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(71) Applicant(s):
The Queen's University of Belfast
University Road, BELFAST, Antrim, BT7 1NN,
United Kingdom

(72) Inventor(s):
Marie Migaud
Philip Redpath

(74) Agent and/or Address for Service:
FRKelly
4 Mount Charles, BELFAST, Northern Ireland,
BT7 1NZ, United Kingdom

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A61P 31/12 (2006.01) ***A61P 35/00*** (2006.01)
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(56) Documents Cited:
WO 2017/079195 A **WO 2017/011788 A**
WO 2016/149395 A **WO 2015/186114 A**
WO 2015/186068 A **WO 2015/014722 A**
WO 2007/061798 A

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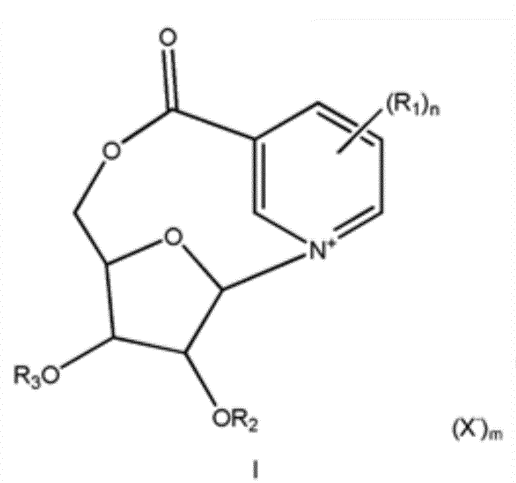
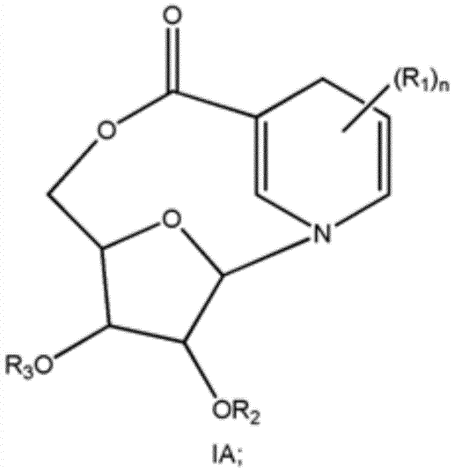
(54) Title of the Invention: **Lactone intermediates of nicotinamide riboside and nicotinate riboside**
Abstract Title: **Lactone intermediates of nicotinamide riboside and nicotinate riboside**

(57) A compound of formula I or IA:



I



IA;

wherein R_1 is an optional substituent; n is 0-4; R_2 and R_3 are selected from hydrogen and a substituent, or R_2 and R_3 join together to form an optional substituted ring; X is an anion. The compounds of formula I or IA can be reduced or decyclised to form nicotinamide ribosides or nicotinate ribosides and thus offer a new route to these compounds (see claim 1 for a new route to a compound of formula V or VA from a compound of formula I or IA). In another aspect, the compound of formula I or IA find use in the treatment of aging, stress, cardiovascular disease, cell death, cancer, metabolic disorder, neuronal disease, blood coagulation disorder, weight control, inflammatory disease, flushing, viral infection, fungal infection, dietary deficiency of vitamin B3, pellagra, pellagra-like condition, vitamin B3 deficiency, or a mitochondrial disease or disorder.

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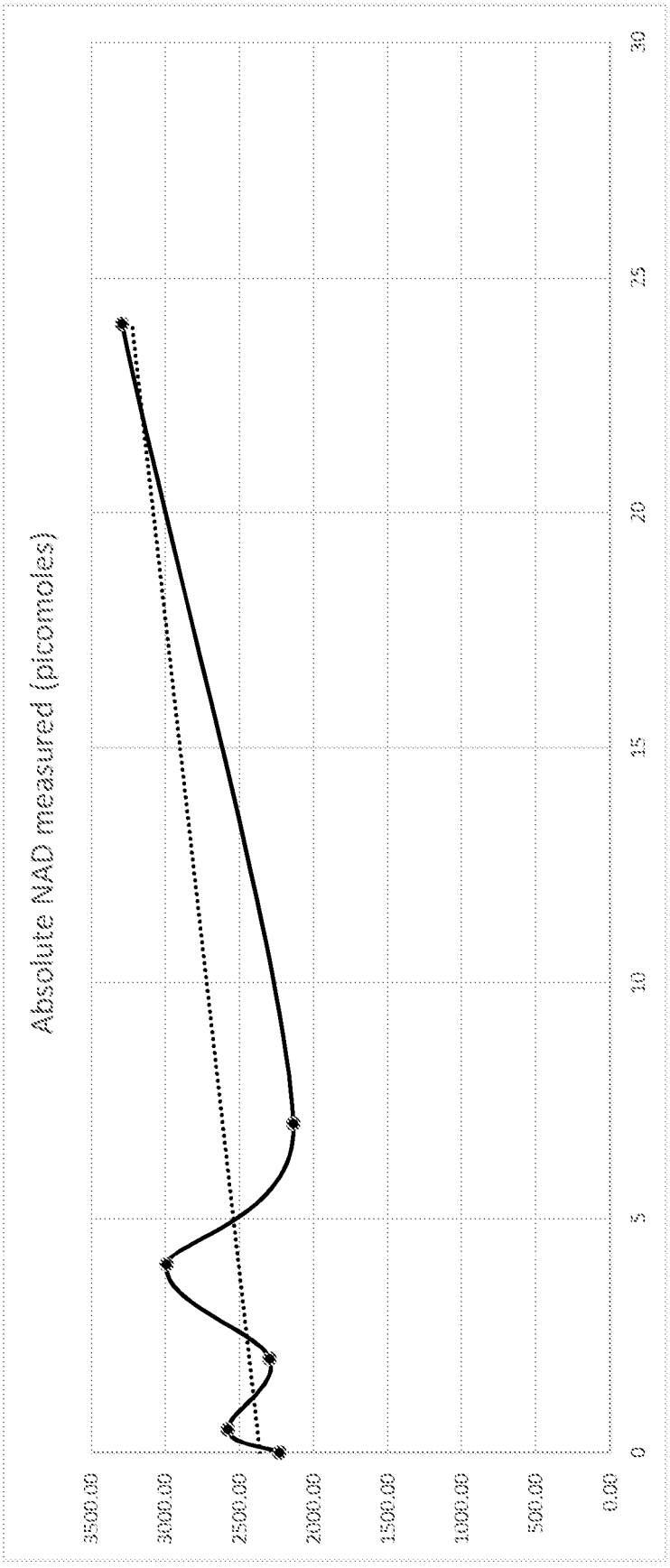

Absolute NAD measured (picomoles)
3500.00
3000.00
2500.00
2000.00
1500.00
1000.00
500.00
0.00
0
5
10
15
20
25
30

FIG. 1

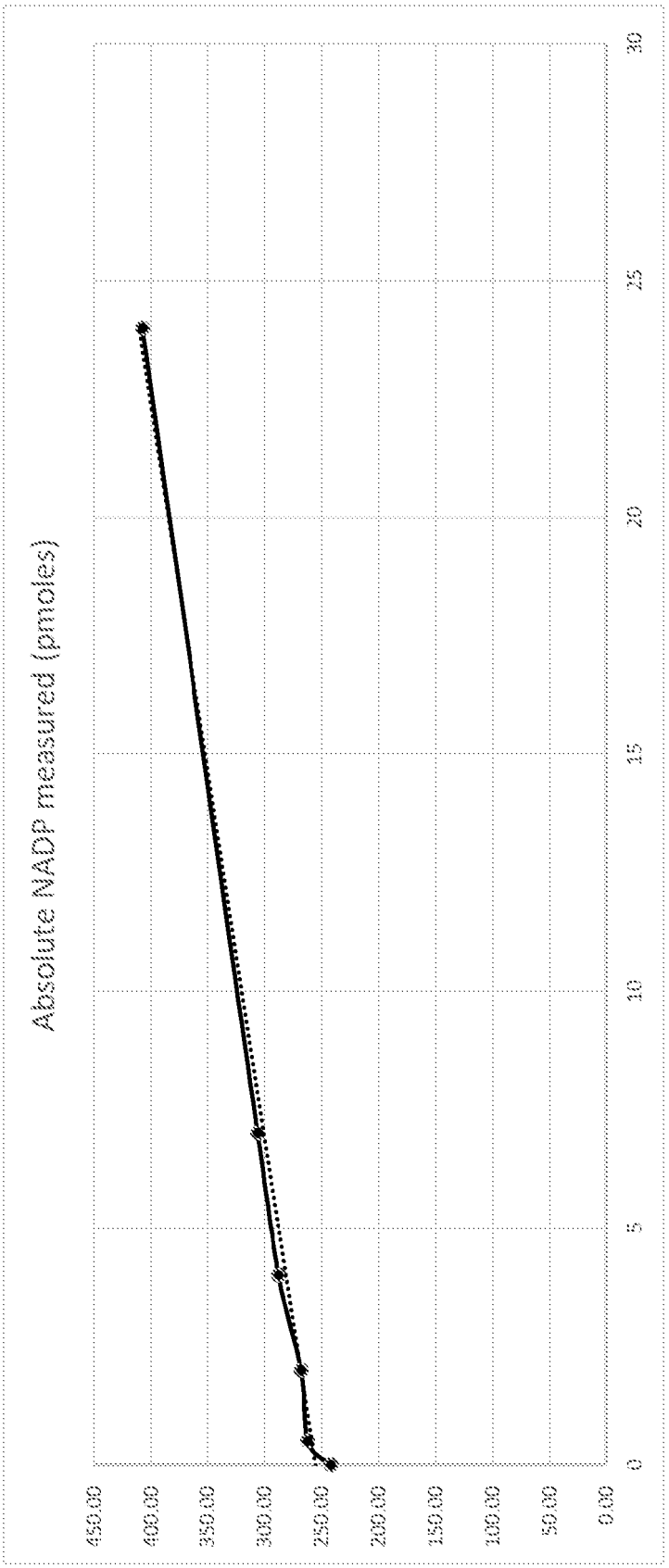

Absolute NADP measured (pmoles)
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0
5
10
15
20
25
30

FIG. 2

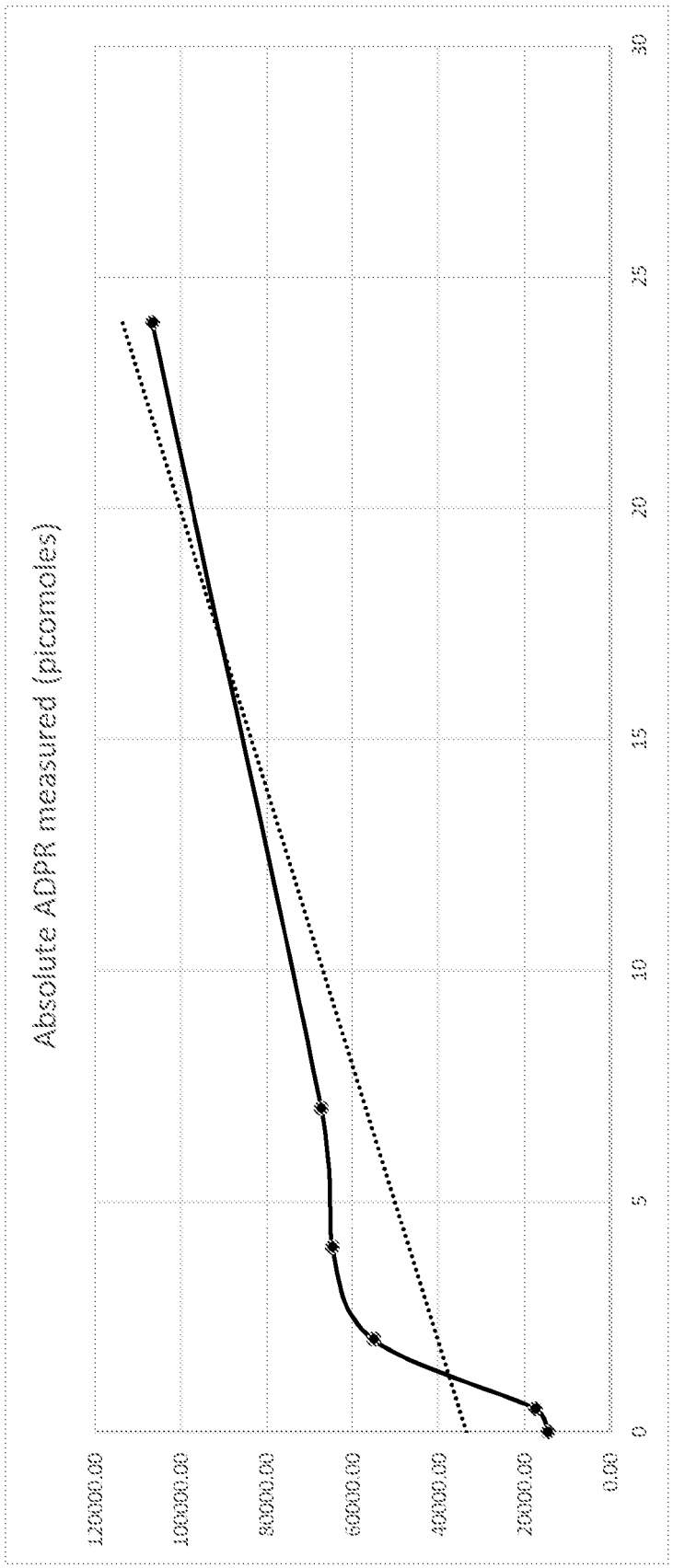

Absolute ADPR measured (picomoles)
120000.00
100000.00
80000.00
60000.00
40000.00
20000.00
0.00
0
5
10
15
20
25
30

FIG. 3

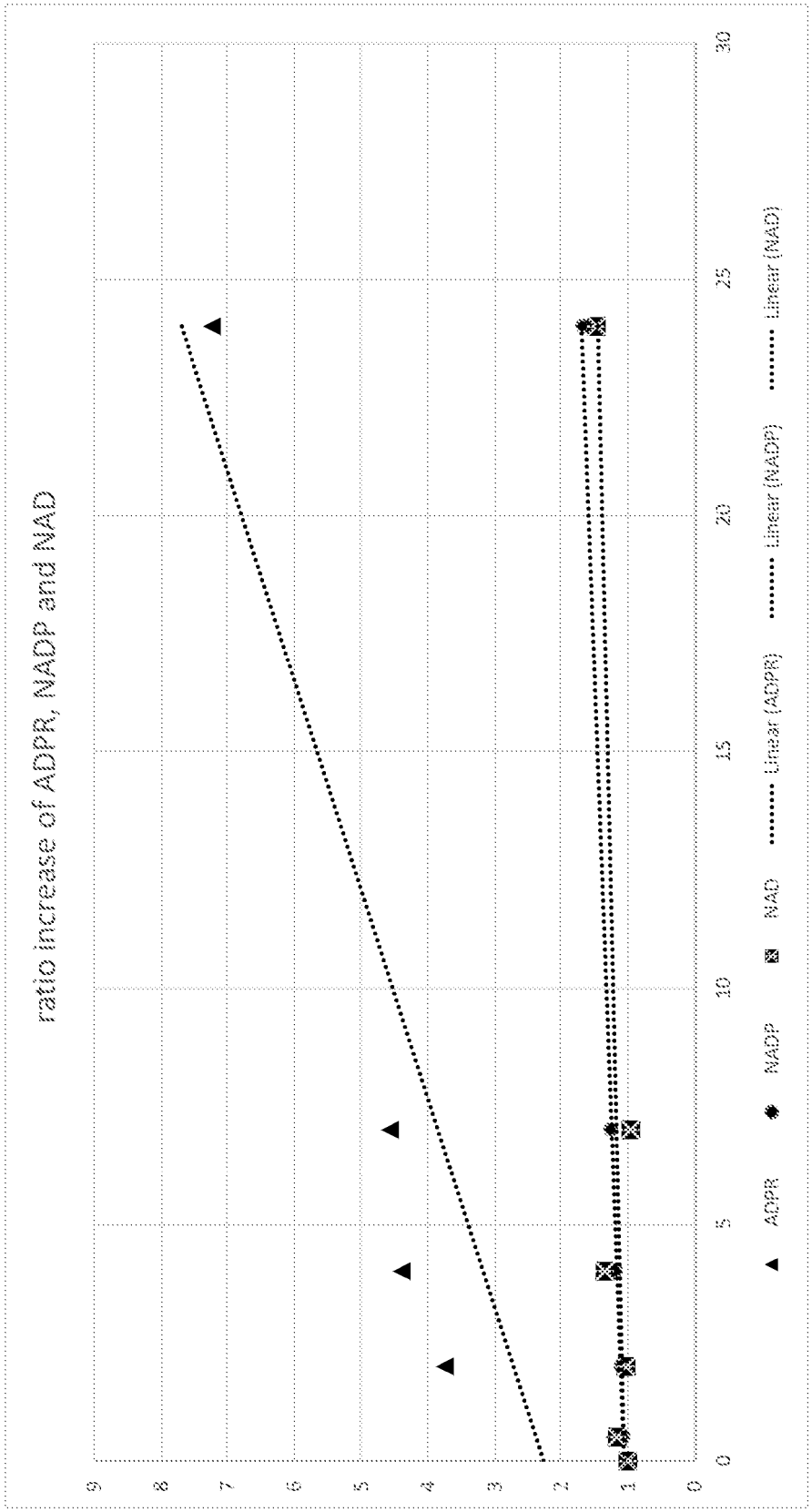

ratio increase of ADPR, NADP and NAD
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
ADPR
NADP
NAD
Linear (ADPR)
Linear (NADP)
Linear (NAD)

