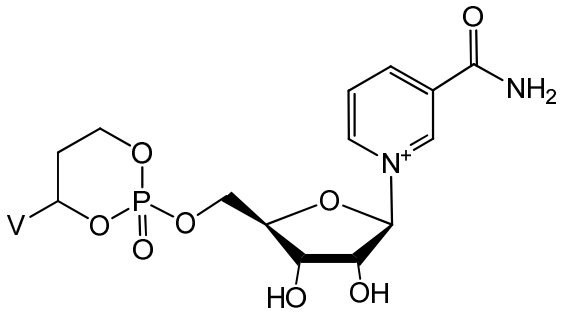
CLAIMS

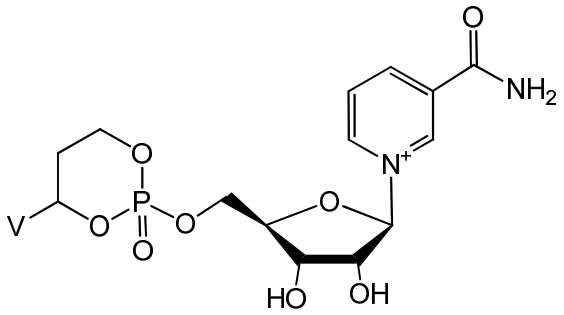
1. A compound, or a salt thereof, wherein the compound has a structure represented by formula I:



I

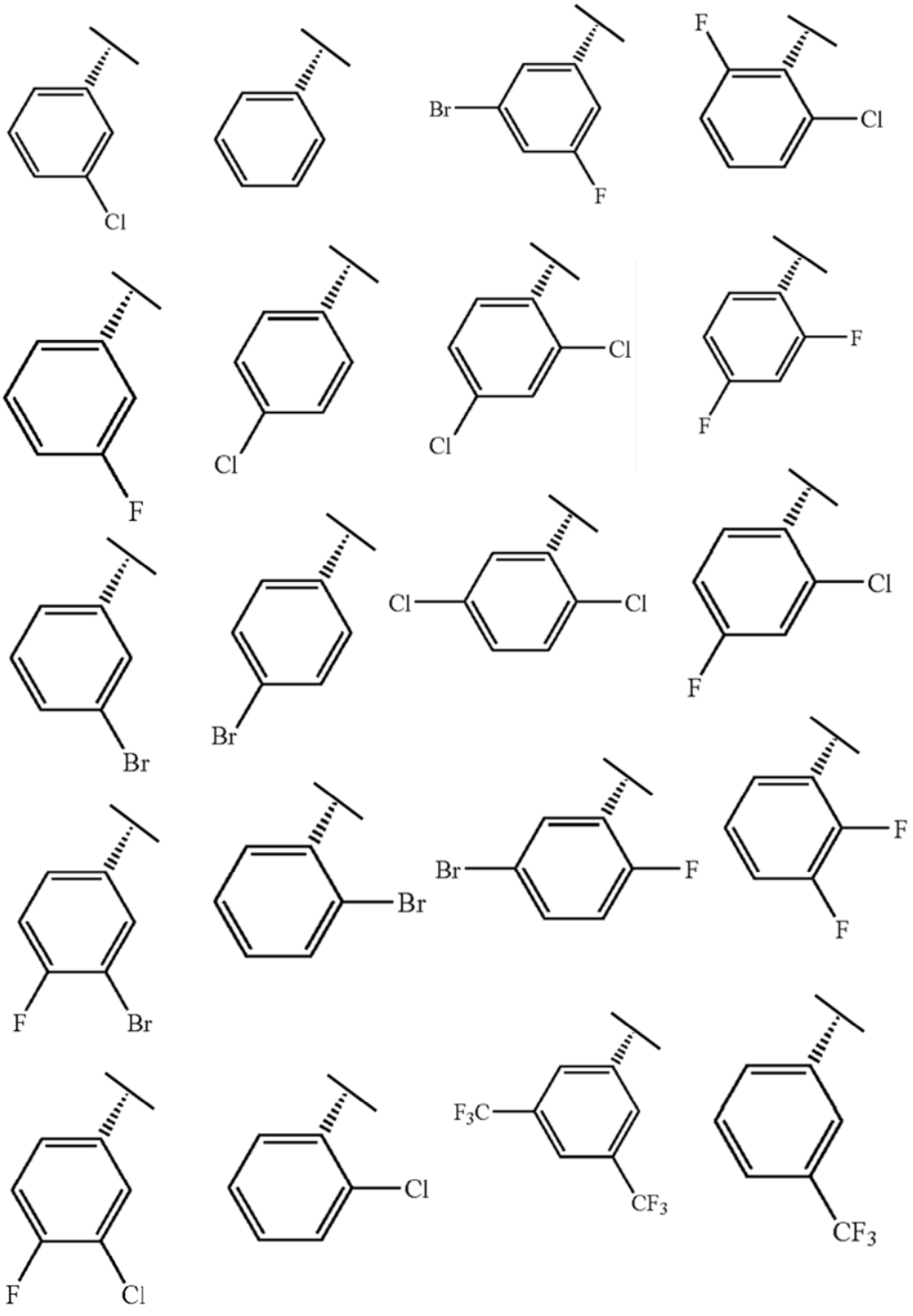
wherein V is selected from hydrogen, phenyl and monocyclic heteroaryl, wherein (i) each said monocyclic heteroaryl contains five or six ring atoms of which 1 or 2 ring atoms are heteroatoms selected from N, S, and O, and the remainder of the ring atoms are carbon, and (ii) each said phenyl or monocyclic heteroaryl is unsubstituted or is substituted by one or two groups selected from halogen, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, and cyano.

