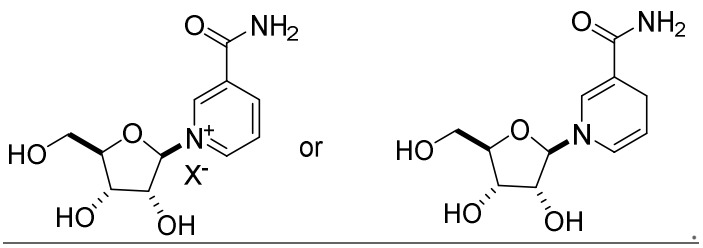
~~12. The use of claim 11, wherein the mitochondrial disease is selected from mitochondrial myopathies; Kearns-Sayre syndrome (KSS); Pearson syndrome; Leigh syndrome; neuropathy, ataxia, retinitis pigmentosa and ptosis (NARP); mitochondrial DNA depletion syndrome (Alper's disease); mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome; mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome; myoclonic epilepsy with ragged red fibers (MERRF); chronic progressive external ophthalmoplegia (CPEO); Leber's hereditary optic neuropathy (LHON); and diabetes mellitus and deafness.~~

~~13. The use of claim 11, wherein the mitochondria-related disease or condition is a neurodegenerative disorder, a neuronal activation disorder, a muscle disorder, a beta oxidation~~

~~disorder, a metabolic disorder, an inflammatory disorder, a vascular disorder, a kidney disorder, a liver disorder, or male or female infertility.~~

The use of claim 8, wherein the therapeutically effective amount of the compound is about 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg or 500 mg.

13. The use of claim 8, wherein the compound is



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14. The use of claim 13, wherein the ~~mitochondria-related disease or condition is an inflammatory disorder selected from neuroinflammation, gastrointestinal disorders, peritonitis, pancreatitis, glomerulonephritis, liver disorders, multiple organ dysfunction syndrome, metabolic disorders, cardiac disorders, vascular disorders, reperfusion injury, airway disorders, arthritis, skin disorders, Sjögren syndrome, eye disorders, systemic lupus erythematosus, hypertension and dysmenorrhea.~~

~~15. The use of claim 11, wherein the disease or condition characterized by acute NAD^+ depletion due to DNA damage is selected from exposure to radiation, radiation or chemotherapy induced disorders, burn injuries, chemical exposure with manifestation of exfoliative dermatitis, exposure to chemical warfare agents, Stevens Johnson syndrome, acute respiratory distress syndrome, inhalational lung injury due to smoke or chemical toxins, trauma-related crush injuries, peripheral nerve injuries, spinal cord injuries, and contusion to internal organs.~~

~~16. The use of any one of claims 11 to 15, wherein the one or more nicotinic riboside compounds comprise one or more of nicotinamide riboside (NR), reduced NR (NRH), nicotinic acid riboside (NAR), reduced NAR (NARH) and pharmaceutically acceptable salts and stereoisomers thereof.~~

~~17. The use of any one of claims 11 to 16, wherein the dose of each of the one or more nicotinic riboside compounds independently is from 1 mg ± 10% to 100 mg ± 10%, from 100 mg~~

~~± 10% to 500 mg ± 10%, or from 500 mg ± 10% to 1000 mg ± 10%.~~

~~18. The use of any one of claims 11 to 17, wherein the~~ PARP inhibitor is ~~selected from niraparib,~~ olaparib~~, rucaparib, talazoparib, veliparib, 4-amino-1,8-naphthalimide, BGB290, CEP9722, E7016 and pharmaceutically acceptable salts thereof.~~

~~19. The use of any one of claims 11 to 18, wherein the dose of the PARP inhibitor~~ and the therapeutically effective amount of olaparib is no more than about 10~~%, 5%, 1%, 0.5% or 0.1% of its recommended dose as an anticancer agent.~~

~~20. The use of any one of claims 11 to 19, wherein the PARP inhibitor is olaparib, and the dose of olaparib is no more than about 10 mg, 5~~ mg, ~~1~~about 5 mg, ~~0.5~~about 1 mg ~~or~~, about 0.~~1~~5 mg~~.~~

~~21. The use of any one of claims 11 to 20, wherein the pharmaceutical composition is formulated for oral administration.~~

or about 0.1 mg.