FIG. 4

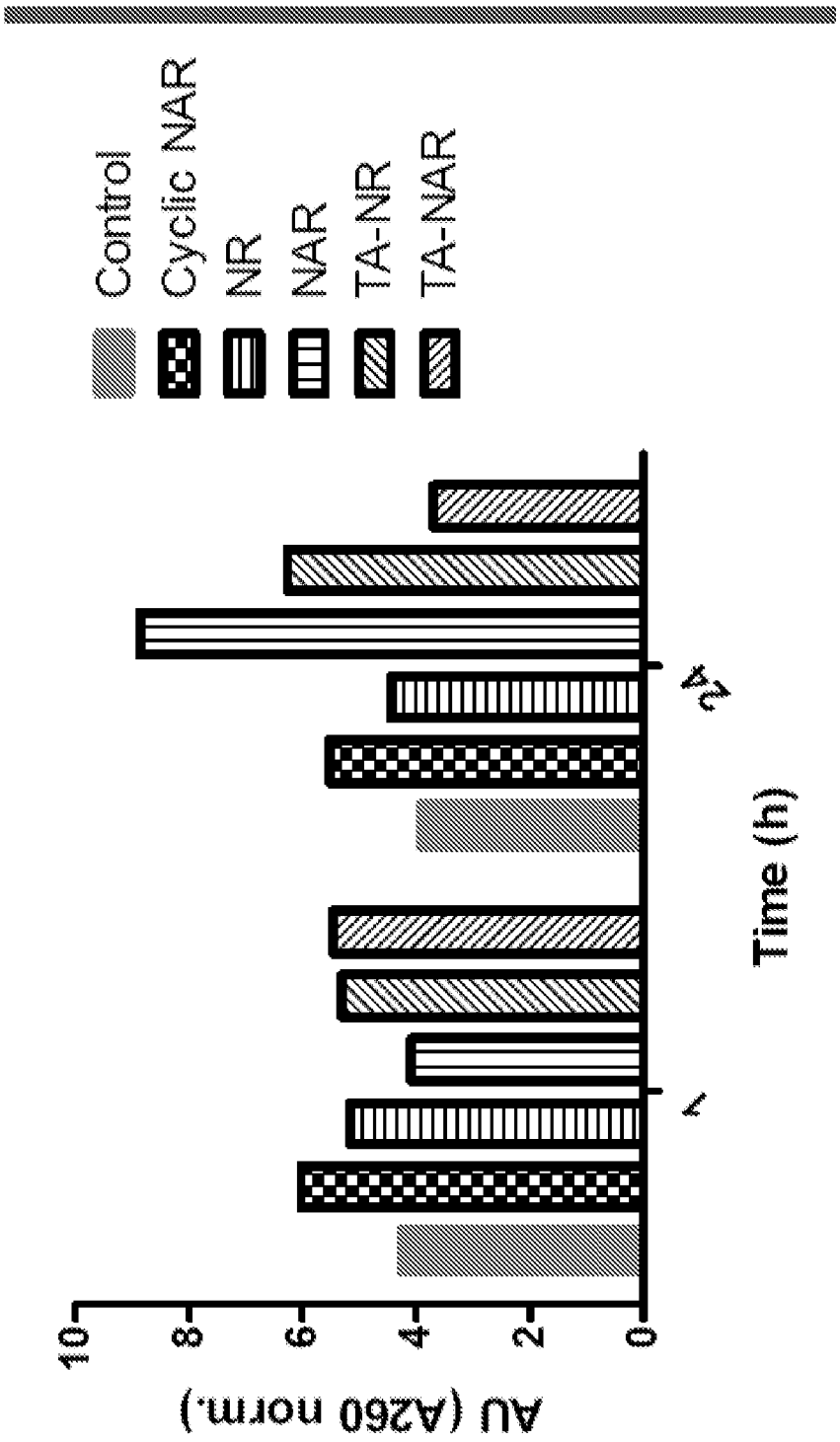

Control
Cyclic NAR
NR
NAR
TA-NR
TA-NAR
AU (A260 norm.)
0
2
4
6
8
10
7
24
Time (h)

FIG. 5

LACTONE INTERMEDIATES OF NICOTINAMIDE RIBOSIDE AND NICOTINATE RIBOSIDE

BACKGROUND

[0001] Nicotinamide riboside (NR), vitamin B3 (nicotinic acid (NA), nicotinamide (Nam) and derivatives thereof, including β-anomer forms of nicotinate riboside (NAR), nicotinamide mononucleotide (NMN) and nicotinate mononucleotide (NaNM), are metabolites of nicotinamide adenine dinucleotide (NAD^+). NAD^+ has well defined redox properties and also serves as a substrate for protein modification including protein deacylation, and mono- and poly-ADP-ribosylation. Additionally NAD^+ can be a precursor of intracellular calcium-mobilizing molecules. It is now beyond doubt that NAD^+ holds a key position in the control of fundamental cellular processes. In fact, vitamin B3 deficiency yields compromised cellular activity through NAD^+ depletion, and the beneficial effect of additional NAD^+ bioavailability through NA, Nam, Nam-mononucleotide (NMN) and NR supplementation is primarily observed in cells and tissues where metabolism and mitochondrial function has been compromised, thus making it relevant to diseases such as type 2 diabetes, cardiovascular diseases and neuropathologies. Initial data indicate that the quantities considered for individuals' treatment are in high milligram/adult/day quantities. While NR has demonstrated potentials as a vitamin supplement and as a therapeutic, its derivatives have received limited attention; even though its nicotinic acid parent (NAR), its acylated and its reduced forms have now been established has biologically active precursors of NAD^+.

[0002] Current synthetic methods to make NR and its derivatives still suffer from drawbacks with respect to reagent costs, variable yields and product instability in polar solvents. Sauve's method for glycosylation (PCT patent publication no. WO 2007/061798 or T. Yang, N. Y. K. Chan and A. A. Sauve, Journal of Medicinal Chemistry, 2007, 50, 6458-6461) employs a reaction which occurs between a nicotinoyl reagent and an acylated ribosugar to access the β-ribonucleoside, known as the Vorbrüggen methodology. To date, this Vorbruggen approach has been used very successfully (see WO2015/186114 and WO2015/186068) while others empoying a halosugar have also been applied, as demonstrated by the published routes reported by Merck (J; *Chem. Commun.,* **1999**; 729-730).

[0003] An alternative synthetic sequence to nicotinoyl riboside derivatives was presented in WO2015/014722 which employed mechanochemistry and included the generation of the lipophilic reduced forms of NR and NAR, as synthetic intermediates and biologically relevant NAD^+ precursors. In this work, they reported a method to prepare nicotinoyl riboside derivatives which employed solvent-based and solventless mechanochemical processes, and for which TMSOTf was used to gain access to the acylated forms of NAR and NR by Vorbrüggen condensation. This synthetic sequence was achieved by combining 3 key elements: Vorbrüggen reaction by mechanical grinding/milling, bi-phasic reduction of the triacetylated NR-NAR and in situ extraction of the organic soluble pure triacetylated reduced nicotinoyl riboside derivatives, which could then be deprotected to the reduced forms of NR and NAR, i.e. NRH and NARH respectively and oxidised to NR and NAR, respectively.

[0004] However, due to the many proposed beneficial health effects of the nicotinoyl ribosides (NR and NAR) and their phosphorylated derivatives (NMN, NAMN) as NAD boosting agents, there is a

need for improved synthetic processes and new versions of NR-like building blocks which demonstrate an ability to boost the NAD levels in cells, while addressing the challenges of chemical and biological stability and organ/tissue specificity which are still plaguing these nutraceuticals.

[0005] Approaches to modulate chemical stability, cellular distribution and overall bioavailability have led to the development of a range of NR derivatives, both in terms of reduced forms and in terms of labile protecting groups such as esters (WO2015/014722, WO2015/186114 and WO2015/186068).

[0006] Krishnamurthy *et al* recently reported the TMSOTf catalysed synthesis of Orotidine via intramolecular cyclization of a reactive Riboside ester and the generation of a reactive lactone intermediate to access this particular nucleoide (Kim E, K; Krishnamurthy R; *Chem. Commun.*, **2015; 51**, 5618-5621.

[0007] Lactones offer a different type of reactivity to esters in terms of hydrolysis as they can have specific reaction rates independent of the biological environment and the presence of specific esterases, even though these can also work to the lactones advantage. Unlike esters, lactones can be structurally strained and as such have intrinsic reactivity towards nucleophiles.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 depicts changes in intracellular concentration of NAD when cyclic NAR diacetate was incubated with TIB73 murine hepatocyte cells for 24hrs measured by LC-MS/MS.

[0009] FIG. 2 depicts changes in intracellular concentration of NADP when cyclic NAR diacetate was incubated with TIB73 murine hepatocyte cells for 24hrs measured by LC-MS/MS.

[0010] FIG. 3 depicts changes in intracellular concentration of ADPR when cyclic NAR diacetate was incubated with TIB73 murine hepatocyte cells for 24hrs measured by LC-MS/MS.

[0011] FIG. 4 depicts the relative ratios of increase in NAD, NADP and ADPR when cyclic NAR diacetate was incubated with TIB73 murine hepatocyte cells for 24hrs measured by LC-MS/MS.

[0012] FIG. 5 depicts NAD levels in TIB73 murine hepatocyte cells after administration of a range of compounds, wherein NAR is nicotinic acid riboside and the TA-NR and NAR are the triacetate form of NR and NAR.

SUMMARY OF THE INVENTION

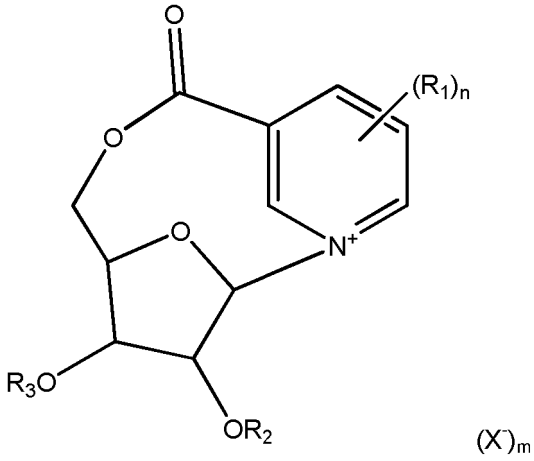
[0013] In one aspect, the present invention relates to a lactone (oxidised or reduced) of structural formula I or IA which is useful as a precursor for NAD. In one aspect, the lactones of the present invention can be used to produce nicotinoyl riboside derivatives and as such are versatile biological and chemical precursors to NAD and this can act as NAD booster agents.

[0014] In one aspect, the lactones of the present invention can be made from a range of sugar esters using conditions selected from solvent, solvent-assisted, and solventless conditions, as described herein.

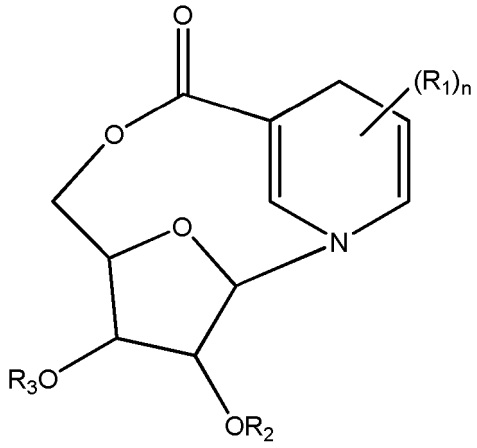
[0015] In one aspect, the present invention demonstrates the synthetic preparation of certain NR, NAR, NRH, and NARH compounds from nicotinoyl ester riboside derivatives, via a novel lactone

intermediate which can be prepared under solvent, or under solvent-assisted or solventless mechanochemical (grinding, ball and planetary milling conditions).

[0016] In another aspect, the present invention provides chemical compounds which are intermediates in the preparation of a broad range of NR, NAR, NRH, and NARH compounds and which are precursors of NAD. These intermediates are represented by the lactones of structural formulae I and IA:



I

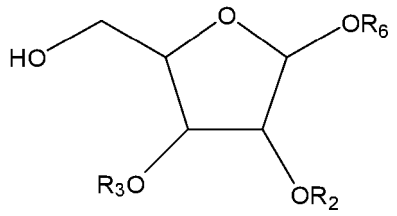


IA;

X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate. Eeach R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a_2$, $-C(O)NR^a_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a_2$, $-C(O)ONR^a_2$, $-OC(O)NR^a_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a_2$, $-NR^aC(=NR^a)NR^a_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a_2$. Each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or

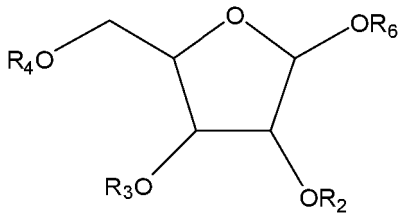
R_2 and R_3 join together to form an optionally substituted ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl. Each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl. n is 0-4. m is 0 or 1.

[0017] In one embodiment, the present invention is a method of producing the compound of structural formula I or IA, comprising the steps of:i) contacting a compound of structural formula II:



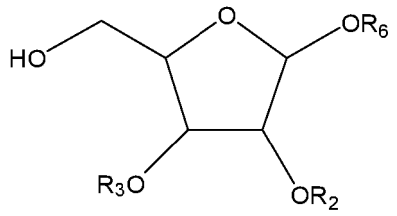
II

wherein; R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a ,-SO_2R^a, -SO_2OR^a or -O-P(=O)-$(OR^a)_2$; with nicotinoyl halide or nicotinoyl anhydride, each of which is optionally substituted with R_1, in the presence of a base, to form a compound of structural formula III:



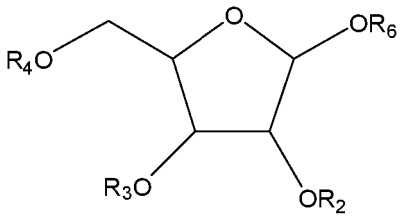
III

wherein: each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -NR^a_2, -$C(O)NR^a_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a_2$, -$C(O)ONR^a_2$, -$OC(O)NR^a_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a_2$, -$NR^aC(=NR^a)NR^a_2$, -OC(O)R^a, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -C(O)OS(O)R^a, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a_2$. R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$. R_4 is –CO(pyridyl optionally substituted with R_1);or i) contacting a compound of structural formula II:



II

wherein: R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a , -SO_2R^a, SO_2OR^a, or -O-P(=O)-$(OR^a)_2$; with nicotinic acid, optionally substituted with R_1 in the presence of a coupling agent to generate compound of formula III:



III

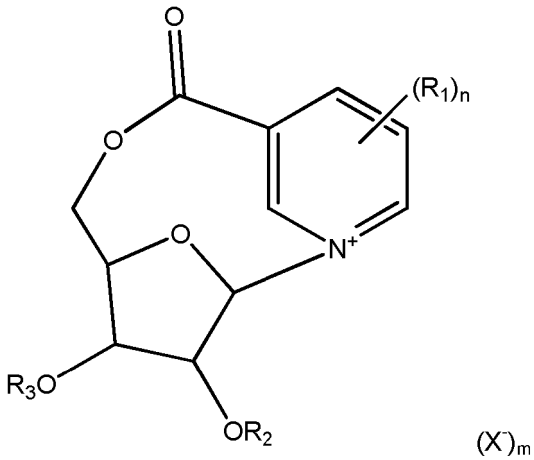
wherein: each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$. R_6, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$. R_4 is –CO(pyridyl optionally substituted with R_1); and ii) cyclizing the compound of formula III in the presence of Lewis Acid to form the compound of formula I; and iii) optionally reducing the compound of formula I to give the compound of formula IA.

[0018] These lactone compounds are useful as lipophilic precursors to NAD/NAD(P). These lactones, as well as being direct precursors to NAD and its metabolites, due to their reactive ester functionality also allow their facile chemical conversion to NR as well as NAR derivatives.

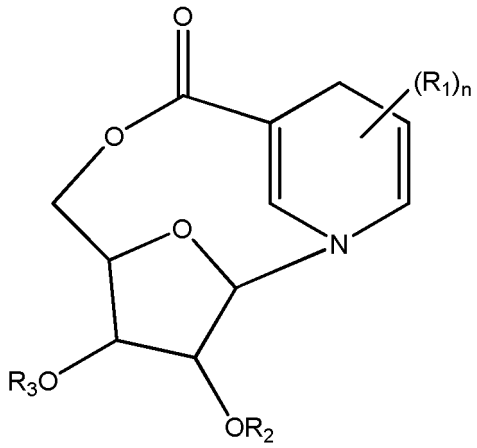
[0019] In one aspect, the lactones of the present invention are useful as precursors to NAD. In one embodiment, the present invention is a method of treating and/or a disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of structural formula I or IA. In one embodiment, the disease or disorder is aging/stress, cardiovascular disease, cell death, cancer, metabolic disorder/diabetes, neuronal disease/neuropathology, blood coagulation disorder, weight control/obesity, inflammatory disease, flushing, viral/fungal infection, dietary deficiency of vitamin B3, pellagra including alcoholic pellagra and pellagra-like conditions following treatments for conditions such as bacterial infection, and viral infection.

DETAILED DESCRIPTION

[0020] In one embodiment, the present invention is a compound represented by structural formula I or IA:



I



IA.

[0021] X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate.

[0022] Each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$.

[0023] Each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring.

[0024] Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl.

[0025] Each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl.

[0026] n is 0-4.

[0027] m is 0 or 1.

[0028] In one embodiment, X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate. Optionally, X^- is triflate, fluoride, chloride, bromide, or iodide. Further optionally, X^- is triflate. Further optionally, X^- is chloride. Alternatively, X^- is not triflate.

[0029] In one embodiment, X^- is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted sulfonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate. Optionally, X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of a substituted or unsubstituted monocarboxylic acid and an anion of a substituted or unsubstituted dicarboxylic acid. Optionally, X^- is an anion of a substituted monocarboxylic acid, further optionally an anion of a substituted propanoic acid or an anion of a substituted acetic acid. Optionally, X^- is an anion of substituted propanoic acid, further optionally an anion of a hydroxy propanoic acid, still further optionally an anion of 2-hydroxypropanoic acid, being lactic acid, the anion of lactic acid being lactate. Optionally, X^- is an anion of a substituted acetic acid, such as a substituted acetate, further optionally a trihaloacetate selected from trichloroacetate, tribromoacetate and trifluoroacetate. Still further optionally, the trihaloacetate is trifluoroacetate. Optionally, X^- is an anion of an unsubstituted monocarboxylic acid selected from formic acid, acetic acid, propionic acid and butyric acid, being formate, acetate, propionate and butyrate, respectively. Optionally, X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a substituted or unsubstituted amino-dicarboxylic acid. Further optionally, X^- is an anion of an amino-dicarboxylic acid, optionally selected from glutamic acid and aspartic acid, being glutamate and aspartate, respectively. Optionally, X^- is an anion of ascorbic acid, being ascorbate. Optionally, X^- is a halide selected from chloride, bromide, fluoride and iodide, further optionally chloride or bromide. Optionally, X^- is a substituted or unsubstituted sulfonate. Further optionally, X^- is a trihalomethanesulfonate selected from trifluoromethanesulfonate, tribromomethanesulfonate and trichloromethanesulfonate. Still further optionally, the trihalomethanesulfonate is trifluoromethanesulfonate. Optionally, X^- is a substituted or unsubstituted carbonate, further optionally hydrogen carbonate. Optionally, X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, aspartate, glutamate and lactate. Further optionally, X^- is selected from chloride, acetate, formate and trifluoroacetate.

[0030] In one embodiment, each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$. Optionally, each R_1 is independently halide, -CN, $-NO_2$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$.

Further optionally, each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$. Further optionally, each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, or $-NR^a{}_2$.

[0031] In one embodiment, each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted $(C_1\text{-}C_8)$aliphatic, optionally substituted $(C_3\text{-}C_8)$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring. Optionally, each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or $(C_1\text{-}C_8)$alkyl; or R_2 and R_3 join together to form an optionally substituted ring. Further optionally, each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is $(C_1\text{-}C_6)$ alkyl. In one embodiment, the ring is a heterocycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a heterocyclic ring. In one embodiment, the ring is a 5 membered heterocyclic ring. In one embodiment, R_2 and R_3 are -C(O)R'. Optionally, R_2 and R_3 are $-C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted heterocyclic ring. Optionally, R_2 and R_3 together to form $–C(CH_3)_2$-.