2. A compound, or a salt thereof, wherein the compound has a structure represented by formula I:



I

wherein V is selected from the following substituents:


Cl
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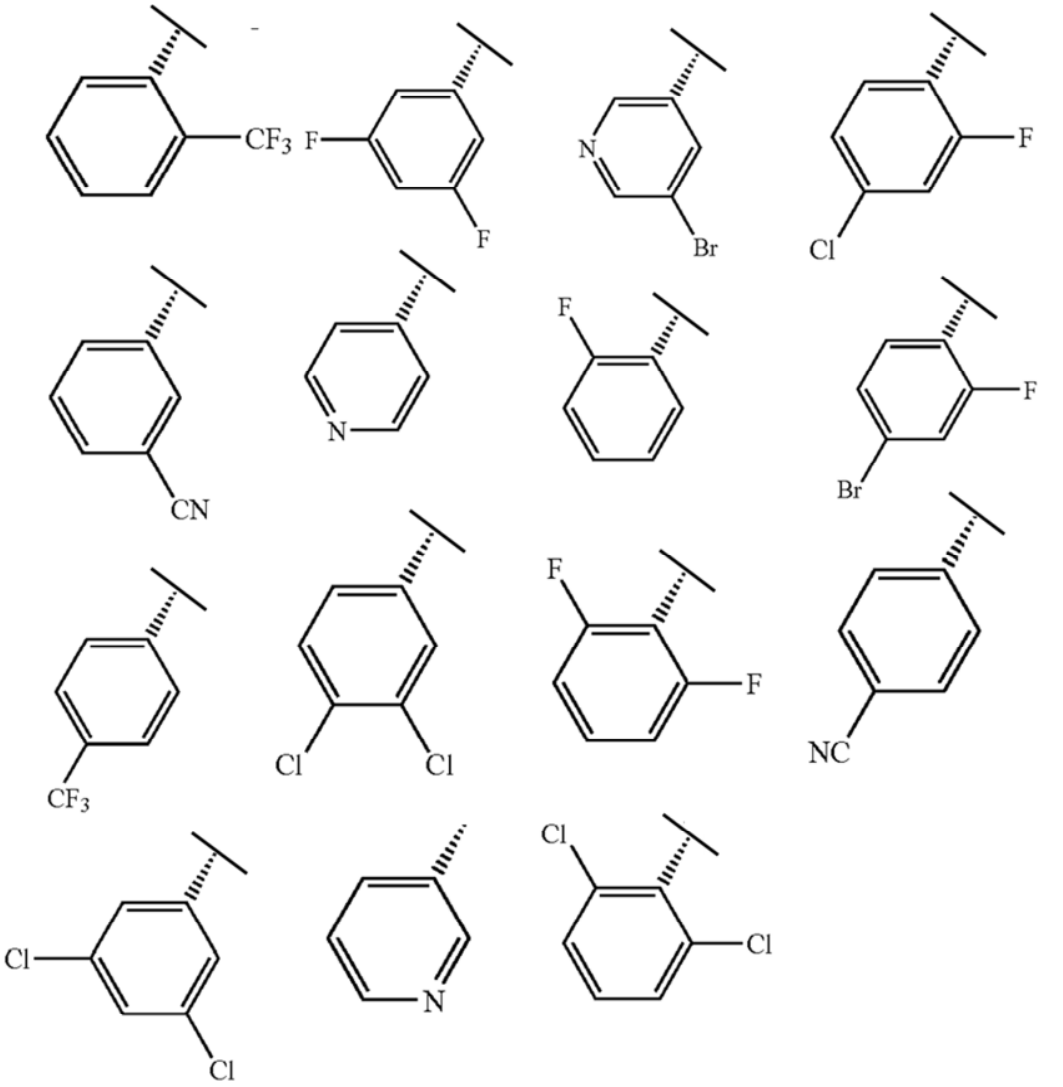
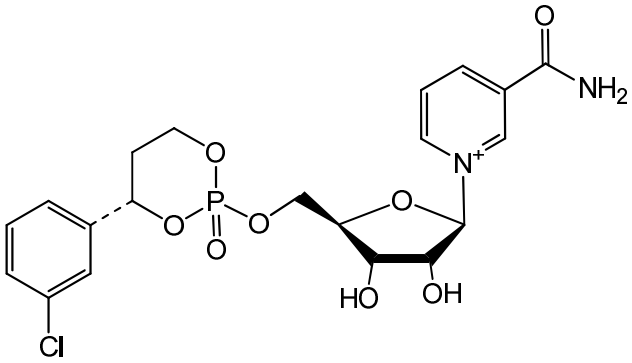