[0032] In one embodiment, R_2 and R_3 include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups. Optionally, the R_2 and R_3 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

[0033] In one embodiment, each R^a is independently hydrogen, optionally substituted $(C_1\text{-}C_8)$aliphatic, optionally substituted $(C_3\text{-}C_8)$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl. Optionally, each R^a is independently hydrogen, optionally substituted $(C_1\text{-}C_8)$aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Further optionally, each R^a is independently hydrogen, optionally substituted $(C_1\text{-}C_8)$alkyl, or optionally substituted aryl. Further optionally, each R^a is independently hydrogen, or optionally substituted $(C_1\text{-}C_6)$alkyl. Further optionally, each R^a is independently hydrogen, or $(C_1\text{-}C_6)$alkyl.

[0034] In one embodiment, each R' is independently hydrogen, $(C_1\text{-}C_8)$aliphatic, $(C_3\text{-}C_8)$cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl. Optionally, each R' is independently hydrogen, or $(C_1\text{-}C_8)$alkyl. Further optionally, each R' is $(C_1\text{-}C_8)$alkyl.

[0035] In one embodiment, n is 0.

[0036] In one embodiment, X^- is triflate, fluoride, chloride, bromide, or iodide. Each R_1 is independently halide, -CN, $-NO_2$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$. Each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or $(C_1\text{-}C_8)$alkyl; or R_2 and R_3 join together to form an optionally substituted ring. Each R^a is independently hydrogen, optionally substituted $(C_1\text{-}C_8)$aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Each R' is independently hydrogen, or $(C_1\text{-}C_8)$alkyl. n is 0. m is 0 or 1.

[0037] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$. Each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is $(C_1\text{-}C_6)$ alkyl. In one embodiment, the ring is a cycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a cycloalkyl ring or a

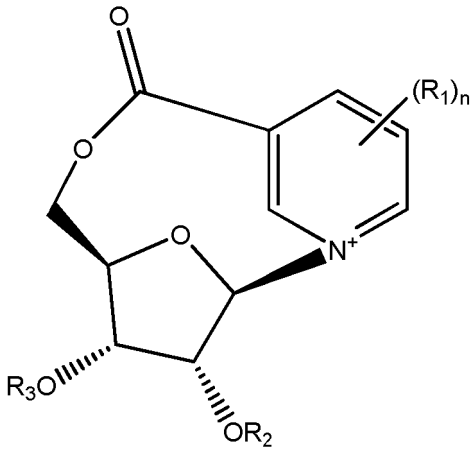
heterocyclic ring. Each R^a is independently hydrogen, optionally substituted $(C_1\text{-}C_8)$alkyl, or optionally substituted aryl. Each R' is $(C_1\text{-}C_8)$alkyl. n is 0. m is 0 or 1.

[0038] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 are -C(O)R'. Each, R_2 and R_3 are $-C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. In one embodiment, the ring is a 5 membered heterocyclic ring. Optionally, R_2 and R_3 join together to form $-C(CH_3)_2-$. Each R^a is independently hydrogen, or $(C_1\text{-}C_8)$alkyl. Optionally, n is 0.

[0039] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 are $-C(O)CH_3$. Each R^a is independently hydrogen, or $(C_1\text{-}C_8)$alkyl. Optionally, n is 0.

[0040] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, $(C_1\text{-}C_6)$alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 join together to form a $C_3\text{-}C_6$ cycloalkyl ring. Optionally, R_2 and R_3 join together to form $-C(CH_3)_2-$. Optionally, each R^a is independently hydrogen, or $(C_1\text{-}C_8)$alkyl. Optionally, n is 0.

[0041] In one embodiment, the compounds of the invention are represented by structural formula 1 or 1A:



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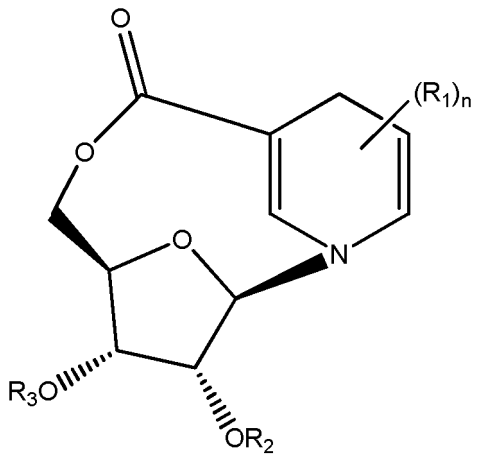


1A .

[0042] X^-, R_1, R_2, R_3, m and n are as described above, or in the following paragraphs.

[0043] In one embodiment, X^- is triflate, fluoride, chloride, bromide, or iodide. Each R_1 is independently halide, -CN, $-NO_2$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$. Each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or (C_1-C_8)alkyl; or R_2 and R_3 join together to form an optionally substituted ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Each R' is independently hydrogen, or (C_1-C_8)alkyl. n is 0.

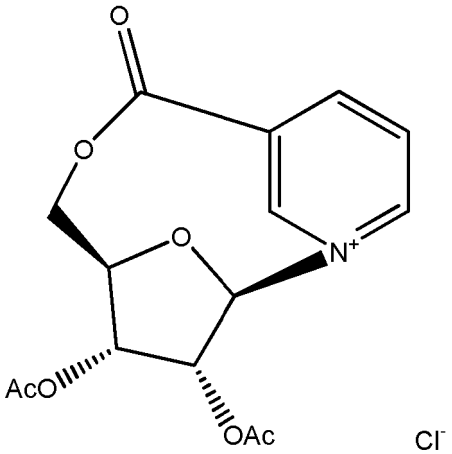
[0044] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$. Each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is (C_1-C_6) alkyl. In one embodiment, the ring is a cycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a cycloalkyl ring or a heterocyclic ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)alkyl, or optionally substituted aryl. Each R' is (C_1-C_8)alkyl. n is 0.

[0045] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 are -C(O)R'. Optionally, R_2 and R_3 are $-C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. In one embodiment, the ring is a 5 membered heterocyclic ring. Optionally, R_2 and R_3 join together to form $-C(CH_3)_2-$. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. n is 0.

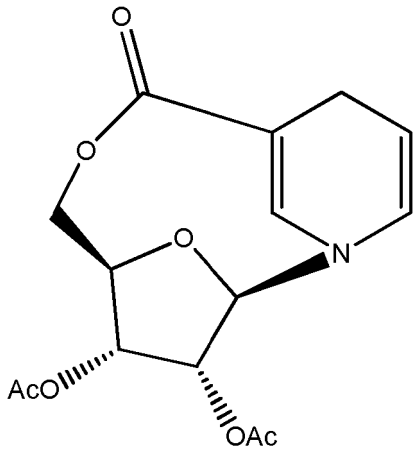
[0046] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 are $-C(O)CH_3$. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. n is 0.

[0047] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, $-OR^a$, or $-NR^a{}_2$. R_2 and R_3 join together to form a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 join together to form $-C(CH_3)_2-$. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. n is 0.

[0048] In one embodiment, the compounds of the invention are represented by structural formula 2 or 2A:

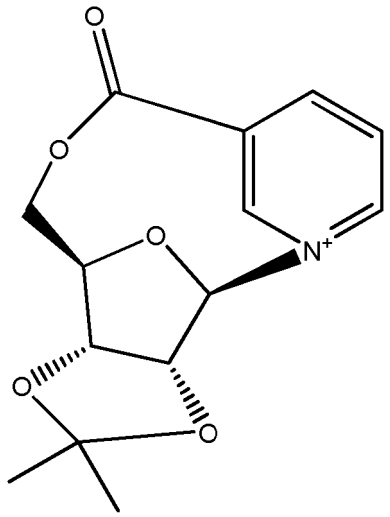


2,

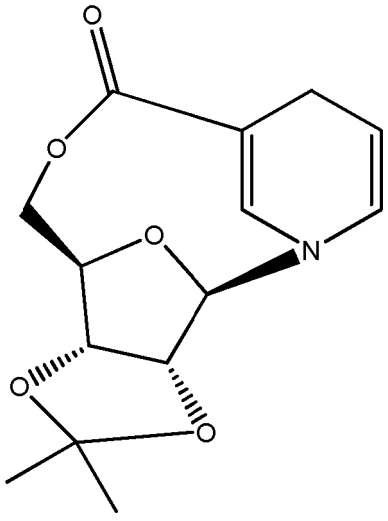


2A.

[0049] In one embodiment, the compounds of the invention are represented by structural formula 3 or 3A:



3,



[0050] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched), or branched, hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation but is non-aromatic. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1 -4 aliphatic carbon atoms. Aliphatic groups may be linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Specific examples include, but are not limited to, methyl, ethyl, isopropyl, n-propyl, sec -butyl, vinyl, n-butenyl, ethynyl, and tert-butyl and acetylene.

[0051] The term "alkyl" as used herein means a saturated straight or branched chain hydrocarbon. The term "alkenyl" as used herein means a straight or branched chain hydrocarbon comprising one or more double bonds. The term "alkynyl" as used herein means a straight or branched chain hydrocarbon comprising one or more triple bonds. Each of the "alkyl", "alkenyl" or "alkynyl" as used herein can be optionally substituted as set forth below. In some embodiments, the "alkyl" is C_1-C_8 alkyl or C_1-C_6 alkyl. In some embodiments, the "alkenyl" is C_2-C_8 alkenyl or C_2-C_6 alkenyl. In some embodiments, the "alkynyl" is C_2-C_8 alkynyl or C_2-C_6 alkynyl.

[0052] The term "cycloaliphatic" refers to a monocyclic, bicyclic or polycyclic fused, spiro or bridged cyclic ring (typically a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon) that is completely saturated or contains one or more units of unsaturation and has a single point of attachment to the rest of the molecule, and wherein any individual ring in said bicyclic ring system has 3-8 members.

[0053] The term "cycloalkyl" (or "carbocycle") refers to a monocyclic, bicyclic or polycyclic fused, spiro or bridged cyclic ring (typically a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon) that is completely saturated and has a single point of attachment to the rest of the molecule, and wherein any individual ring in said bicyclic ring system has 3-8 members. Suitable cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0054] The term "heterocycle" (or "heterocyclyl", or "heterocyclic" or "non-aromatic heterocycle") as used herein refers to a non-aromatic ring system which can be saturated or contain one or more units of unsaturation, having three to fourteen ring atoms in which one or more ring carbons is replaced by a heteroatom such as, N, S, or O and each ring in the system contains 3 to 8 members. In some embodiments, non-aromatic heterocyclic rings comprise up to three heteroatoms selected from N, S and O within the ring. In other embodiments, non-aromatic heterocyclic rings comprise up to two heteroatoms selected from N, S and O within the ring system. In yet other embodiments, non-aromatic heterocyclic rings comprise up to two heteroatoms selected from N and O within the ring system. The term includes monocyclic, bicyclic or polycyclic fused, spiro or bridged heterocyclic ring systems. Examples of heterocycles include, but are not limited to, piperidinyl, piperizinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, azepanyl, diazepanyl, triazepanyl, azocanyl, diazocanyl, triazocanyl,

oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, oxazocanyl, oxazepanyl, thiazepanyl, thiazocanyl, benzimidazolonyl, tetrahydrofuranyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophenyl, morpholino, including, for example, 3 -morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1 -piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1 -piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3 -thiazolidinyl, 4-thiazolidinyl, 1 -imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5 -imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolanyl, benzodithianyl, 3-(1-alkyl)-benzimidazol-2-onyl, and 1,3-dihydro-imidazol-2-onyl.

[0055] As used herein, the term “heterocycloalkyl”, is a heterocyclic group, as defined herein, attached to the rest of the molecule through an alkyl group, as defined herein.

[0056] As used herein, an “azido” group is $–N_3$.

[0057] The term "heteroatom" means one or more of oxygen, sulphur, nitrogen, or phosphorus, including any oxidized form of nitrogen, sulphur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

[0058] The term “aryl” herein refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the poly-carbocyclic ring systems may be fused or attached to each other via a single bond. Suitable “aryl” groups comprise, but are not limited to, phenyl, naphthyl, biphenyl, and the like.

[0059] The term “heteroaryl” herein refers to an aromatic mono- and poly-carbocyclic ring system comprising at least a heteroatom in the ring system, wherein said heteroatom is selected in the group comprising, but not limited to, nitrogen, sulphur, oxygen and the like, and wherein the individual cyclic rings in the poly-carbocyclic ring systems may be fused or attached to each other via a single bond. Suitable “heteroaryl” groups comprise, but are not limited to, pyridyl, imidazolyl, pyrrolyl, furyl, benzimidazolyl, thiofuranyl and the like.

[0060] As used herein, the term “aralkyl” is an aryl group, as defined herein, attached to the rest of the molecule through an alkyl group, as defined herein.

[0061] The term “ring” can be any of cycloaliphatic, heterocyclic, aryl or heteroaryl. In one embodiment, the ring is cycloaliphatic. In one embodiment, the ring is cycloalkyl.

[0062] The term "ring atom" is an atom such as C, N, O or S that is in the ring of an aromatic group, cycloalkyl group or non-aromatic heterocyclic ring.

[0063] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0064] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as illustrated generally herein, or as exemplified by particular species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the

term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. When the term "optionally substituted" precedes a list, said term refers to all of the subsequent substitutable groups in that list. If a substituent radical or structure is not identified or defined as "optionally substituted", the substituent radical or structure is unsubstituted.

[0065] Selection of substituents and combinations of substituents envisioned by this invention are those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, specifically, their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week. Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

[0066] Suitable substituents on a carbon of an aliphatic, cycloaliphatic, heterocyclic, aryl or heteroaryl ring are C_1-C_6 alkyl, halogen, cyano, -NCO, -OR^b, -SR^b, -$S(O)R^b$, -SO_2R^b, -NR^bR^b, -$C(O)R^b$, -$C(O)OR^b$, -$OC(O)R^b$, -$NRC(O)R^b$, -$C(O)NR^bR^b$, -$NR^bC(O)NR^bR^b$, -$NR^bC(O)OR^b$, -$OCONR^bR^b$, -$C(O)NRCO_2R^b$, -$NR^bC(O)NR^bC(O)OR^b$, -$C(O)NR(OR^b)$, -$SO_2NR^bR^b$, -$NR^bSO_2R^b$, -$NR^bSO_2NR^bR^b$, or -$P(O)(OR^b)_2$-; or two substituents join together with the atoms to which they are attached to form a 5-7-membered cycloalkyl or heterocyclic ring. Each R^b is independently –H or C_1-C_6 alkyl. Other suitable substituents for a saturated carbon of an aliphatic, cycloaliphatic or heterocyclic include the following: =O, =S, =$NNHR^b$, =$NN(R^b)_2$, =$NNHC(O)R^b$, =$NNHCO_2$(alkyl), =$NNHSO_2$(alkyl), or =NR^b, wherein each R^b is independently selected from –H or C_1-C_6 alkyl.

[0067] In some embodiments, optional substituents on the nitrogen of a heterocyclic ring include those used above. Other suitable substituents include -R^+, -$N(R^b)_2$, -$C(O)R^b$, -CO_2R^b, -$C(O)C(O)R^b$, -$C(O)C(R^b)_2C(O)R^b$, -SO_2R^b, -$SO_2N(R^b)_2$, -$C(=S)N(R^b)_2$, -$C(=NR^b)$-$N(R^b)_2$, or –$R^bSO_2R^b$. Each R^b is independently –H or C_1-C_6 alkyl.

[0068] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, cis-trans, conformational, and rotational) forms of the structure. For example, the R and S configurations for each asymmetric centre, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers are included in this invention, unless only one of the isomers is drawn specifically. As would be understood to one skilled in the art, a substituent can freely rotate around any rotatable bonds. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, cis/trans, conformational, and rotational mixtures of the present compounds are within the scope of the invention.

[0069] Unless otherwise indicated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[0070] Additionally, unless otherwise indicated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays. Such compounds, especially deuterium analogues, can also be therapeutically useful.

[0071] The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

[0072] The term “approximately” herein refers to the range of the experimental error, which may occur in a measurement.

[0073] The terms “comprising”, “having”, “including” and “containing” are to be construed as open-ended terms (i.e. meaning “including, but not limited to”) and are to be considered as including and/or providing support also for terms as “consist essentially of”, “consisting essentially of”, “consist of” or “consisting of”.

[0074] The terms “consist essentially of”, “consisting essentially of” are to be construed as a semi-closed terms, meaning that no other ingredients which materially affects the basic and novel characteristics of the invention are included (optional excipients may thus be included).

[0075] The terms “consists of” and “consisting of” are to be construed as closed terms.

[0076] Certain functional groups which would be sensitive to reaction conditions may be protected by protecting groups. A protecting group is a derivative of a chemical functional group which would otherwise be incompatible with the conditions required to perform a particular reaction which, after the reaction has been carried out, can be removed to re-generate the original functional group, which is thereby considered to have been “protected.” Any chemical functionality that is a structural component of any of the reagents used to synthesize compounds of this invention may be optionally protected with a chemical protecting group if such a protecting group is useful in the synthesis of compounds of this invention. The person skilled in the art knows when protecting groups are indicated, how to select such groups, and processes that can be used for selectively introducing and selectively removing them, because methods of selecting and using protecting groups have been extensively documented in the chemical literature. Techniques for selecting, incorporating and removing chemical protecting groups may be found, for example, in *Protective Groups in Organic Synthesis* by Theodora W. Greene, Peter G. M. Wuts (John Wiley & Sons, Inc. 1999), the entire disclosure of which is incorporated herein by reference.

[0077] In addition to use of a protecting group, sensitive functional groups may be introduced as synthetic precursors to the functional group desired in the intermediate or final product. An example

of this is an aromatic nitro (-NO_2) group. The aromatic nitro group does not undergo any of the nucleophilic reactions of an aromatic amino group. However, the nitro group can serves as the equivalent of a protected amino group because it is readily reduced to the amino group under mild conditions that are selective for the nitro group over most other functional groups.

[0078] The term "protecting group" and "protective group" as used herein, are interchangeable and refer to an agent used to temporarily block one or more desired functional groups in a compound with multiple reactive sites. In certain embodiments, a protecting group has one or more, or specifically all, of the following characteristics: a) is added selectively to a functional group in good yield to give a protected substrate that is b) stable to reactions occurring at one or more of the other reactive sites; and c) is selectively removable in good yield by reagents that do not attack the regenerated, deprotected functional group. As would be understood by one skilled in the art, in some cases, the reagents do not attack other reactive groups in the compound. In other cases, the reagents may also react with other reactive groups in the compound. The term "nitrogen protecting group", as used herein, refers to an agent used to temporarily block one or more desired nitrogen reactive sites in a multifunctional compound. Preferred nitrogen protecting groups also possess the characteristics exemplified for a protecting group above, and certain exemplary nitrogen protecting groups are also detailed in Chapter 7 in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

[0079] As used herein, the term "ester-type protecting group" is intended to mean a protecting group that forms an ester bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ester-type protecting groups include, but are not limited to, acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl, optionally trifluoroacetyl or trichloroacetyl.

[0080] As used herein, the term "ether-type protecting group" is intended to mean a protecting group that forms an ether bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ether-type protecting groups include, but are not limited to, benzyl, *p*-methoxybenzyl, methoxymethyl and allyl ethers.

[0081] As used herein, the term "silyl-type protecting group" refers to a protecting group that forms a silyloxy bond for the purpose of hydroxyl protection. Examples thereof from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

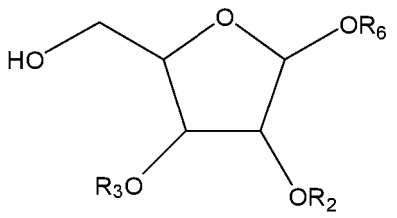
[0082] Optionally, the deprotecting agent is an acid or a base. Deprotection can also be achieved by catalytic hydrogenation (Pd/C; H_2) for the aromatic ether protecting groups and by fluoride-catalysed chemistry (e.g. Tetra-n-butylammonium fluoride (TBAF) or tetrahydrofurna (THF)) for all the silyl ethers. Optionally, when R_2, and R_3 each comprise unsubstituted acetyl or unsubstituted benzoyl, the deprotecting agent is a base, optionally selected from NH_3, Na_2CO_3 and NaOH. It will be appreciated by a skilled person that any other conventional deprotecting agent may be used.

[0083] As used herein, the term "displaceable moiety" or "leaving group" refers to a group that is associated with an aliphatic or aromatic group as defined herein and is subject to being displaced by nucleophilic attack by a nucleophile.

PREPARATION

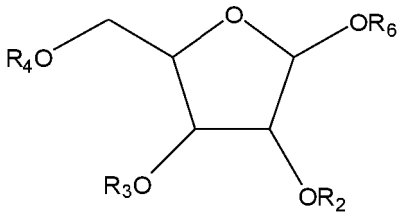
[0084] In one embodiment, the present invention is a method of producing the compound of structural formula I or IA as described above, comprising the steps of:

i) contacting a compound of structural formula II:



II

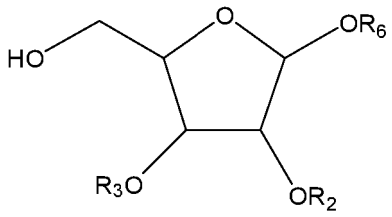
R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a ,-SO_2R^a, -SO_2OR^a or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinoyl halide or nicotinoyl anhydride, optionally substituted with R_1, in the presence of a base, to form a compound of structural formula III:



III

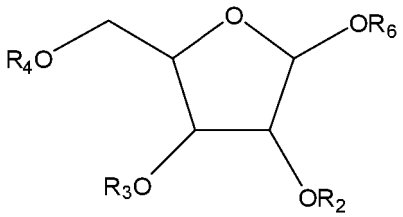
each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -NR^a_2, -$C(O)NR^a_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a_2$, -$C(O)ONR^a_2$, -$OC(O)NR^a_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a_2$, -$NR^aC(=NR^a)NR^a_2$, -OC(O)R^a, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a_2$; R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; R_4 is –$CO(C_5NH_4)$; each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; or

i) contacting a compound of structural formula II:



II

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a , -SO_2R^a, SO_2OR^a, or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinic acid, optionally substituted with R_1 in the presence of a coupling agent to generate compound of formula III:



III

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -NR^a_2, -$C(O)NR^a_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a_2$, -$C(O)ONR^a_2$, -$OC(O)NR^a_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a_2$, -$NR^aC(=NR^a)NR^a_2$, -OC(O)R^a, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a_2$; R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$. R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

ii) cyclizing the compound of formula III in the presence of Lewis Acid to form the compound of formula I; and

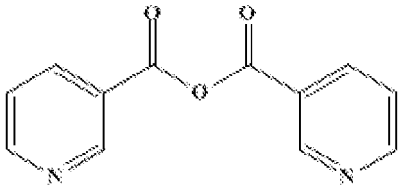
iii) optionally reducing the compound of formula I to give the compound of formula IA.

[0085] In one embodiment, the base is trialkyl amine, imidazole, pyridine, or 4-dimethylaminopyridine (DMAP).

[0086] A “coupling agent”, as used herein is any reagent which can be useful to facilitate the bonding of two molecules to form one mocleule. In one embodiment, the coupling agent is hydroxybenzotriazole (HOBT), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), carbonyldiimidazole (CDI) or N,N'-dicyclohexylcarbodiimide (DCC).

[0087] In one embodiment, the nicotinoyl halide is nicotinoyl chloride.

[0088] In one embodiment, nicotinoyl anhydride is represented by the following structural formula:



[0089] In one embodiment, the Lewis Acid is $SnCl_4$, $TiCl_4$, $GeCl_4$, trimethylsilyl trifluoromethanesulfonate or substituted pyridinium triflate. Optionally, the Lewis Acid is a metal based Lewis Acid. Further optionally, the metal based Lewis Acid is a silicon based Lewis Acid. Still further optionally, the metal based Lewis Acid is trimethylsilyl trifluoromethanesulfonate.

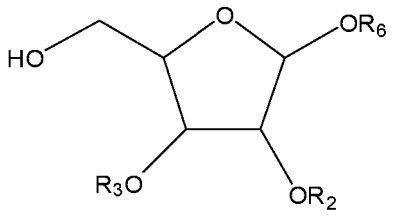
[0090] In one embodiment, R_2 and R_3 are -C(O)R’. Optionally, R_2 and R_3 are $-C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. Optionally, R_2 and R_3 together to form $–C(CH_3)_2$-.

[0091] In one embodiment, the cyclization step ii) comprises cyclizing the compound of formula III in the presence of an organic solvent. In one embodiment, the organic solvent is dichloroethane (DCE), acetonitrile or dichloromethane (DCM).

[0092] Suitable organic solvents include, but are not limited to, substituted or unsubstituted ethers, substituted or unsubstituted esters, substituted or unsubstituted ketones, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof. Optionally, the organic solvent, when present, comprises an ether selected from diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, di-tert-butyl ether, diisopropyl ether, dimethoxymethane, tetrahydrofuran, 2-methyltetrahydrofuran, and tetrahydropyran, or a combination thereof. Optionally, the organic solvent, when present, comprises an ester selected from methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate and n-butyl acetate, or a combination thereof. Optionally, the organic solvent, when present, comprises a ketone selected from methyl isobutyl ketone and methyl isopropyl ketone, or a combination thereof. Optionally, the organic solvent, when present, comprises an unsubstituted aliphatic hydrocarbon solvent selected from pentane, hexane, cyclohexane and heptane, or a combination thereof. Optionally, the organic solvent, when present, comprises a substituted aliphatic hydrocarbon solvent, optionally a halogenated aliphatic hydrocarbon solvent, further optionally a chlorinated aliphatic hydrocarbon solvent selected from dichloromethane, trichloromethane, tetrachloromethane, 1 ,2-chloroethane, 1, 1, 1-trichloroethane and trichloroethylene, or a combination thereof. Optionally the organic solvent, when present, comprises an aromatic hydrocarbon solvent selected from benzene, toluene, ethylbenzene and xylene, or a combination thereof.

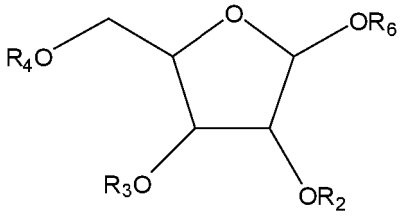
[0093] In one embodiment, the present invention is a method producing the compound of structural formula I or IA as described above, comprising the steps of:

i) contacting a compound of structural formula II:



II

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a ,-SO_2R^a, SO_2OR or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinoyl halide or nicotinoyl anhydride, each of which is optionally substituted with R_1, in the presence of a base and a solvent for between about 1 minute to about 60 minutes, between about 1 minutes to about 30 minutes, or between about 1 minutes to about 10 minutes at between about 1 to about 60 Hz between about 5 to about 30 Hz, or between about 20 to about 40 Hz to form a compound of structural formula III:



III

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -OC(O)R^a, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$; R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$. R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

ii) cyclizing the compound of formula III in the presence of Lewis Acid under a) solvent based b) solvent-assisted mechanochemical or c) solventless mechanochemical conditions to form the compound of formula I; and

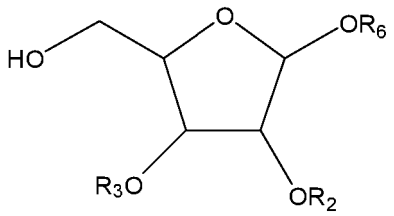
iii) optionally reducing the compound of formula I to give the compound of formula IA.

[0094] In one embodiment, the base is trialkyl amine imidazole, pyridine, or DMAP.

[0095] In one embodiment, the solvent is pyridine, THF, or diethylether.

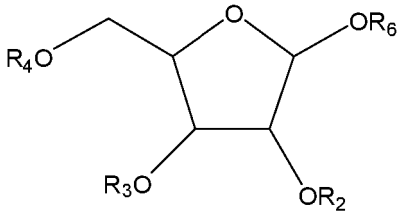
[0096] In one embodiment, the present invention is a method producing the compound of structural formula I or IA as described above, comprising the steps of:

i) contacting a compound of structural formula II:



II

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a , -SO_2R^a, SO_2OR, or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinic acid, optionally substituted with R_1, in the presence of a coupling agent and a solvent for between about 1 minute to about 60 minutes, between about 1 minutes to about 30 minutes, or between about 1 minutes to about 10 minutes at between about 1 to about 60 Hz between about 5 to about 30 Hz, or between about 20 to about 40 Hz to generate compound of formula III:



III

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$; R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-

C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

ii) cyclizing the compound of formula III in the presence of Lewis Acid under a) solvent based b) solvent-assisted mechanochemical or c) solventless mechanochemical conditions to form the compound of formula I; and

iii) optionally reducing the compound of formula I to give the compound of formula IA.

[0097] In one embodiment, the coupling agent is HOBT, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), CDI or DCC.

[0098] In one embodiment, the solvent is pyridine, THF, or diethylether.

MECHANOCHEMISTRY

[0099] As used herein, the terms "mechano-chemical mixing" and "mechanochemistry" refer to a technique in which chemical starting materials and/or reagents with disparate solubility properties are reacted, for example by direct milling or grinding generally in the absence of solvents. Interchangeable terms may include "mechanico-chemical," or the like. See, Ravalico, et al., Org. Biomol. Chem. (2011) 9:6946-6947, and references cited therein.

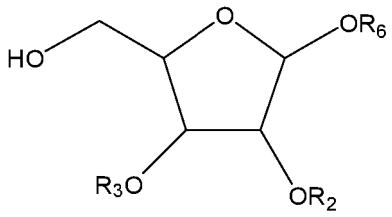
[00100] In one embodiment, the process for preparation of the compounds of the invention involves grinding the respective compounds together by mechano-chemical mixing utilizing mills such as ball mills, planetary mills, extruders etc.

[00101] In one embodiment, the compounds of the present invention are subjected to mechanical grinding, optionally using a ball milling or planetary ball milling machine. In one embodiment, the milling step takes place i) in the absence of solvent to carry out a mechanochemical reaction; ii) in the presence of molar equivalent of solvent to carry out a "solvent-assisted" mechanochemical reaction; or iii) in the presence of solvent. In "solvent-assisted" reactions, the solvents are used in reagent proportions rather than in excess, and remain inert.

[00102] In one embodiment, the cyclization step ii) comprises milling the compound of formula III in the absence of solvent to form the compound of structural formula I. In one embodiment of the present invention, the solvent in step ii) is not used as solvent but a co-reagent in molar proportion with the other solid form reagents. Here reagents like DCM or DCE can be used in molar equivalent to the sugar reagent and the Lewis acid to facilitate the grinding process, hence as used herein such "solvent-assisted" milling conditions can be considered equivalent to solventless conditions as the reagents are not "solvated" as per solvent-based chemical conditions.

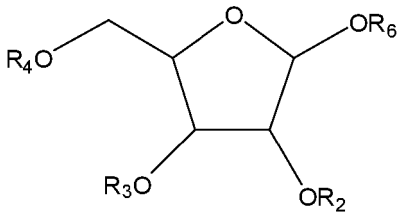
[00103] In one embodiment, the present invention is a method of producing the compound of structural formula I or IA as described above, comprising the steps of:

i) milling a compound of structural formula II:



II

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a ,-SO_2R^a, SO_2OR or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinoyl halide or nicotinoyl anhydride, each of which is optionally substituted with R_1, in the presence of a base, and optionally a molar equivalent of a solvent, for between between about 1 minute to about 60 minutes, between about 5 minutes to about 30 minutes, or between about 1 minutes to about 10 minutes at between about 1 to about 60 Hz, between about 5 to about 30 Hz, or between about 20 to about 40 Hz, to form a compound of structural formula III:



III

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$; R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$. R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

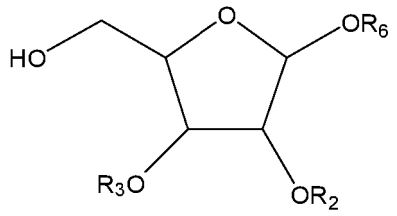
ii) cyclizing the compound of formula III in the presence of Lewis Acid under a) solvent based b) solvent-assisted mechanochemical or c) solventless mechanochemical conditions to form the compound of formula I; and

iii) optionally reducing the compound of formula I to give the compound of formula IA.

[00104] In one embodiment, the base is triethyl amine, imidazole, pyridine, or DMAP.

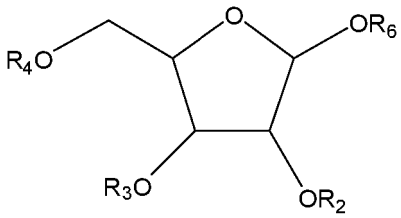
[00105] In one embodiment, the present invention is a method of producing the compound of structural formula I or IA as described above, comprising the steps of:

i) milling a compound of structural formula II:



II

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a , -SO_2R^a, SO_2OR, or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl; with nicotinic acid, optionally susbstitued with R_1, in the presence of a coupling agent, and optionally a molar equivalent of a solvent, for between about 1 minute to about 60 minutes, between about 5 minutes to about 30 minutes, or between about 1 minutes to about 10 minutes at between about 1 to about 60 Hz, between about 5 to about 30 Hz, or between about 20 to about 40 Hz to generate a compound of formula III:



III

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$; $R_6$is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is

independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

ii) cyclizing the compound of formula III, under a) solvent based b) solvent-assisted mechanochemical or c) solventless mechanochemical conditions in the presence of Lewis Acid to form the compound of formula I; and

iii) optionally reducing the compound of formula I to give the compound of formula IA.

[00106] In one embodiment, the the coupling agent is HOBT 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), CDI or DCC.

[00107] In one embodiment for a compound of formula II, R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a ,-SO_2R^a, -SO_2OR^a or -O-P(=O)-$(OR^a)_2$; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

[00108] In one embodiment, R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$. Each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is (C_1-C_6) alkyl. In one embodiment, the ring is a cycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a cycloalkyl ring or a heterocyclic ring. Each R' is (C_1-C_8)alkyl.

[00109] In one embodiment, R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)NR^a_2$. Each R_2 and R_3 are -$C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. In one embodiment the ring is a 5 membered heterocyclic ring. Optionally, R_2 and R_3 together to form –$C(CH_3)_2$-. Each R' is (C_1-C_8)alkyl.

[00110] In one embodiment, R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)NR^a_2$. R_2 and R_3 are -$C(O)CH_3$. Each R' is (C_1-C_8)alkyl.

[00111] In one embodiment, R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)NR^a_2$. R_2 and R_3 join together to form a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 join together to form –$C(CH_3)_2$-. Each R' is (C_1-C_8)alkyl.

[00112] In one embodiment for a compound of formula III, R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; R_4 is –CO(pyridyl optionally substituted with R_1); each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl; each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring; each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl.

[00113] In one embodiment for a compound of formula III, R_6 is $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, or $-OC(O)NHR^a$; R_4 is –CO(pyridyl optionally substituted with R_1). Each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is (C_1-C_6) alkyl. In one embodiment the ring is a cycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a cycloalkyl ring or a heterocyclic ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Each R' is (C_1-C_8)alkyl.

[00114] In one embodiment for a compound of formula III, R_6 is $-OR^a$, $-OC(O)R^a$. R_4 is –CO(pyridyl optionally substituted with R_1). Each, R_2 and R_3 are $-C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. In one embodiment the ring is a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 together to form $–C(CH_3)_2$-. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)alkyl, or optionally substituted aryl. Each R' is (C_1-C_8)alkyl.

[00115] In one embodiment for a compound of formula III, R_6 is $-OR^a$, $-OC(O)R^a$. R_4 is $–CO(C_5NH_4)$. R_2 and R_3 are $-C(O)CH_3$. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. Each R' is (C_1-C_8)alkyl.

[00116] In one embodiment for a compound of formula III R_6 is $-OR^a$, $-OC(O)R^a$. R_4 is $–CO(C_5NH_4)$. R_2 and R_3 join together to form a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 join together to form $–C(CH_3)_2$-. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. Each R' is (C_1-C_8)alkyl.

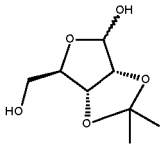
[00117] The synthesis of cyclized NAR ester derivatives is shown in **Scheme 1a**. The reduced forms were then generated (**Scheme 1b)**. These lactones are synthetic precursors to nicotinoyl riboside derivatives which include NR, NAR, NRH, NAD, and NARH derivatives.

[00118] In one embodiment, the present invention is a method to make compound **(3)** comprising the steps (a) providing a compound or derivative having formula **(2)**; (b) treating the compound of formula **(2)** with a Lewis acid; (c) mechanically grinding, mixing and/or milling the compound **(2)** with in a ball mill under Lewis acid conditions; and optionally, (d) purifying and/or isolating the compound of formula **(3)**.

[00119] In one embodiment, the present invention is a method to make compound **(3)** comprising the steps (a) providing a 5' O-nicotinoyl 1'2'3-triacetate compound formula **(4)**; (b) treating the compound of formula **(4)** with a Lewis acid; (c) mechanically grinding, mixing and/or milling the components in a ball mill; and optionally, (d) purifying and/or isolating the compound of formula **(3)**.

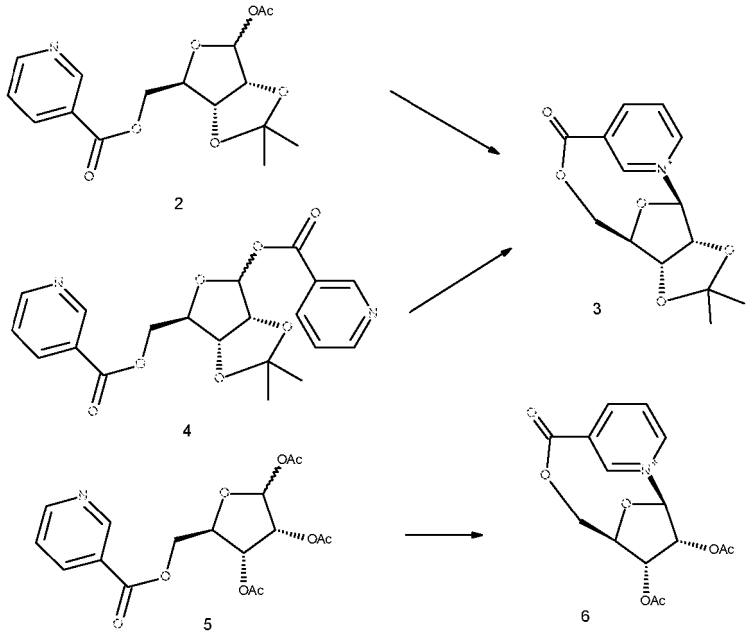
[00120] In one embodiment, the present invention is a method to make compound **(6)** comprising the steps (a) providing a 5' O-riboside compound or derivative having formula **(5)**; (b) treating the compound of formula **(5)** with a Lewis acid; and optionally, (c) purifying and/or isolating the compound of formula **(6)**.