3. The compound of claim 1 or 2, or a salt thereof, wherein the compound is selected from



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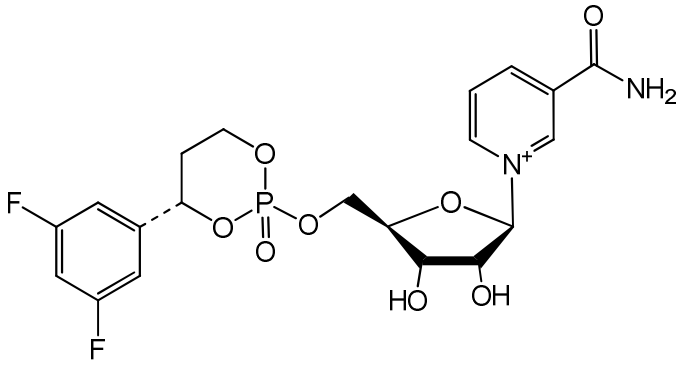

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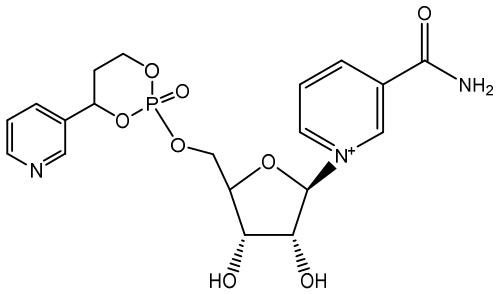

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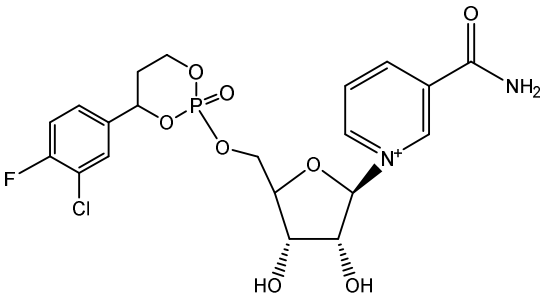

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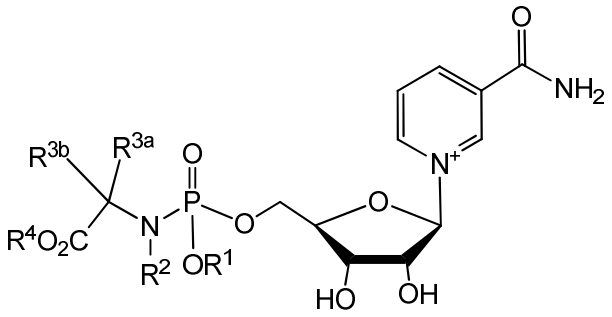
4. A compound, or a salt thereof, wherein the compound has a structure represented by formula II:



II

(a) R^1 is hydrogen; n-alkyl; branched alkyl; cycloalkyl; or aryl, where aryl is optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, --$N(R^{1'})_2$, C_{1-6} acylamino, --$NHSO_2C_{1-6}$ alkyl, --$SO_2N(R^{1'})_2$, $COR^{1"}$, and --SO_2C_{1-6} alkyl;

$R^{1'}$ is independently hydrogen or alkyl selected from C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, and

$R^{1"}$ is --OR' or --$N(R^{1'})_2$;

(b) R^2 is hydrogen, C_{1-10} alkyl; or $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4; or

R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ forming a cyclic ring that includes the adjoining N and C atoms;

(c) R^{3a} and R^{3b} are

(i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, --$(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, --CH_2SH, --$(CH_2)_2S(O)_dMe$, --$(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, --$(CH_2)_eCOR^{3"}$, aryl and aryl C_{1-3} alkyl, said aryl groups are optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; or

(ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; or

(iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; or

(iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ forming a ring that includes the adjoining N and C atoms; or

(v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ forming a ring that includes the adjoining N and C atoms; or

(vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, $CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'--OH)-Ph), CH_2SH, or lower cycloalkyl; or

(vii) R^{3a} is CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, --$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H;

c is from 1 to 6,

d is from 0 to 2,

e is from 0 to 3,

f is from 2 to 5,

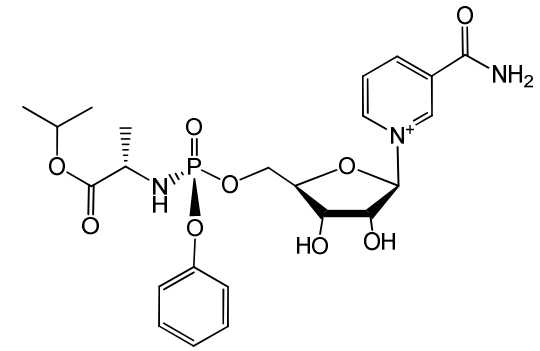
n is from 2 to 4, and

(d) R^4 is hydrogen; $C_{1\text{-}10}$ alkyl optionally substituted with lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen; $C_{1\text{-}10}$ haloalkyl; $C_{3\text{-}10}$ cycloalkyl; cycloalkyl alkyl; cycloheteroalkyl; aminoacyl; aryl; heteroaryl; substituted aryl; or substituted heteroaryl.

5. The compound of claim 4, wherein R^1 is optionally substituted phenyl or naphthyl.

6. The compound of claim 4 or 5, wherein $R^{1'}$ is selected from $C_{1\text{-}20}$ alkyl, $C_{1\text{-}10}$ alkyl, and $C_{1\text{-}6}$ alkyl.

7. The compound of any one of claims 4-6, or a salt thereof, wherein the compound is selected from



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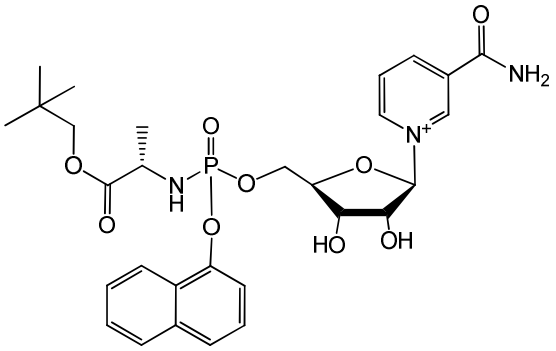

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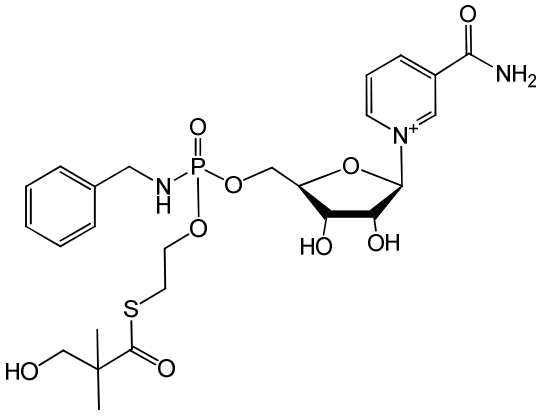