[00121] In **Scheme 1a**, the intramolecular Vorbrüggen glycosylation of nicotinate esters of a protected riboside can be catalysed under TMSOTf catalysed conditions. This work can be conducted in solution and under mechanochemistry conditions. The cyclization of compound **2** requires the dinicotinoylation of the 2',3'-*O,O*-acetonide riboside **1** using nicotinoyl chloride under basic conditions (e.g. pyridine).



1

[00122] The 1'O-nicotinoyl group of compound **2** serves as leaving group under the TMSOTf catalysed conditions to generate the lactone intermediate **3**. This same product **3** can also be generated from the 5'O-nicotinoyl 1'2'3-triacetate **4** under TMSOTf catalysed conditions. Similarly, the triacetylated 5'-O-riboside **5** can be substrate for the lactonisation catalysed by TMSOTf to yield **6**.



Scheme 1a TMSOTf catalysed lactonisation

[00123] The nicotinoyl lactones **3** and **6** are examples of formula I and IA, with protecting groups which could include esters, or carbonates, or acetal groups.

[00124] Finally, the nicotinoyl riboside lactones can be reduced to yield the lactone equivalent of NARH (protected **7**, **8** and non-protected forms **9**, **Scheme.1b**). These can be bioprecursors of NARH. As used herein, a "bioprecursor" is molecularly modified, *in vivo*, to an active principle (Mini Rev Med Chem. 2010 Dec;10(14):1316-30).

[00125] In one embodiment, the compounds of **3** and *6* are contacted with a reducing agent, optionally; the reducing agent is selected from sodium dithionite or sodium borohydride. Optionally, the method may comprise the simultaneous addition of the reducing agent, aqueous solution and organic solvent; or the sequential addition of the reducing agent, aqueous solution and organic solvent, in any order; or a combination thereof.

[00126] In one embodiment, the reduction takes place in the presence of an aqueous solution and an organic solvent. Optionally, the organic solvent is selected from dichloromethane, 1 ,2-chloroethane, n-butyl acetate, chloroform and ethyl acetate, trichloroethylene, carbon tetrachloride, diisopropyl ether, toluene, methyl tert-butyl ether, benzene and diethyl ether, or a combination thereof.

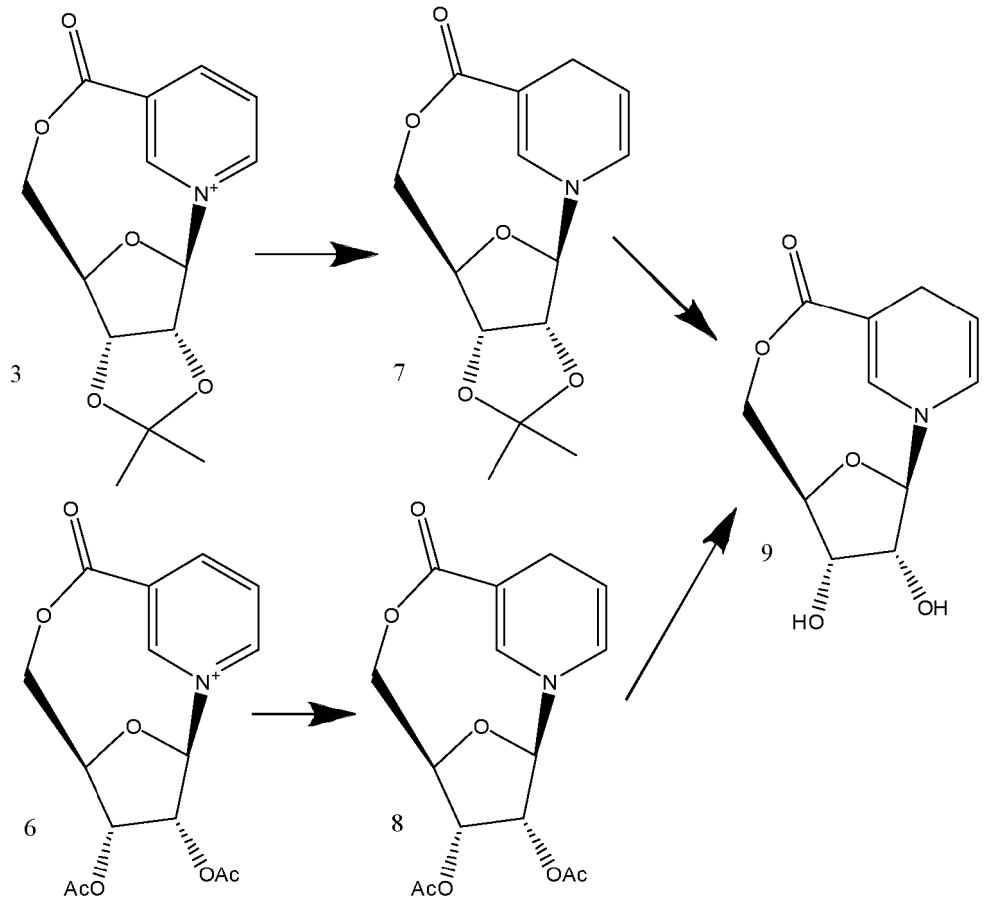
[00127] Optionally, the aqueous solution consists essentially of water.

[00128] It will be appreciated that, optionally, the aqueous solution and the organic solvent form a bi-phasic solution comprising an aqueous phase and an organic phase.

[00129] Optionally, the method comprises the additional steps of separating the organic phase from the aqueous phase; and extracting the compound of **7** or **8** from the organic solvent.

[00130] It will be appreciated by a skilled person that the hydroxyl protecting groups are required to be lipophilic to the extent that the reduced compound of **7** or **8**, once prepared, migrates into the organic phase of the bi-phasic reaction medium formed by the aqueous solution (aqueous phase) and organic solvent (organic phase).

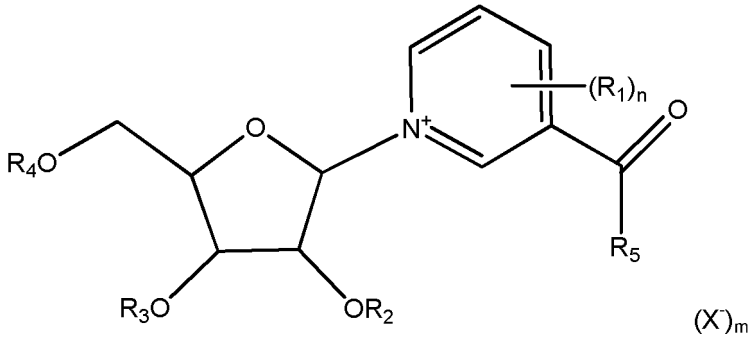
[00131] In one embodiment, these reduced lactones provide the NR and NAR derivatives *via* oxidation according to the protocols in WO2015/014722, the entire contents of which are incorporated herein by reference.



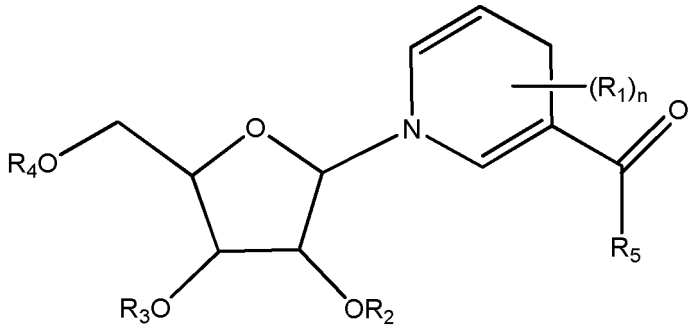
Scheme 1b. Reduction of the lactones

[00132] In one embodiment, the β-anomers of the compounds of I and IA are produced.

[00133] In one embodiment, the present invention is a method of making a compound of structural formula V or VA:



V



VA.

[00134] X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate.

[00135] Each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$.

[00136] R_2 and R_3 are each independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring.

[00137] R_4 is hydrogen.

[00138] R_5 is $-(Y)_oR''$;

[00139] Each Y is independently –O-, –S- or –N-;

[00140] Each R is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted heterocycloalky.

[00141] Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl.

[00142] Each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl.

[00143] R'' is hydrogen, optionally substituted (C_1-C_8) aliphatic, optionally substituted aryl, optionally substituted primary or secondary amino, or optionally substituted azido.

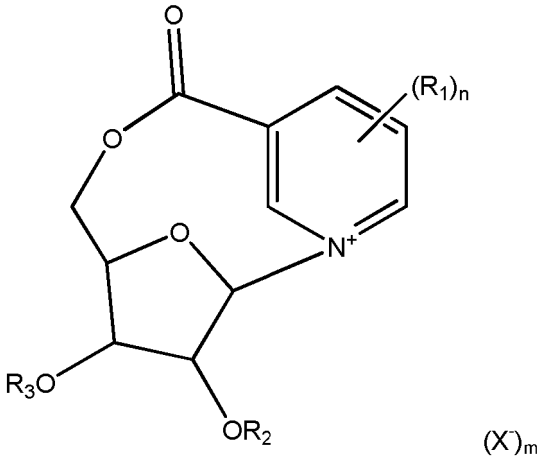
[00144] n is 0-4.

[00145] m is 0 or 1.

[00146] o is 0 or 1.

[00147] The method comprises the steps of:

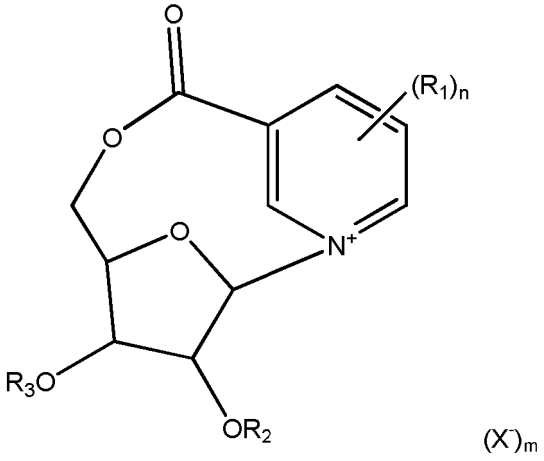
i) decyclizing a compound of structural formula I:



I

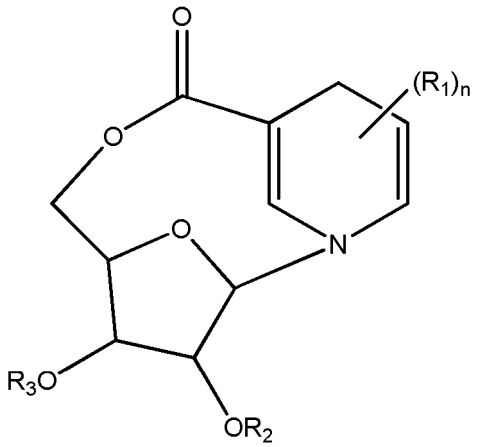
in the prescence of a nucleophilic reagent, to give the compound of structural formula V; or

i) reducing a compound of structural formula I:



I

in the presence of a reducing agent, to give a compound of structural formula IA:



IA;

and

ii) decyclizing a compound of structural formula IA to give a compound of structural formula VA.

[00148] In one embodiment, the decylizing step takes place in the presence of:

i) ammonia, potassium carbonate, potassium hydroxide or an amine; and

ii) an alcohol or water. Optionally, the alcohol is methanol, ethanol or isopropanol.

[00149] In one embodiment, the decylizing step takes place in the presence of:

i) ammonia, potassium carbonate, potassium hydroxide or an amine; and

ii) an alcohol comprising an alkoxide version of the alcohol in catalytic amount; or water.

[00150] In one embodiment, the alkoxide is generated from the alcohol by addition of a strong inorganic base (e.g. NaH, LiH, etc.,) As used herein, a "catalytic amount" is preferable, for example, <0.1 molequivalent.

[00151] In one embodiment, the reducing step takes place in the presence of:

i) a solvent selected from dichloromethane, 1,2-dichloroethane, n-butyl acetate, chloroform, ethyl acetate, or any combination thereof; and

ii) a reducing agent selected from aqueous sodium dithionite or sodium borohydride.

[00152] In one embodiment the reducing agent is sodium dithioinite.

[00153] In one embodiment, the reduced opened deprotected products are NR and NRH (using paragraphs [00148] i) and [00151] i/ii)) or NAR and NARH (using paragraphs [00149] ii) and [00151] i)/ii)), respectively.

[00154] X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate.

[00155] Each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$.

[00156] R_2 and R_3 are each independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring.

[00157] R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$ optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl.

[00158] R_5 is $-(Y)_oR''$;

[00159] Each Y is independently –O- or –S-;

[00160] Each R is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted heterocycloalky.

[00161] Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl.

[00162] Each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl.

[00163] R'' is hydrogen, optionally substituted (C_1-C_8) aliphatic, optionally substituted aryl, optionally substituted primary or secondary amino, or optionally substituted azido.

[00164] n is 0-4.

[00165] m is 0 or 1.

[00166] o is 0 or 1.

[00167] In one embodiment for compounds of formula V or VA, X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate. Each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$. R_2 and R_3 are each independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring. R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$ optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl.

[00168] R_5 is $-(Y)_oR''$. Each Y is independently –O- or –S-. Each R is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted heterocycloalky. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl. Each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl. R'' is hydrogen, optionally substituted (C_1-C_8) aliphatic, optionally substituted aryl, optionally substituted primary or secondary amino, or optionally substituted azido. n is 0-4. m is 0 or 1. o is 0 or 1.

[00169] In one embodiment, for compounds of formula V and VA, X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate. Optionally, X^- is triflate, fluoride, chloride, bromide, or iodide. Further optionally, X^- is triflate. Further optionally, X^- is chloride. Alternatively, X^- is not triflate.

[00170] In one embodiment, X^- is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted sulphonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate. Optionally, X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of a substituted or unsubstituted monocarboxylic acid and an anion of a substituted or unsubstituted dicarboxylic acid. Optionally, X^- is an anion of a substituted monocarboxylic acid, further optionally an anion of a substituted propanoic acid or an anion of a substituted acetic acid. Optionally, X^- is an anion of substituted propanoic acid, further optionally an anion of a hydroxy propanoic acid, still further optionally an anion of 2-hydroxypropanoic acid, being lactic acid, the anion of lactic acid being lactate. Optionally, X^- is an anion of a substituted acetic acid, being a substituted acetate, further optionally a trihaloacetate selected from trichloroacetate, tribromoacetate and trifluoroacetate. Still further optionally, the trihaloacetate is trifluoroacetate. Optionally, X^- is an anion of an unsubstituted monocarboxylic acid selected from formic acid, acetic acid, propionic acid and butyric acid, being formate, acetate, propionate and butyrate, respectively. Optionally, X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a substituted or unsubstituted amino-dicarboxylic acid. Further optionally, X^- is an anion of an amino-dicarboxylic acid, optionally selected from glutamic acid and aspartic acid, being glutamate and aspartate, respectively. Optionally, X^- is an anion of ascorbic acid, being ascorbate. Optionally, X^- is a halide selected from chloride, bromide, fluoride and iodide, further optionally chloride or bromide. Optionally, X^- is a substituted or unsubstituted sulfonate. Further optionally, X^- is a trihalomethanesulfonate selected from trifluoromethanesulfonate, tribromomethanesulfonate and trichloromethanesulfonate. Still further optionally, the trihalomethanesulfonate is trifluoromethanesulfonate. Optionally, X^- is a substituted or unsubstituted carbonate, further optionally hydrogen carbonate. Optionally, X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, aspartate, glutamate and lactate. Further optionally, X^- is selected from chloride, acetate, formate and trifluoroacetate.

[00171] In one embodiment, each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$. Optionally, each R_1 is independently halide, -CN, -NO_2, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -OR^a, -$NR^a{}_2$, -$C(O)R^a$, -$C(O)OR^a$, or -$C(O)NR^a{}_2$. . Further optionally, each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, -$NR^a{}_2$, -$C(O)R^a$, -$C(O)OR^a$, or -$C(O)NR^a{}_2$. Further optionally, each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, or -$NR^a{}_2$.

[00172] In one embodiment, each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or R_2 and R_3 join together to form an optionally substituted ring. Optionally, each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or (C_1-C_8)alkyl; or R_2 and R_3 join together to form an optionally substituted ring. Further optionally, each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is (C_1-C_6) alkyl. In one embodiment the ring is a heterocycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a heterocyclic ring. In one embodiment, R_2 and R_3 are -C(O)R'. Optionally, R_2 and R_3 are -$C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted heterocyclic ring. Optionally, R_2 and R_3 together to form –$C(CH_3)_2$-.

[00173] In one embodiment, each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl. Optionally, each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Further optionally, each R^a is independently hydrogen, optionally substituted (C_1-C_8)alkyl, or optionally substituted aryl. Further optionally, each R^a is independently hydrogen, or optionally substituted (C_1-C_6)alkyl. Further optionally, each R^a is independently hydrogen, or (C_1-C_6)alkyl.

[00174] In one embodiment, each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl. Optionally, each R' is independently hydrogen, or (C_1-C_8)alkyl. Further optionally, each R' is (C_1-C_8)alkyl.

[00175] R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$ optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl. Optionally, R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$ (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl. Further optionally, R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$, or (C_1-C_8)alkyl. Further optionally, R_4 is hydrogen, -C(O)R', -C(O)OR', or (C_1-C_8)alkyl.

[00176] R_5 is -$(Y)_oR$";

[00177] Each Y is independently –O- or –S-;

[00178] R'' is hydrogen, optionally substituted (C_1-C_8) aliphatic, optionally substituted aryl, optionally substituted primary or secondary amino, or optionally substituted azido. Optionally, R'' is hydrogen, C_1-C_8) alkyl, aryl, primary or secondary amino, or azido. Further optionally, R'' is hydrogen, or C_1-C_8) alkyl.

[00179] n is 0.

[00180] m is 0 or 1.

[00181] o is 0 or 1.

[00182] In one embodiment, X^- is triflate, fluoride, chloride, bromide, or iodide. Each R_1 is independently halide, -CN, -NO_2, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -OR^a, -NR^a_2, -C(O)R^a, -C(O)OR^a, or -C(O)NR^a_2. Each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or (C_1-C_8)alkyl; or R_2 and R_3 join together to form an optionally substituted ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted aryl, or optionally substituted heteroaryl. Each R' is independently hydrogen, or (C_1-C_8)alkyl. R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$ (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl. R'' is hydrogen, C_1-C_8) alkyl, aryl, primary or secondary amino, or azido. n is 0. m is 0 or 1. o is 0 or 1.

[00183] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, -NR^a_2, -C(O)R^a, -C(O)OR^a, or -C(O)NR^a_2. Each R_2 and R_3 are -C(O)R'; or R_2 and R_3 join together to form a ring substituted with R*. R* is (C_1-C_6) alkyl. In one embodiment the ring is a cycloaliphatic ring, or a heterocyclic ring. In one embodiment, the ring is a cycloalkyl ring or a heterocyclic ring. Each R^a is independently hydrogen, optionally substituted (C_1-C_8)alkyl, or optionally substituted aryl. Each R' is (C_1-C_8)alkyl. R_4 is hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', -OP $(OR)_2$, or (C_1-C_8)alkyl. R'' is hydrogen, or C_1-C_8) alkyl. n is 0. m is 0 or 1. o is 0 or 1.

[00184] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, or -NR^a_2. R_2 and R_3 are -C(O)R'. Each, R_2 and R_3 are -$C(O)CH_3$. Alternatively, R_2 and R_3 join together to form an optionally substituted ring. In one embodiment the ring is a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 join together to form –$C(CH_3)_2$-. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. R_4 is hydrogen, -C(O)R', -C(O)OR', or (C_1-C_8)alkyl. R'' is hydrogen, or C_1-C_8) alkyl. n is 0. m is 0 or 1. o is 0 or 1.

[00185] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, or -NR^a_2. R_2 and R_3 are -$C(O)CH_3$. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. R_4 is hydrogen, -C(O)R', -C(O)OR', or (C_1-C_8)alkyl. R'' is hydrogen, or (C_1-C_8) alkyl. n is 0. m is 0 or 1. o is 0 or 1.

[00186] In one embodiment, X^- is triflate or chloride. Each R_1 is independently halide, (C_1-C_6)alkyl, -OR^a, or -NR^a_2. R_2 and R_3 join together to form a C_3-C_6 cycloalkyl ring. Optionally, R_2 and R_3 join together to form –$C(CH_3)_2$-. Each R^a is independently hydrogen, or (C_1-C_8)alkyl. R_4 is hydrogen, -C(O)R', -C(O)OR', or (C_1-C_8)alkyl. R'' is hydrogen, or (C_1-C_8) alkyl. n is 0. m is 0 or 1. o is 0 or 1.

[00187] It will be appreciated by one skilled in the art that the processes described herein are not the exclusive means by which compounds of the invention may be synthesized and that an extremely broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds of the invention. The person skilled in the art knows how to select and implement appropriate synthetic routes. Suitable synthetic methods may be identified by reference to the literature, including reference sources such as *Comprehensive Organic Synthesis*, Ed. B.M. Trost and I. Fleming (Pergamon Press, 1991), *Comprehensive Organic Functional Group Transformations*, Ed. A. R. Katritzky, O. Meth-Cohn, and C. W. Reese (Pergamon Press, 1996), *Comprehensive Organic Functional Group Transformations II*, Ed. A. R. Katritzky and R. J. K. Taylor (Editor) (Elsevier, 2nd Edition, 2004), *Comprehensive Heterocyclic Chemistry*, Ed. A. R. Katritzky and C.W. Rees (Pergamon Press, 1984), *Comprehensive Heterocyclic Chemistry II*, Ed. A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (Pergamon Press, 1996), and *Advanced Organic Chemistry, 4th Ed.*, J. March (John Wiley & Sons, 1992).

[00188] The synthetic methods described above can also include a convergent synthesis strategy. Thus two components may be synthesized and elaborated separately prior to condensing or coupling the two compounds to form the target compounds. These convergent synthetic schemes allow for arrangement of the assembly steps of the backbone of the target compounds and derivatization of derivatizable functionalities to accommodate functional group sensitivity and/or to allow for functional groups or elements to be introduced either before or after the assembly of the backbone of the target compounds via the condensation or coupling reactions described.

[00189] Optionally, the reaction is carried out in a pH range of from about 6 to about 8, optionally from about 6.5 to about 7.5.

[00190] Optionally, the reaction is carried out at a temperature of from about 10°C to about 40°C, optionally from about 15°C to about 35°C, further optionally from about 15°C to about 30°C, still further optionally from about 15°C to about 20°C, even further optionally from about 20°C to about 25°C, even further optionally at a temperature of about 20°C or 21°C or 22°C or 23°C or 24°C or 25°C.

[00191] Optionally, the reaction is carried out for a period of time of from about 1 minute to about 180 minutes, optionally, from about 2 minutes to about 120 minutes, further optionally from about 5 minutes to about 120 minutes, still further optionally from about 10 minutes to about 120 minutes, even further optionally from about 20 minutes to about 120 minutes, even further optionally from about 30 minutes to about 120 minutes, still further optionally from about 60 minutes to about 120 minutes, even further optionally from about 60 minutes to about 90 minutes, still further optionally 30 about 60 minutes or 70 minutes or 80 minutes.

PURIFICATION

[00192] The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration, liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, preparative TLC, HPTLC, HPLC, or rp-HPLC. One preferred method for purification of the

compounds or salts thereof comprises crystallizing the compound or salt from a solvent to form, preferably, a crystalline form of the compounds or salts thereof. Following crystallization, the crystallization solvent is removed by a process other than evaporation, for example filtration or decanting, and the crystals are then preferably washed using pure solvent (or a mixture of pure solvents). Preferred solvents for crystallization include water, alcohols, particularly alcohols containing up to four carbon atoms such as methanol, ethanol, isopropanol, and butan-1-ol, butan-2-ol, and 2-methyl-2-propanol, ethers, for example diethyl ether, diisopropyl ether, t-butyl methyl ether, 1,2-dimethoxyethane, tetrahydrofuran and 1,4-dioxane, carboxylic acids, for example formic acid and acetic acid, and hydrocarbon solvents, for example pentane, hexane, toluene, and mixtures thereof, particularly aqueous mixtures such as aqueous ethanol. Pure solvents, preferably at least analytical grade, and more preferably pharmaceutical grade are preferably used. In a preferred embodiment of the processes of the invention, the products are so isolated. Alternatively, the compounds or salts thereof can be isolated using lyophilization or freeze-drying techniques, thus avoiding use of non-aqueous solvents.

[00193] Optionally, the method further comprises a filtration step to remove the carbon-containing catalyst from the prepared compound. Suitable filtration means for use in the filtration step include, but are not limited to, syringe filters and/or paper filters, and/or any inert, insoluble substance capable of acting as a filter, e.g. alumina and/or silica and/or diatomaceous earth. It will be appreciated any other suitable filtration means may be used.

PHARMACEUTICALLY ACCEPTABLE SALTS, SOLVATES, CHLATRATES, AND OTHER DERIVATIVES

[00194] The compounds described herein can exist in free form, or, where appropriate, as salts. Those salts that are pharmaceutically acceptable are of particular interest since they are useful in administering the compounds described below for medical purposes. Salts that are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of the invention or intermediates thereof.

[00195] As used herein, the term "pharmaceutically acceptable salt" refers to salts of a compound which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue side effects, such as, toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[00196] Pharmaceutically acceptable salts are well known in the art. For example, S.M. Berge et al, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. These salts can be prepared in situ during the final isolation and purification of the compounds.

[00197] Where the compound described herein contains a basic group, acid addition salts can be prepared by 1) reacting the purified compound in its free-base form with a suitable organic or

inorganic acid and 2) isolating the salt thus formed. In practice, acid addition salts might be a more convenient form for use and use of the salt amounts to use of the free basic form.

[00198] Examples of pharmaceutically acceptable, non-toxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[00199] Basic addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminium. The sodium and potassium salts are usually preferred. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are prepared from amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. Ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N, N'-dibenzylethylenediamine, chloroprocaine, dietanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, dicyclohexylamine and the like.

[00200] Other acids and bases, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid or base addition salts.

[00201] In one embodiment, the salt is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate.

[00202] It should be understood that this invention includes mixtures/combinations of different pharmaceutically acceptable salts and also mixtures/combinations of compounds in free form and pharmaceutically acceptable salts.

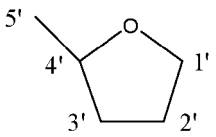
[00203] The compounds described herein can also exist as pharmaceutically acceptable solvates (e.g., hydrates) and clathrates. As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds described herein. The term solvate includes hydrates (e.g., hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and the like).

[00204] As used herein, the term "hydrate" means a compound described herein or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00205] As used herein, the term "clathrate" means a compound described herein or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

USES

[00206] In one embodiment, the invention provides a method of treating a disease or disorder in a subject that would benefit from increased NAD levels, the method comprising administering to the subject a compound of the present invention, of formula I or IA. In certain aspects, the invention provides methods of treating or preventing a disease or disorder that would benefit from increased NAD levels, for example by increasing *in vivo* levels of NAD (e.g. intracellular NAD levels, levels of NAD in tissues or plasma, and/or overall NAD levels in an organism). Without wishing to be limited to a single mechanism, increased NAD levels serve to modulate the level and/or activity of one or more sirtuin proteins, e.g. by activating SIRT1 and or SIRT3. In certain embodiments, the invention provides methods for using the compounds of the invention to activate a sirtuin protein, e.g., increase the level and/or activity of a sirtuin protein. Increased sirtuin protein activity and/or increased sirtuin levels may be useful for a variety of therapeutic applications including, for example, increasing the lifespan of a cell, and treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing, etc. In one embodiment, the compounds of the present invention are precursors for NAD, NAR and NR and their reduced forms. Without wishing to be bound by theory, the compounds of the present invention have a better circulating profile *in vivo* compared to their nicotinoyl parents, NAR and NR, as phosphorylation at C5:



cannot occur until esterase or chemical cleavage occurs while in circulation, and C1-hydrolysis to nicotinamide and ribose by common PNP enzymes (pyrimidine and purine nucleoside phosphorylases) cannot take place until the carboxylic acid has been exposed by hydrolysis of the cyclic lactone by esterases or through chemical hydrolysis.

[00207] The term "subject" refers to an animal (e.g., a bird such as a chicken, quail or turkey, or a mammal), specifically a "mammal" including a non-primate (e.g., a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (e.g., a monkey, chimpanzee and a human), and more specifically a human. In one embodiment, the subject is a non-human animal such as a farm animal (e.g., a horse, cow, pig or sheep), or a pet (e.g., a dog, cat, guinea pig or rabbit). In another embodiment, the subject is a "human".

[00208] As used herein, the terms "treat", "treatment" and "treating" refer to therapeutic treatments includes the reduction or amelioration of the progression, severity and/or duration of a disease, disorder or condition, or the amelioration of one or more symptoms (specifically, one or more discernible symptoms) of a disease, disorder or condition, resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a compound or composition of the invention). In specific embodiments, the therapeutic treatment includes the amelioration of at least one measurable physical parameter of a disease, disorder or condition. In other embodiments the therapeutic treatment includes the inhibition of the progression of a condition, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the therapeutic treatment includes the reduction or stabilization of a disease, disorder or condition. The term “curative treatment” as used herein refers to a treatment that aims to cure a disease or to improve symptoms associated with a disease.

[00209] As used herein the terms "prophylaxis" or "prophylactic use" and "prophylactic treatment", refer to any medical or public health procedure whose purpose is to prevent, rather than treat or cure a disease. As used herein, the terms "prevent", "prevention" and "preventing" refer to the reduction in the risk of acquiring or developing a given disease or disorder, or the reduction or inhibition of the recurrence or said condition in a subject who is not ill, but who has been or may be near a person with the disease.

[00210] An "effective amount" includes a "therapeutically effective amount" and a "prophylactically effective amount". The term "therapeutically effective amount" refers to an amount effective in treating and/or ameliorating a disease or disorder in a subject. The term "prophylactically effective amount" refers to an amount effective in preventing and/or substantially lessening the chances of a subject getting a disease or disorder.

[00211] In one embodiment, the present invention is a method for using the compounds of the invention in the prevention or treatment of a disease or disorder in a subject, for which increased NAD levels are indicated, which comprises administering to the subject a therapeutically effective amount of a compound of formula I or IA.

[00212] In one embodiment the present invention is a method of treating a disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of formula I or IA.

[00213] In one embodiment the present invention is a method of preventing or treating a disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of formula I or IA.

[00214] In one embodiment, the present invention is the use of compounds of formula I or IA as a medicament.

[00215] In one embodiment, the present invention is the use of compounds of formula I or IA of treating a disease or disorder in a subject.

[00216] In one embodiment, the present invention is the use of compounds of formula I or IA of treating or preventing a disease or disorder in a subject.

[00217] In particular, the present invention provides such methods for the prevention or treatment of a disease or disorder that would benefit from increased NAD levels such as aging/stress, cardiovascular disease, cell death, cancer, metabolic disorder/diabetes, neuronal disease/neuropathology, blood coagulation disorder, weight control/obesity, inflammatory disease, flushing, viral/fungal infection, dietary deficiency of vitamin B3 and pellagra including alcoholic pellagra, pellagra-like condition following treatments for conditions such as bacterial infection, and viral infection and vitamin B3 deficiency in subjects receiving chemotherapies which compromise vitamin B3 uptake and include antibacterial and anti-viral treatments, patient undertaking antiproliferative treatment compromising tryptophan availability and de novo synthesis of NAD, or a mitochondrial disease or disorder.

[00218] In certain embodiments, the mitochondrial disease or disorder is a neuromuscular disorder, a disorder of neuronal instability, a neurodegenerative disorder, or a mitochondrial myopathy. In further embodiments, the mitochondrial disease or disorder is Friedreich's Ataxia, muscular dystrophy, multiple sclerosis, seizure disorders, migraine, Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, ischemia, renal tubular acidosis, age-related neurodegeneration and cognitive decline, chemotherapy fatigue, age-related or chemotherapy-induced menopause or irregularities of menstrual cycling or ovulation, mitochondrial myopathies, mitochondrial damage (e.g., calcium accumulation, excitotoxicity, nitric oxide exposure, drug induced toxic damage or hypoxia), or mitochondrial deregulation. In still further embodiments, the mitochondrial disease or disorder is a mitochondrial myopathy such as progressive external ophthalmoplegia, Keams-Sayre syndrome, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), MERFF syndrome (myoclonic epilepsy and ragged red fibres), limb-girdle distribution weakness, or infantile myopathy (benign or severe and fatal).

[00219] In one aspect of the invention, the disease or disorder is aging and/or stress. Accordingly, in one embodiment the invention provides a method extending the lifespan of a cell, 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. For example, the methods described herein may be used to increase the amount of time that cells, particularly primary cells (i.e., cells obtained from an organism, e.g., a human), may be kept alive in a cell culture. Embryonic stem (ES) cells and pluripotent cells, and cells differentiated therefrom, may also be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein to keep the cells, or progeny thereof, in culture for longer periods of time. Such cells can also be used for transplantation into a subject, e.g., after ex vivo modification.

[00220] In yet other embodiments, cells may be treated with the compounds of the invention in vivo, e.g., to increase their lifespan or prevent apoptosis. For example, skin can be protected from aging (e.g., developing wrinkles, loss of elasticity, etc.) by treating skin or epithelial cells with the compound of the invention. Exemplary skin afflictions or skin conditions that may be treated in accordance with the methods described herein include disorders or diseases associated with or caused by inflammation, sun damage or natural aging. For example, the prevention or treatment of contact dermatitis (including irritant contact dermatitis and allergic contact dermatitis), atopic dermatitis (also known as allergic eczema), actinic keratosis, keratinization disorders (including eczema), epidermolysis bullosa diseases (including penfigus), exfoliative dermatitis, seborrheic dermatitis, erythemas (including erythema multiforme and erythema nodosum), damage caused by the sun or other light sources, discoid lupus erythematosus, dermatomyositis, psoriasis, skin cancer and the effects of natural aging. In another embodiment, the compounds of the invention may be used for the treatment of wounds and/or burns to promote healing, including, for example, first-, second- or third-degree burns and/or thermal, chemical or electrical burns.

[00221] In another embodiment, a compound of the invention may be used for treating or preventing a disease or condition induced or exacerbated by cellular senescence in a subject; methods for decreasing the rate of senescence of a subject, e.g., after onset of senescence; methods for extending the lifespan of a subject; methods for treating or preventing a disease or condition relating to lifespan; methods for treating or preventing a disease or condition relating to the proliferative capacity of cells; and methods for treating or preventing a disease or condition resulting from cell damage or death. In certain embodiments, the method does not act by decreasing the rate of occurrence of diseases that shorten the lifespan of a subject. In certain embodiments, a method does not act by reducing the lethality caused by a disease, such as cancer.

[00222] The compounds of the invention can also be administered to subjects for treatment and/or prevention of diseases, e.g., chronic diseases, associated with cell death, in order to protect the cells from cell death. Exemplary diseases include those associated with neural cell death, neuronal dysfunction, or muscular cell death or dysfunction, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and muscular dystrophy; AIDS; fulminant hepatitis; diseases linked to degeneration of the brain, such as Creutzfeldt-Jakob disease, retinitis pigmentosa and cerebellar degeneration; myelodysplasis such as aplastic anaemia; ischemic diseases such as myocardial infarction and stroke; hepatic diseases such as alcoholic hepatitis, hepatitis B and hepatitis C; joint-diseases such as osteoarthritis; atherosclerosis; alopecia; damage to the skin due to UV light; lichen planus; atrophy of the skin; cataract; and graft rejections. Cell death can also be caused by surgery, drug therapy, chemical exposure or radiation exposure.

[00223] The compounds of the invention can also be administered to a subject suffering from an acute disease, e.g., damage to an organ or tissue, e.g., a subject suffering from stroke or myocardial infarction or a subject suffering from a spinal cord injury. The compounds of the invention may also be used to repair an alcoholic's liver.

[00224] In another embodiment, the invention provides a method for treating and/or preventing a cardiovascular disease by administering to a subject in need thereof a compound of the invention.

Cardiovascular diseases include cardiomyopathy or myocarditis; such as idiopathic cardiomyopathy, metabolic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy. Also treatable or preventable using compositions and methods described herein are atheromatous disorders of the major blood vessels (macro vascular disease) such as the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries. Other vascular diseases that can be treated or prevented include those related to platelet aggregation, the retinal arterioles, the glomerular arterioles, the vasa nervorum, cardiac arterioles, and associated capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems. The compounds of the invention may also be used for increasing HDL levels in plasma of an individual. Yet other disorders that may be treated with the compounds of the invention include restenosis, e.g., following coronary intervention, and disorders relating to an abnormal level of high density and low density cholesterol.

[00225] The compounds of the invention may be administered to subjects who have recently received or are likely to receive a dose of radiation or toxin.

[00226] The compounds of the invention may also be used for treating and/or preventing cancer.

[00227] In certain aspects, the compounds of the invention can be used to treat patients suffering from neurodegenerative diseases, and traumatic or mechanical injury to the central nervous system (CNS) or peripheral nervous system (PNS). Examples of neurodegenerative diseases include, but are not limited to, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), diffuse Lewy body disease, chorea-acanthocytosis, primary lateral sclerosis, ocular diseases (ocular neuritis), chemotherapy-induced neuropathies (e.g., from vincristine, paclitaxel, bortezomib), diabetes-induced neuropathies and Friedreich's ataxia. Compounds of the invention can be used to treat these disorders and others including, Tay-Sachs disease and Sandhoff disease, HIV-1 neurological disease, neuronal loss in Creutzfeldt-Jakob disease in human, BSE in cattle (mad cow disease), Scrapie Disease in sheep and goats, and feline spongiform encephalopathy (FSE) in cats.