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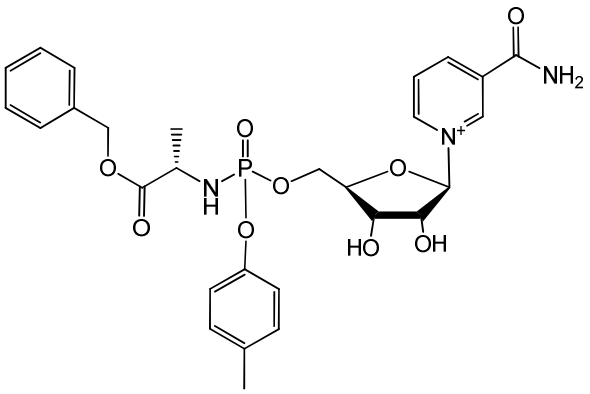

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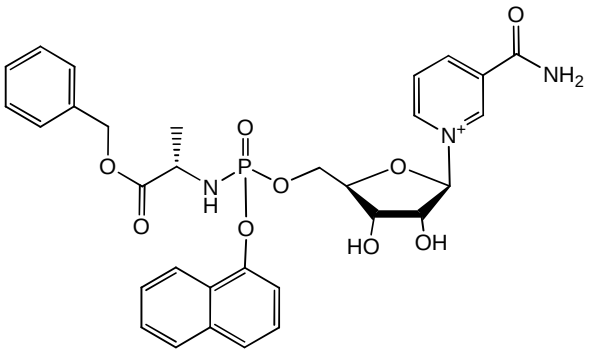

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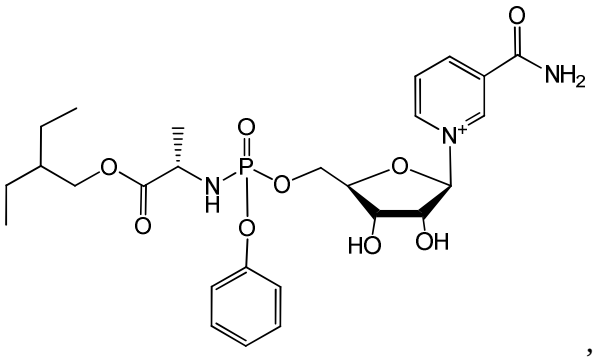

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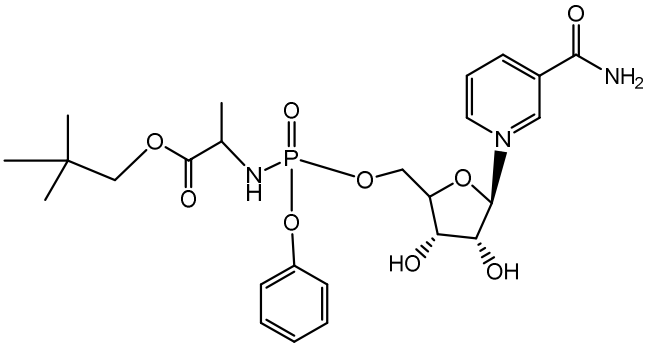

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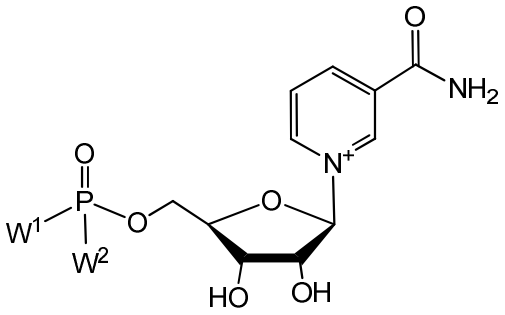
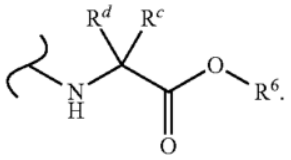
8. A compound, or a salt thereof, wherein the compound has a structure represented by formula III:



III

wherein each W^1 and W^2 is independently



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(i) each R^c and R^d is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl; or

(ii) each R^c is H and each R^d is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl; or

(iii) each R^c is H and each R^d is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl wherein the chirality of the carbon to which said R^c and R^d is attached is S; or

(iv) each R^c is H and each R^d is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl wherein the chirality of the carbon to which said R^c and R^d is attached is R; or

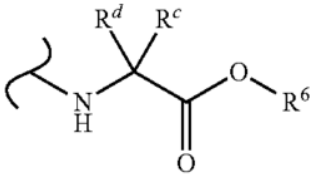
(v) each R^c is H and each R^d is independently (C_1-C_8)alkyl; or

(vi) each R^c is H and each R^d is independently (C_1-C_8)alkyl wherein the chirality of the carbon to which said R^c and R^d is attached is S; or

(vii) each R^c is H and each R^d is independently (C_1-C_8)alkyl wherein the chirality of the carbon to which said R^c and R^d is attached is R; and

each R^6 is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl or (C_4-C_8)carbocyclylalkyl.