[00228] In another embodiment, a compound of the invention may be used to treat and/or prevent any disease or disorder involving axonopathy.

[00229] In another embodiment, a compound of the invention may be used to treat and/or prevent diabetic neuropathies.

[00230] In an exemplary embodiment, a compound of the invention may be used to treat and/or prevent multiple sclerosis (MS), including relapsing MS and monosymptomatic MS, and other demyelinating conditions, such as, for example, chromic inflammatory demyelinating polyneuropathy (CIDP), or symptoms associated therewith.

[00231] Compounds of the invention may also be useful to prevent and/or treat various PNS disorders. Compounds of the invention may also be useful to prevent, treat Peripheral neuropathy. Peripheral neuropathy may also be referred to as peripheral neuritis, or if many nerves are involved, the terms polyneuropathy or polyneuritis may be used. Peripheral neuropathy, such as, diabetes-related polyneuropathy, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, Epstein-Barr virus,

and human immunodeficiency virus (HIV), or bacterial infection, including Campylobacter jejuni and Lyme disease. chronic alcoholism, infection of the varicella-zoster virus, botulism, and poliomyelitis. Peripheral neuropathy may develop as a primary symptom, or it may be due to another disease. For example, peripheral neuropathy is only one symptom of diseases such as amyloid neuropathy, certain cancers, or inherited neurologic disorders. Other PNS diseases treatable with compounds of the present invention include: Brachial Plexus Neuropathies (diseases of the cervical and first thoracic roots, nerve trunks, cords, and peripheral nerve components of the brachial plexus.

[00232] In other aspects, compounds of the invention can be used to treat and/or prevent blood coagulation disorders (or haemostatic disorders). As used interchangeably herein, the terms "haemostasis", "blood coagulation," and "blood clotting" refer to the control of bleeding, including the physiological properties of vasoconstriction and coagulation. Accordingly, the present invention provides anticoagulation and antithrombotic treatments aiming at inhibiting the formation of blood clots in order to prevent or treat blood coagulation disorders, such as myocardial infarction, stroke, loss of a limb by peripheral artery disease or pulmonary embolism.

[00233] The compositions and methods disclosed herein are useful for the treatment and/or prevention of thrombotic disorders. As used herein, the term "thrombotic disorder" includes any disorder or condition characterized by excessive or unwanted coagulation or haemostatic activity, or a hypercoagulable state. Examples of thrombotic disorders include, but are not limited to, thromboembolism, deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, miscarriage, thrombophilia associated with anti-thrombin III deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C, dysfibrinogenemia, fibrinolytic disorders, homocystinuria, pregnancy, inflammatory disorders, myeloproliferative disorders, arteriosclerosis, angina, e.g., unstable angina, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, cancer metastasis, sickle cell disease, glomerular nephritis, and drug induced thrombocytopenia (including, for example, heparin induced thrombocytopenia). In addition compounds of the invention may be administered to prevent thrombotic events or to prevent re-occlusion during or after therapeutic clot lysis or procedures such as angioplasty or surgery.

[00234] In another aspect, compounds of the invention may be used for treating or preventing weight gain or obesity in a subject and related diseases including, for example, high blood pressure, hypertension, high blood cholesterol, dyslipidemia, type 2 diabetes, insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, angina pectoris, congestive heart failure, stroke, gallstones, cholescystitis and cholelithiasis, gout, osteoarthritis, obstructive sleep apnea and respiratory problems, some types of cancer (such as endometrial, breast, prostate, and colon), complications of pregnancy, poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation), bladder control problems (such as stress incontinence); uric acid nephrolithiasis; psychological disorders (such as depression, eating disorders, distorted body image, and low self esteem). Stunkard AJ, Wadden TA. (Editors) Obesity: theory and therapy, Second Edition. New York: Raven Press, 1993. Finally, patients with AIDS can develop lipodystrophy or insulin resistance in response to combination therapies for AIDS.

[00235] In another embodiment, compounds of the invention may be used for inhibiting adipogenesis or fat cell differentiation, whether in vitro or in vivo. In particular, high circulating levels of insulin and/or insulin like growth factor (IGF) 1 will be prevented from recruiting preadipocytes to differentiate into adipocytes. Such methods may be used for treating or preventing obesity.

[00236] In other embodiments, compounds of the invention may be used for reducing appetite and/or increasing satiety, thereby causing weight loss or avoidance of weight gain.

[00237] In other embodiments, compounds of the invention may be used for treating a subject who has cachexia or may be likely to develop cachexia.

[00238] In another aspect, the compounds of the present invention may be used for treating and/or preventing a metabolic disorder, such as insulin resistance, a pre-diabetic state, type II diabetes, and/or complications thereof. Administration of a compound of the present invention may increase insulin sensitivity and/or decrease insulin levels in a subject. A subject in need of such a treatment may be a subject who has insulin resistance or other precursor symptom of type II diabetes, who has type II diabetes, or who is likely to develop any of these conditions. For example, the subject may be a subject having insulin resistance, e.g., having high circulating levels of insulin and/or associated conditions, such as hyperlipidaemia, dyslipogenesis, hypercholesterolemia, impaired glucose tolerance, high blood glucose sugar level, other manifestations of syndrome X, hypertension, atherosclerosis and lipodystrophy.

[00239] In other aspects, compounds of the invention can be used to treat and/or prevent a disease or disorder associated with inflammation and may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the compositions are preferably provided in advance of any inflammatory response or symptom. Administration of the compositions may prevent or attenuate inflammatory responses or symptoms. Exemplary inflammatory conditions include, for example, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, degenerative joint disease, spondouloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), menstrual cramps, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, esophagitis, pancreatitis, peritonitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicaemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, vasculitis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome. Exemplary inflammatory conditions of the skin include, for example, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, and dermatosis with acute inflammatory components.

[00240] In another embodiment, compounds of the present invention may be used to treat or prevent allergies and respiratory conditions, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD). The compounds may be used to treat chronic hepatitis infection, including hepatitis B and hepatitis C. Additionally, compounds of the present invention may

be used to treat autoimmune diseases and/or inflammation associated with autoimmune diseases such as organ-tissue autoimmune diseases (e.g., Raynaud's syndrome), scleroderma, myasthenia gravis, transplant rejection, endotoxin shock, sepsis, psoriasis, eczema, dermatitis, multiple sclerosis, autoimmune thyroiditis, uveitis, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease. In another aspect, compounds of the present invention may be used for reducing the incidence or severity of flushing and/or hot flashes which are symptoms of a disorder. For instance, the subject method includes the use of the compounds of the invention, alone or in combination with other agents, for reducing incidence or severity of flushing and/or hot flashes in cancer patients. In other embodiments, the method provides for the use of the compounds of the invention to reduce the incidence or severity of flushing and/or hot flashes in menopausal and post-menopausal woman.

[00241] In another aspect, compounds of the invention may be used as a therapy for reducing the incidence or severity of flushing and/or hot flashes which are side-effects of another drug therapy, e.g., drug-induced flushing.

[00242] Compounds of the invention may be used for treating and/or preventing viral infections (such as infections by influenza, herpes or papilloma virus) or as antifungal agents.

PHARMACEUTICAL COMPOSITIONS

[00243] The compounds described herein can be formulated into pharmaceutical compositions that further comprise a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. In one embodiment, the present invention relates to a pharmaceutical composition comprising a compound of the invention described above, and a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. In one embodiment, the present invention is a pharmaceutical composition comprising an effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. Pharmaceutically acceptable carriers include, for example, pharmaceutical diluents, excipients or carriers suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices.

[00244] A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, e.g., non-toxic, non-inflammatory, non- immunogenic or devoid of other undesired reactions or side-effects upon the administration to a subject.

[00245] The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds described herein, such as by producing any undesirable biological effect or otherwise interacting in a

deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (e.g., a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (e.g., prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Side effects include, but are not limited to fever, chills, lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anaemia), dry mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances and sexual dysfunction.

[00246] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as twin 80, phosphates, glycine, sorbic acid, or potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, or zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, methylcellulose, hydroxypropyl methylcellulose, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as colouring agents, releasing agents, coating agents, sweetening, flavouring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

ADMINISTRATION METHODS

[00247] The compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes, but is not limited to, subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In one embodiment, the compositions are administered orally.

[00248] The pharmaceutical compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or

solutions. In the case of tablets for oral use, carriers commonly used include, but are not limited to, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavouring or colouring agents may also be added.

[00249] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavouring, and perfuming agents.

[00250] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar— agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00251] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00252] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other

coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00253] The powders and tablets preferably contain from five or ten to about seventy percent of the active compound(s). Suitable carriers are microcrystalline cellulose, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethlycellulose, a low melting wax, cocoa butter, and the like, and other excipients may include magnesium stearate, stearic acid, talc, silicon dioxide, etc.

[00254] Tablets, capsules and lozenges for oral administration and liquids for oral use are preferred compositions. Solutions or suspensions for application to the nasal cavity or to the respiratory tract are preferred compositions. Transdermal patches for topical administration to the epidermis are preferred.

[00255] The compositions of the present invention may be administered as neutraceutical compositions in combination with a nutraceutically acceptable carrier. The active ingredients in such formulations may comprise from 1% by weight to 99% by weight, or alternatively, 0.1% by weight to 99.9% by weight. "Nutraceutically acceptable carrier" means any carrier, diluent or excipient that is compatible with the other ingredients of the formulation and not deleterious to the user. In accordance with one embodiment, suitable nutraceutically acceptable carriers can include ethanol, aqueous ethanol mixtures, water, fruit and/or vegetable juices, and combinations thereof.

[00256] Dosage forms for topical or transdermal administration of a compound described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00257] Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA).

[00258] Solid nutritional compositions for oral administration may optionally contain, in addition to the above enumerated nutritional composition ingredients or compounds: carrier materials such as corn starch, gelatin, acacia, microcrystalline cellulose, kaolin, dicalcium phosphate, calcium

carbonate, sodium chloride, alginic acid, and the like; disintegrators including, microcrystalline cellulose, alginic acid, and the like; binders including acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropyl methylcellulose, ethyl cellulose, and the like; and lubricants such as magnesium stearate, stearic acid, silicone fluid, talc, waxes, oils, colloidal silica, and the like. The usefulness of such excipients is well known in the art.

[00259] Liquid nutritional compositions for oral administration in connection with a method for preventing and/or treating inflammation, colds and/or flu can be prepared in water or other aqueous vehicles. In addition to the above enumerated ingredients or compounds, liquid nutritional compositions can include suspending agents such as, for example, methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, polyvinyl alcohol, and the like. The liquid nutritional compositions can be in the form of a solution, emulsion, syrup, gel, or elixir including or containing, together with the above enumerated ingredients or compounds, wetting agents, sweeteners, and colouring and flavouring agents. Various liquid and powder nutritional compositions can be prepared by conventional methods. Various ready-to-drink formulations (RTD's) are contemplated.

[00260] The compounds for use in the methods of the invention can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily dose or one of multiple daily doses (e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose.

COMBINATION THERAPY

[00261] In one embodiment, the compounds or pharmaceutical composition of the invention may be administered with one or more therapeutic agents for the treatment or prevention of various diseases, including, for example, cancer, diabetes, neurodegenerative diseases, cardiovascular disease, blood clotting, inflammation, flushing, obesity, ageing, stress, etc. In various embodiments, combination therapies comprising the compounds or pharmaceutical composition of the invention may refer to (1) pharmaceutical compositions that comprise one or more of the compounds of the invention in combination with one or more therapeutic agents; and (2) co-administration of one or more of the compounds of the invention with one or more therapeutic agents wherein the compounds of the invention have not been formulated in the same compositions. When using separate formulations, the compounds of the invention may be administered at the same, intermittent, staggered, prior to, subsequent to, or combinations of times thereof, with the administration of another therapeutic agent.

[00262] In one embodiment, the compounds of the present invention can be co-administrated with chemotherapeutic agents including: aminoglutethimide, amsacrine, anastrozole, asparaginase, beg, bicalutamide, bleomycin, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin,

epirubicin, estradiol, estramustine, etoposide, exernestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine. These chemotherapeutic agents may be categorized by their mechanism of action into, for example, following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (5-fiuorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products .such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, Cytoxan, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, hexamethylmelamineoxaliplatin, iphosphamide, melphalan, merchlorethamine, mitomycin, mitoxantrone, nitrosourea, paclitaxel, plicamycin, procarbazine, teniposide, tri ethyl enethiophosphoramide and etoposide (VP 16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes—dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, COX-2 inhibitors, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetii); anti-angio genie compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor (FGF) inhibitors, epidermal growth factor (EGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), amsacrine,

camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan (CPT-II) and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylpednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; chromatin disrupters.

[00263] These chemotherapeutic agents may be used by themselves with a compound of the present invention as inducing cell death or reducing lifespan or increasing sensitivity to stress and/or in combination with other chemotherapeutics agents. Exemplary combinatorial therapies for the treatment of cancer: ABV Doxorubicin, Bleomycin, Vinblastine ABVD Doxorubicin, Bleomycin, Vinblastine, Dacarbazine AC (Breast) Doxorubicin, Cyclophosphamide AC (Sarcoma) Doxorubicin, Cisplatin AC (Neuro-Cyclophosphamide, Doxorubicin blastoma) ACE Cyclophosphamide, Doxorubicin, Etoposide ACe Cyclophosphamide, Doxorubicin AD Doxorubicin, Dacarbazine AP Doxorubicin, Cisplatin ARAC-DNR Cytarabine, Daunorubicin B-CAVe Bleomycin, Lomustine, Doxorubicin, Vinblastine BCVPP Carmustine, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone BEACOPP Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Filgrastim BEP Bleomycin, Etoposide, Cisplatin BIP Bleomycin, Cisplatin, Ifosfamide, Mesna BOMP Bleomycin, Vincristine, Cisplatin, Mitomycin CA Cytarabine, Asparaginase CABO Cisplatin, Methotrexate, Bleomycin, Vincristine CAF Cyclophosphamide, Doxorubicin, Fluorouracil CAL-G Cyclophosphamide, Daunorubicin, Vincristine, Prednisone, Asparaginase CAMP Cyclophosphamide, Doxorubicin, Methotrexate, Procarbazine CAP Cyclophosphamide, Doxorubicin, Cisplatin CaT Carboplatin, Paclitaxel CAV Cyclophosphamide, Doxorubicin, Vincristine CAVE ADD CAV and Etoposide CA-VP 16 Cyclophosphamide, Doxorubicin, Etoposide CC Cyclophosphamide, Carboplatin CDDP/VP- 16 Cisplatin, Etoposide CEF Cyclophosphamide, Epirubicin, Fluorouracil CEPP(B) Cyclophosphamide, Etoposide, Prednisone, with or without/Bleomycin CEV Cyclophosphamide, Etoposide, Vincristine CF Cisplatin, Fluorouracil or Carboplatin Fluorouracil CHAP Cyclophosphamide or Cyclophosphamide, Altretamine, Doxorubicin, Cisplatin ChlVPP Chlorambucil, Vinblastine, Procarbazine, Prednisone CHOP Cyclophosphamide, Doxorubicin, Vincristine, Prednisone CHOP-BLEO Add Bleomycin to CHOP CISCA Cyclophosphamide, Doxorubicin, Cisplatin CLD-BOMP Bleomycin, Cisplatin, Vincristine, Mitomycin CMF Methotrexate, Fluorouracil, Cyclophosphamide CMFP Cyclophosphamide, Methotrexate, Fluorouracil, Prednisone CMFVP Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone CMV Cisplatin, Methotrexate, Vinblastine CNF Cyclophosphamide, Mitoxantrone, Fluorouracil CNOP Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone COB Cisplatin, Vincristine, Bleomycin CODE Cisplatin, Vincristine, Doxorubicin, Etoposide COMLA Cyclophosphamide, Vincristine, Methotrexate, Leucovorin, Cytarabine COMP Cyclophosphamide, Vincristine, Methotrexate, Prednisone Cooper Cyclophosphamide, Methotrexate, Fhiorouracil, Regimen Vincristine, Prednisone COP Cyclophosphamide, Vincristine, Prednisone COPE Cyclophosphamide, Vincristine, Cisplatin, Etoposide COPP Cyclophosphamide, Vincristine, Procarbazine, Prednisone CP(Chronic Chlorambucil, Prednisone lymphocytic leukemia) CP (Ovarian Cyclophosphamide, Cisplatin Cancer) CT Cisplatin, Paclitaxel CVD Cisplatin, Vinblastine, Dacarbazine CVI Carboplatin, Etoposide, Ifosfamide, Mesna CVP Cyclophosphamide, Vincristine, Prednisome CVPP Lomustine, Procarbazine,

Prednisone CYVADIC Cyclophosphamide, Vincristine, Doxorubicin, Dacarbazine DA Daunorubicin, Cytarabine DAT Daunorubicin, Cytarabine, Thioguanine DAV Daunorubicin, Cytarabine, Etoposide DCT Daunorubicin, Cytarabine, Thioguanine DHAP Cisplatin, Cytarabine, Dexamethasone DI Doxorubicin, Ifosfamide DTIC/ Dacarbazine, Tamoxifen Tamoxifen DVP Daunorubicin, Vincristine, Prednisone EAP Etoposide, Doxorubicin, Cisplatin EC Etoposide, Carboplatin EFP Etoposie, Fluorouracil, Cisplatin ELF Etoposide, Leucovorin, Fluorouracil EMA 86 Mitoxantrone, Etoposide, Cytarabine EP Etoposide, Cisplatin EVA Etoposide, Vinblastine FAC Fluorouracil, Doxorubicin, Cyclophosphamide FAM Fluorouracil, Doxorubicin, Mitomycin FAMTX Methotrexate, Leucovorin, Doxorubicin FAP Fluorouracil, Doxorubicin, Cisplatin F-CL Fluorouracil, Leucovorin FEC Fluorouracil, Cyclophosphamide, Epirubicin FED Fluorouracil, Etoposide, Cisplatin FL Flutamide, Leuprolide FZ Flutamide, Goserelin acetate implant HDMTX Methotrexate, Leucovorin Hexa-CAF Altretamine, Cyclophosphamide, Methotrexate, Fluorouracil ICE-T Ifosfamide, Carboplatin, Etoposide, Paclitaxel, Mesna IDMTX/6-MP Methotrexate, Mercaptopurine, Leucovorin IE Ifosfamide, Etoposie, Mesna IfoVP Ifosfamide, Etoposide, Mesna IPA Ifosfamide, Cisplatin, Doxorubicin M-2 Vincristine, Carmustine, Cyclophosphamide, Prednisone, Melphalan MAC-III Methotrexate, Leucovorin, Dactinomycin, Cyclophosphamide MACC Methotrexate, Doxorubicin, Cyclophosphamide, Lomustine MACOP-B Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Bleomycin, Prednisone MAID Mesna, Doxorubicin, Ifosfamide, Dacarbazine m-BACOD Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone, Methotrexate, Leucovorin MBC Methotrexate, Bleomycin, Cisplatin MC Mitoxantrone, Cytarabine MF Methotrexate, Fluorouracil, Leucovorin MICE Ifosfamide, Carboplatin, Etoposide, Mesna MINE Mesna, Ifosfamide, Mitoxantrone, Etoposide mini-BEAM Carmustine, Etoposide, Cytarabine, Melphalan MOBP Bleomycin, Vincristine, Cisplatin, Mitomycin MOP Mechlorethamine, Vincristine, Procarbazine MOPP Mechlorethamine, Vincristine, Procarbazine, Prednisone MOPP/ABV Mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine MP Melphalan, Prednisone (multiple myeloma) MP (prostate Mitoxantrone, Prednisone cancer) MTX/6-M0 Methotrexate, Mercaptopurine MTX/6-MP/VP Methotrexate, Mercaptopurine, Vincristine, Prednisone MTX-CDDPAdr Methotrexate, Leucovorin, Cisplatin, Doxorubicin MV (breast Mitomycin, Vinblastine cancer) MV (acute Mitoxantrone, Etoposide myelocytic leukemia) M-VAC Vinblastine, Doxorubicin, Cisplatin Methotrexate MVP Vinblastine, Cisplatin Mitomycin MVPP Mechlorethamine, Vinblastine, Procarbazine, Prednisone NFL Mitoxantrone, Fluorouracil, Leucovorin NOVP Mitoxantrone, Vinblastine, Vincristine OPA Vincristine, Prednisone, Doxorubicin OPPA Add Procarbazine to OPA. PAC Cisplatin, Doxorubicin PAC-I Cisplatin, Doxorubicin, Cyclophosphamide PA-CI Cisplatin, Doxorubicin PC Paclitaxel, Carbop latin or Paclitaxel, Cisplatin PCV Lomustine, Procarbazine, Vincristine PE Paclitaxel, Estramustine PFL Cisplatin, Fluorouracil, Leucovorin POC Prednisone, Vincristine, Lomustine ProMACE Prednisone, Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Etoposide ProMACE/ Prednisone, Doxorubicin, Cyclophosphamide, cytaBOM Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Leucovorin, Cotrimoxazole PRoMACE/ Prednisone, Doxorubicin, Cyclophosphamide, MOPP Etoposide, Mechlorethamine, Vincristine, Procarbazine, Methotrexate, Leucovorin Pt/VM Cisplatin, Teniposide PVA Prednisone, Vincristine, Asparaginase PVB Cisplatin, Vinblastine,