9. The compound of claim 8, wherein each



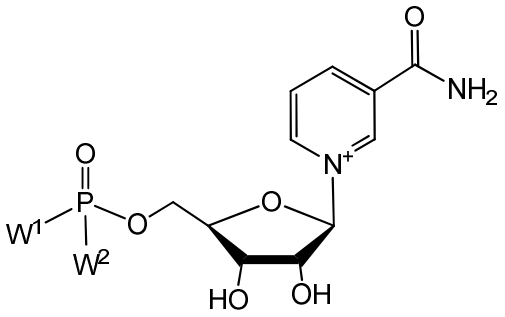
comprises a nitrogen-linked naturally occurring α-amino acid ester.

10. The compound of claim 7 or 8, wherein each R^c is H and each R^d is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl.

11. The compound of any one of claims 8-10, wherein each R^c is H and each R^d is independently (C_1-C_8)alkyl.

12. The compound of any one of claims 8-11, wherein each R^6 is independently (C_1-C_8)alkyl.

13. A compound, or a salt thereof wherein the compound has a structure represented by formula III:

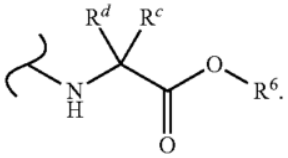


III

wherein one of W^1 or W^2 is OR^5

R^5 is $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$carbocyclyl, $(C_4\text{-}C_8)$carbocyclylalkyl, aryl$(C_1\text{-}C_8)$alkyl, heterocyclyl$(C_1\text{-}C_8)$alkyl, $(C_6\text{-}C_{20})$aryl, $(C_2\text{-}C_{20})$heterocyclyl or heteroaryl; and

the other of W^1 or W^2 is



;

(i) each R^c and R^d is independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$carbocyclyl, $(C_4\text{-}C_8)$carbocyclylalkyl, aryl$(C_1\text{-}C_8)$alkyl, heterocyclyl$(C_1\text{-}C_8)$alkyl, $(C_6\text{-}C_{20})$aryl, $(C_2\text{-}C_{20})$heterocyclyl or heteroaryl; or

(ii) each R^c is H and each R^d is independently $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$carbocyclyl, $(C_4\text{-}C_8)$carbocyclylalkyl, aryl$(C_1\text{-}C_8)$alkyl, heterocyclyl$(C_1\text{-}C_8)$alkyl, $(C_6\text{-}C_{20})$aryl, $(C_2\text{-}C_{20})$heterocyclyl or heteroaryl; or

(iii) each R^c is H and each R^d is independently $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$carbocyclyl, $(C_4\text{-}C_8)$carbocyclylalkyl, aryl$(C_1\text{-}C_8)$alkyl, heterocyclyl$(C_1\text{-}C_8)$alkyl, $(C_6\text{-}C_{20})$aryl, $(C_2\text{-}C_{20})$heterocyclyl or heteroaryl wherein the chirality of the carbon to which said R^c and R^d is attached is S; or

(iv) each R^c is H and each R^d is independently $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$carbocyclyl, $(C_4\text{-}C_8)$carbocyclylalkyl, aryl$(C_1\text{-}C_8)$alkyl, heterocyclyl$(C_1\text{-}$

C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl wherein the chirality of the carbon to which said R^c and R^d is attached is R; or

(v) each R^c is H and each R^d is independently (C_1-C_8)alkyl; or

(vi) each R^c is H and each R^d is independently (C_1-C_8)alkyl wherein the chirality of the carbon to which said R^c and R^d is attached is S; or

(vii) each R^c is H and each R^d is independently (C_1-C_8)alkyl wherein the chirality of the carbon to which said R^c and R^d is attached is R; and

each R^6 is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl or (C_4-C_8)carbocyclylalkyl.

14. The compound of claim 13, wherein R^5 is (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl.

15. The compound of claim 13 or 14, wherein R^5 is unsubstituted phenyl.

16. The compound of claim 13 or 14, wherein R^5 is pyridyl.

17. The compound of any one of claims 13-16, wherein one of R^c or R^d is H and the other of R^c or R^d is (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl.

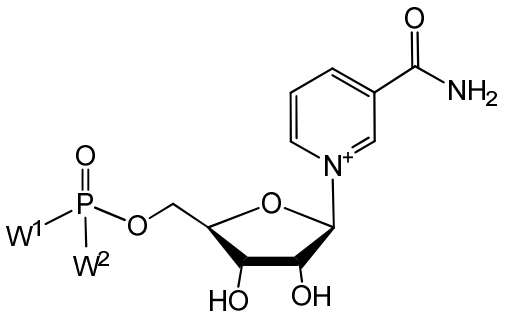
18. The compound of any one of claims 13-17, wherein one of R^c or R^d is H and the other of R^c or R^d is (C_1-C_8)alkyl.

19. The compound of any one of claims 13-18, wherein R^5 is unsubstituted phenyl, one of R^c or R^d is H and the other of R^c or R^d is methyl.

20. The compound of claim 13 any one of claims 13-19, wherein R^6 is (C_1-C_8)alkyl.

21. The compound of claim 13, wherein R^5 is unsubstituted phenyl and R^6 is $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, or $(C_4$-$C_8)$carbocyclylalkyl.

22. A compound, or a salt thereof, wherein the compound has a structure represented by formula III:



III

wherein W^1 and W^2 are independently selected from the substituents in Table 1, and

each R^{21} is independently H or $(C_1$-$C_8)$alkyl;

each R^{22} is independently H, R^{21}, R^{23} or R^{24}, wherein each R^{24} is independently substituted with 0 to 3 R^{23};

each R^{23} is independently R^{23a}, R^{23b}, R^{23c} or R^{23d}, provided that when R^{23} is bound to a heteroatom, then R^{23} is R^{23c} or R^{23d};

each R^{23a} is independently F, Cl, Br, I, --CN, $--N_3$ or $--NO_2$;

each R^{23b} is independently Y^{21};

each R^{23c} is independently $--R^{2x}$, $--OR^{2x}$, $--N(R^{2x})(R^{2x})$, $--SR^{2x}$, $--S(O)R^{2x}$; $--S(O)_2R^{2x}$, $--S(O)(OR^{2x})$, $--S(O)_2(OR^{2x})$, $--OC(=Y^{21})R^{2x}$, $--OC(=Y^{21})OR^{2x}$, $--OC(=Y^{21})(N(R^{2x})(R^{2x}))$; $--SC(=Y^{21})R^{2x}$; $--SC(=Y^{21})OR^{2x}$, $--SC(=Y^{21})(N(R^{2x})(R^{2x}))$, $--N(R^{2x})C(=Y^{21})R^{2x}$, $--N(R^{2x})C(=Y^{21})OR^{2x}$, or $--N(R^{2x})C(=Y^{21})(N(R^{2x})(R^{2x}))$;

each R^{23d} is independently $--C(=Y^{21})R^{2x}$; $--C(=Y^{21})OR^{2x}$ or $--C(=Y^{21})(N(R^{2x})(R^{2x}))$;

each R^{2x} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, aryl, heteroaryl; or two R^{2x} taken together with a nitrogen or oxygen to which they are both

attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with --O--, --S-- or --NR^{21}--; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl may be optionally replaced with --O--, --S-- or --NR^{21}--;

each R^{24} is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, or (C_2-C_8)alkynyl;

each R^{25} is independently R^{24}, wherein each R^{24} is substituted with 0 to 3 R^{23} groups;

each R^{25a} is independently (C_1-C_8)alkylene, (C_2-C_8)alkenylene, or (C_2-C_8)alkynylene, any one of which said (C_1-C_8)alkylene, (C_2-C_8)alkenylene, or (C_2-C_8)alkynylene is substituted with 0-3 R^{23} groups;

each W^{23} is independently W^{24} or W^{25};

each W^{24} is independently R^{25}, --$C(=Y^{21})R^{25}$, --$C(=Y^{21})W^{25}$, --SO_2R^{25}, or --SO_2W^{25};

each W^{25} is independently carbocycle or heterocycle wherein W^{25} is independently substituted with 0 to 3 R^{22} groups; and

each Y^{21} is independently O or S.

23. A stereoisomer of a compound of any one of claims 1-22, or a salt thereof.

24. The compound of any one of claims 1-22, wherein the compound is a salt formed with an anion selected from acetate, triflate, halide, trifluoroacetate, and formate.

25. The compound of any one of claims 1-22, wherein the compound is a salt formed with an anion selected from OH^-, $H_2PO_4^-$, HPO_4^{2-}, HSO_4^-, SO_4^{2-}, NO_3^- HCO_3^-, and CO_3^{2-}.

26. A composition comprising a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, stabilizer or excipient.

27. Use of a compound of any one of claims 1-25, or a salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with NAD+ biosynthesis.

28. The use of claim 27, wherein the disease or condition associated with NAD+ biosynthesis is selected from neurodegenerative diseases, regulating abnormal blood glucose concentration, repair of DNA damaged by drug or radiation toxicity, extending the lifespan of a cell, cellular senescence, cardiovascular diseases and conditions, circadian rhythm disorders, mitochondrial diseases, increasing mitochondrial metabolism, and retinal diseases and disorders.

29. The use of claim 28, wherein the drug or radiation toxicity is associated with one or more toxins selected from pharmaceuticals, drugs of abuse, radiation, UV light and X-ray light.

30. The use of claim 28, wherein the DNA damage occurs through the production of reactive oxygen species selected from superoxide, peroxides, and hydroxyl radicals.

31. The use of claim 28, wherein extending the lifespan of a cell comprises one or more of extending the proliferative capacity of a cell, slowing aging of a cell, promoting the survival of a cell, delaying cellular senescence in a cell, mimicking the effects of calorie restriction, increasing the resistance of a cell to stress, or preventing apoptosis of a cell.

32. The use of claim 31, wherein the cell is present in blood in a subject or an ex vivo cell culture comprising serum or biological growth media.

33. The use of claim 31, wherein the cell is present in a tissue or organ in a subject.

34. The use of claim 31, wherein the cell is present in a tissue or organ for transplantation or cell therapy,

wherein the transplantation is selected from solid tissue grafts, autografts, allografts, syngrafts, xenografts and organ transplants; and

the cell used in cell therapy is a stem cell or bone marrow cell.

35. The use of claim 34, wherein the medicament is for administration prior to implantation, concurrently with implantation, and/or post implantation into a subject.

36. The use of claim 28, wherein extending the cell's lifespan comprises treatment of a disease, disorder, or condition selected from developing skin wrinkles, contact dermatitis, atopic dermatitis, eczema, actinic keratosis, keratinization disorders, epidermolysis bullosa diseases, penfigus, exfoliative dermatitis, seborrheic dermatitis, erythemas, erythema multiforme, erythema nodosum, damage caused by the sun or other light sources, discoid lupus erythematosus, dermatomyositis, psoriasis, and skin cancer.

37. The use of claim 36, wherein extending the cell's lifespan comprises treatment of a burn selected from first-, second- or third-degree burns, thermal burns, chemical burns, and electrical burns.

38. The use of claim 28, wherein the cardiovascular disease or condition is selected from cardiomyopathy, myocarditis, idiopathic cardiomyopathy, metabolic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy; atheromatous disorders of major blood vessels selected from the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries; and platelet aggregation in vessels selected from retinal arterioles, glomerular arterioles, vasa nervorum, cardiac arterioles, and capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems.

39. The use of claim 28, wherein treatment of mitochondrial diseases and increasing mitochondrial metabolism comprises increasing the activity level of SIRT3.

40. The use of claim 36, wherein increasing the activity level of SIRT3 has one or more

effects selected from mimicking calorie restriction or exercise, increasing mitochodrial biogenesis, sensitizing a cell to glucose uptake, increasing fatty acid oxidation, decreasing reactive oxygen species, and promoting cell survival during genotoxic stress.

41. The use of claim 40, wherein increasing the activity level of SIRT3 increases metabolic activation of muscles selected from smooth muscles, gut and digestive muscles, skeletal muscles, and cardiac muscles; and/or treats cachexia and muscle wasting.

42. The use of claim 28, wherein the mitochondrial disease is selected from chronic progressive external ophthalmoplegia, myoclonus epilepsy associated with ragged-red fibers, Fukuhara syndrome, Leber's disease, Leigh encephalopathia and Pearson's disease.

43. The use of claim 28, wherein the retinal disease or disorder is selected from age-related macular degeneration, retinitis pigmentosa, rod and cone dystrophism, Leber's congenital amaurosis, photoreceptor degeneration, aberrant retinal structure, and vision loss.