Bleomycin PVDA Prednisone, Vincristine, Daunorubicin, Asparaginase SMF Streptozocin, Mitomycin, Fluorouracil TAD Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide, Prednisone TCF Paclitaxel, Cisplatin, Fluorouracil TIP Paclitaxel, Ifosfamide, Mesna, Cisplatin TTT Methotrexate, Cytarabine, Hydrocortisone Topo/CTX Cyclophosphamide, Topotecan, Mesna VAB-6 Cyclophosphamide, Dactinomycin, Vinblastine, Cisplatin, Bleomycin VAC Vincristine, Dactinomycin, Cyclophosphamide VACAdr Vincristine, Cyclophosphamide, Doxorubicin, Dactinomycin, Vincristine VAD Vincristine, Doxorubicin, Dexamethasone VATH Vinblastine, Doxorubicin, Thiotepa, Flouxymesterone VBAP Vincristine, Carmustine, Doxorubicin, Prednisone VBCMP Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone VC Vinorelbine, Cisplatin VCAP Vincristine, Cyclophosphamide, Doxorubicin, Prednisone VD Vinorelbine, Doxorubicin VeIP Vinblastine, Cisplatin, Ifosfamide, Mesna VIP Etoposide, Cisplatin, Ifosfamide, Mesna VM Mitomycin, Vinblastine VMCP Vincristine, Melphalan, Cyclophosphamide, Prednisone VP Etoposide, Cisplatin V-TAD Etoposide, Thioguanine, Daunorubicin, Cytarabine 5 + 2 Cytarabine, Daunorubicin, Mitoxantrone 7 + 3 Cytarabine with/, Daunorubicin or Idarubicin or Mitoxantrone "8 in 1" Methylprednisolone, Vincristine, Lomustine, Procarbazine, Hydroxyurea, Cisplatin, Cytarabine, Dacarbazine.

[00264] In addition to conventional chemotherapeutics, the compounds of the present invention can also be used with antisense RNA, RNAi or other polynucleotides to inhibit the expression of the cellular components that contribute to unwanted cellular proliferation that are targets of conventional chemotherapy. Such targets are, merely to illustrate, growth factors, growth factor receptors, cell cycle regulatory proteins, transcription factors, or signal transduction kinases.

[00265] In one embodiment, the compounds of the present invention may be administered to a subject in need thereof in conjunction with a sirtuin-modulating compound (e.g., an allosteric SIRT1 activators described in, e.g. WO 2007/019346, WO 2007/019344, WO 2008/156866, W02008/156869, W02010/071853, W02009/134973, W02010/003048, W02010/037127, W02010/037129, W02013/059587, W02013/059589, W02013/059594, and WO 2011/059839). In another embodiment, the compounds of the present invention may be administered with one or more of the following compounds: resveratrol, butein, fisetin, piceatannol, or quercetin. In an exemplary embodiment, the compounds of the present invention may be administered in combination with nicotinic acid (i.e., niacin).

[00266] In another embodiment, the compounds of the invention may be administered with one or more of the following compounds that decrease the level and/or activity of a sirtuin protein: nicotinamide (NAM), suranim; EX527 (6-Chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide); NF023 (a G-protein antagonist); NF279 (a purinergic receptor antagonist); Trolox (6-hydroxy-2,5,7,8,tetramethylchroman-2-carboxylic acid); (-)-epigallocatechin (hydroxy on sites 3,5, 7,3 ',4', 5'); (-)-epigallocatechin gallate (Hydroxy sites 5, 7,3 ',4' ,5' and gallate ester on 3); cyanidin chloride (3,5, 7,3 ',4' -pentahydroxyflavylium chloride); delphinidin chloride (3,5,7,3 ',4' ,5' -hexahydroxyflavylium chloride); myricetin (cannabiscetin; 3,5,7,3 ',4' ,5' -hexahydroxyflavone); 3, 7,3 ',4' ,5' -pentahydroxyflavone; gossypetin (3,5,7,8,3 ',4' -hexahydroxyflavone), sirtinol; and splitomicin (see e.g., Howitz et al. (2003) Nature 425: 191; Grozinger et al. (2001) J. Biol. Chern. 276:38837; Dedalov et al. (2001) PNAS 98:15113; and Hirao et al. (2003) J. Biol. Chern 278:52773).

[00267] In certain embodiments, methods for reducing, preventing or treating diseases or disorders using of the compounds of the invention may also comprise increasing the protein level of a sirtuin, such as human SIRT1 or homologs thereof Increasing protein levels can be achieved by introducing into a cell one or more copies of a nucleic acid that encodes a sirtuin. For example, the level of a sirtuin can be increased in a mammalian cell by introducing into the mammalian cell a nucleic acid encoding the sirtuin, e.g., increasing the level of SIRT1 by introducing a nucleic acid encoding the amino acid sequence set forth in GenBank Accession No. NP 036370. The nucleic acid may be under the control of a promoter that regulates the expression of the SIRT1 nucleic acid. Alternatively, the nucleic acid may be introduced into the cell at a location in the genome that is downstream of a promoter. Methods for increasing the level of a protein using these methods are well known in the art.

[00268] A nucleic acid that is introduced into a cell to increase the protein level of a sirtuin may encode a protein that is at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to the sequence of a sirtuin, e.g., GenBank Accession No. NP 036370. For example, the nucleic acid encoding the protein may be at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to GenBank Accession No. NM_012238. The nucleic acid may also be a nucleic acid that hybridizes, preferably under stringent hybridization conditions, to a nucleic acid encoding a wild-type sirtuin, e.g., GenBank Accession No. NM_012238. Stringent hybridization conditions may include hybridization and a wash in 0.2 x SSC at 65 °C. When using a nucleic acid that encodes a protein that is different from a wild-type sirtuin protein, such as a protein that is a fragment of a wild-type sirtuin, the protein is preferably biologically active, e.g., is capable of deacetylation. It is only necessary to express in a cell a portion of the sirtuin that is biologically active. For example, a protein that differs from wild-type SIRT1 having GenBank Accession No. NP 036370, preferably contains the core structure thereof The core structure sometimes refers to amino acids 62-293 of GenBank Accession No. NP 036370, which are encoded by nucleotides 237 to 932 of GenBank Accession No. NM_012238, which encompasses the NAD binding as well as the substrate binding domains. The core domain of SIRT1 may also refer to about amino acids 261 to 447 of GenBank Accession No. NP 036370, which are encoded by nucleotides 834 to 1394 of GenBank Accession No. NM_012238; to about amino acids 242 to 493 of GenBank Accession No. NP 036370, which are encoded by nucleotides 777 to 1532 of GenBank Accession No. NM_012238; or to about amino acids 254 to 495 of GenBank Accession No. NP 036370, which are encoded by nucleotides 813 to 1538 of GenBank Accession No. NM 012238. Whether a protein retains a biological function, e.g., deacetylation capabilities, can be determined according to methods known in the art.

[00269] In one embodiment, a compound of the invention may be administered as part of a combination therapeutic with another cardiovascular agent including, for example, an anti-arrhythmic agent, an antihypertensive agent, a calcium channel blocker, a cardioplegic solution, a cardiotonic agent, a fibrinolytic agent, a sclerosing solution, a vasoconstrictor agent, a vasodilator agent, a nitric oxide donor, a potassium channel blocker, a sodium channel blocker, statins, or a naturiuretic agent. In one embodiment, a compound of the invention that increases the level and/or activity of NAD and/or the activity of a sirtuin protein may be administered as part of a combination therapeutic with an anti -arrhythmia agent. Anti -arrhythmia agents are often organized into four main groups

according to their mechanism of action: type I, sodium channel blockade; type II, beta-adrenergic blockade; type III, repolarization prolongation; and type IV, calcium channel blockade. Type I anti-arrhythmic agents include lidocaine, moricizine, mexiletine, tocainide, procainamide, encainide, flecanide, tocainide, phenytoin, propafenone, quinidine, disopyramide, and flecainide. Type II anti-arrhythmic agents include propranolol and esmolol. Type III includes agents that act by prolonging the duration of the action potential, such as amiodarone, artilide, bretylium, clofilium, isobutilide, sotalol, azimilide, dofetilide, dronedarone, ersentilide, ibutilide, tedisamil, and trecetilide. Type IV anti-arrhythmic agents include verapamil, diltaizem, digitalis, adenosine, nickel chloride, and magnesium ions.

[00270] In another embodiment, a compound of the invention may be administered as part of a combination therapeutic with another cardiovascular agent. Examples of cardiovascular agents include vasodilators, for example, hydralazine; angiotensin converting enzyme inhibitors, for example, captopril; anti-anginal agents, for example, isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate; anti-arrhythmic agents, for example, quinidine, procainaltide and lignocaine; cardioglycosides, for example, digoxin and digitoxin; calcium antagonists, for example, verapamil and nifedipine; diuretics, such as thiazides and related compounds, for example, bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide and other diuretics, for example, fursemide and triamterene, and sedatives, for example, nitrazepam, flurazepam and diazepam. Other exemplary cardiovascular agents include, for example, a cyclooxygenase inhibitor such as aspirin or indomethacin, a platelet aggregation inhibitor such as clopidogrel, ticlopidene or aspirin, fibrinogen antagonists or a diuretic such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorthiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds, angiotensin converting enzyme inhibitors such as captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril, and salts of such compounds, angiotensin II antagonists such as losartan, irbesartan or valsartan, thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC, Eminase, Beecham Laboratories), or animal salivary gland plasminogen activators, calcium channel blocking agents such as verapamil, nifedipine or diltiazem, thromboxane receptor antagonists such as ifetroban, prostacyclin mimetics, or phosphodiesterase inhibitors. Such combination products if formulated as a fixed dose employ the compounds of this invention within the dose range described above and the other pharmaceutically active agent within its approved dose range.

[00271] Yet other exemplary cardiovascular agents include, for example, vasodilators, e.g., bencyclane, cinnarizine, citicoline, cyclandelate, cyclonicate, ebumamonine, phenoxezyl, flunarizine, ibudilast, ifenprodil, lomerizine, naphlole, nikamate, nosergoline, nimodipine, papaverine, pentifylline, nofedoline, vincamin, vinpocetine, vichizyl, pentoxifylline, prostacyclin derivatives (such as prostaglandin El and prostaglandin 12), an endothelin receptor blocking drug (such as bosentan), diltiazem, nicorandil, and nitroglycerin. Examples of the cerebral protecting drug include radical

scavengers (such as edaravone, vitamin E, and vitamin C), glutamate antagonists, AMP A antagonists, kainate antagonists, NMDA antagonists, GABA agonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, Na+/Ca2+ channel inhibitory drugs, and K + channel opening drugs. Examples of the brain metabolic stimulants include amantadine, tiapride, and gamma-aminobutyric acid. Examples of the anticoagulant include heparins (such as heparin sodium, heparin potassium, dalteparin sodium, dalteparin calcium, heparin calcium, parnaparin sodium, reviparin sodium, and danaparoid sodium), warfarin, enoxaparin, argatroban, batroxobin, and sodium citrate. Examples of the anti platelet drug include ticlopidine hydrochloride, dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate hydrochloride, dilazep hydrochloride, trapidil, a nonsteroidal antiinflammatory agent (such as aspirin), beraprostsodium, iloprost, and indobufene. Examples of the thrombolytic drug include urokinase, tissue-type plasminogen activators (such as alteplase, tisokinase, nateplase, pamiteplase, monteplase, and rateplase), and nasaruplase. Examples of the antihypertensive drug include angiotensin converting enzyme inhibitors (such as captopril, alacepril, lisinopril, imidapril, quinapril, temocapril, delapril, benazepril, cilazapril, trandolapril, enalapril, ceronapril, fosinopril, imadapril, mobertpril, perindopril, ramipril, spirapril, and randolapril), angiotensin II antagonists (such as losartan, candesartan, valsartan, eprosartan, and irbesartan), calcium channel blocking drugs (such as aranidipine, efonidipine, nicardipine, bamidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine, diltiazem, bepridil, clentiazem, phendilin, galopamil, mibefradil, prenylamine, semotiadil,terodiline, verapamil, cilnidipine, elgodipine, isradipine, lacidipine, lercanidipine,nimodipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline), beta-adrenaline receptor blocking drugs (propranolol, pindolol, indenolol, carteolol, bunitrolol, atenolol, acebutolol, metoprolol, timolol, nipradilol, penbutolol, nadolol, tilisolol, carvedilol, bisoprolol, betaxolol, celiprolol, bopindolol, bevantolol,labetalol, alprenolol, amosulalol, arotinolol, befunolol, bucumolol, bufetolol, buferalol, buprandolol, butylidine, butofilolol, carazolol, cetamolol, cloranolol, dilevalol, epanolol, levobunolol, mepindolol, metipranolol, moprolol, nadoxolol, nevibolol, oxprenolol, practol, pronetalol, sotalol, sufinalol, talindolol, tertalol, toliprolol, xybenolol, and esmolol), alpha- receptor blocking drugs (such as amosulalol, prazosin, terazosin, doxazosin, bunazosin, urapidil, phentolamine, arotinolol, dapiprazole, fenspiride, indoramin, labetalol, naftopidil, nicergoline, tamsulosin, tolazoline, trimazosin, and yohimbine), sympathetic nerve inhibitors (such as clonidine, guanfacine, guanabenz, methyldopa, and reserpine), hydralazine, todralazine, budralazine, and cadralazine. Examples of the anti anginal drug include nitrate drugs (such as amyl nitrite, nitroglycerin, and isosorbide), beta-adrenaline receptor blocking drugs (such as propranolol, pindolol, indenolol, carteolol, bunitrolol, atenolol, acebutolol, metoprolol, timolol, nipradilol, penbutolol, nadolol, tilisolol, carvedilol, bisoprolol, betaxolol, celiprolol, bopindolol, bevantolol, labetalol, alprenolol, amosulalol, arotinolol, befunolol, bucumolol, bufetolol, buferalol, buprandolol, butylidine, butofilolol, carazolol, cetamolol, cloranolol, dilevalol, epanolol, levobunolol, mepindolol, metipranolol, moprolol, nadoxolol, nevibolol, oxprenolol, practol, pronetalol, sotalol, sufinalol, talindolol, tertalol, toliprolol, andxybenolol), calcium channel blocking drugs (such as aranidipine, efonidipine, nicardipine, bamidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine,

felodipine, amlodipine, diltiazem, bepridil, clentiazem, phendiline, galopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, cilnidipine, elgodipine, isradipine, lacidipine, lercanidipine, nimodipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline) trimetazidine, dipyridamole, etafenone, dilazep, trapidil, nicorandil, enoxaparin, and aspirin. Examples of the diuretic include thiazide diuretics (such as hydrochlorothiazide, methyclothiazide, trichlormethiazide, benzylhydrochlorothiazide, and penflutizide), loop diuretics (such as furosemide, etacrynic acid, bumetanide, piretanide, azosemide, and torasemide), K + sparing diuretics (spironolactone, triamterene, andpotassiumcanrenoate), osmotic diuretics (such as isosorbide, D-mannitol, and glycerin), nonthiazide diuretics (such as meticrane, tripamide, chlorthalidone, and mefruside), and acetazolamide. Examples of the cardiotonic include digitalis formulations (such as digitoxin, digoxin, methyldigoxin, deslanoside, vesnarinone, lanatoside C, and proscillaridin), xanthine formulations (such as aminophylline, choline theophylline, diprophylline, and proxyphylline), catecholamine formulations (such as dopamine, dobutamine, and docarpamine), PDE III inhibitors (such as amrinone, olprinone, and milrinone), denopamine, ubidecarenone, pimobendan, levosimendan, aminoethylsulfonic acid, vesnarinone, carperitide, and colforsin daropate. Examples of the antiarrhythmic drug include ajmaline, pirmenol, procainamide, cibenzoline, disopyramide, quinidine, aprindine, mexiletine, lidocaine, phenyloin, pilsicainide, propafenone, flecainide, atenolol, acebutolol, sotalol, propranolol, metoprolol, pindolol, amiodarone, nifekalant, diltiazem, bepridil, and verapamil. Examples of the antihyperlipidemic drug include atorvastatin, simvastatin, pravastatin sodium, fluvastatin sodium, clinofibrate, clofibrate, simfibrate, fenofibrate, bezafibrate, colestimide, and colestyramine. Examples of the immunosuppressant include azathioprine, mizoribine, cyclosporine, tacrolimus, gusperimus, and methotrexate. In one embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of neurodegenerative disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more compounds of the invention and one or more anti-neurodegeneration agents. For example, one or more compounds of the invention of the invention can be combined with an effective amount of one or more of: L-DOPA; a dopamine agonist; an adenosine A2A receptor antagonists; a COMT inhibitor; a MAO inhibitor; an NOS inhibitor; a sodium channel antagonist; a selective N-methyl D-aspartate (NMDA) receptor antagonists; an AMPA/kainate receptor antagonist; a calcium channel antagonist; a GABA-A receptor agonist; an acetyl-choline esterase inhibitor; a matrix metalloprotease inhibitor; an inhibitor ofp38 MAP kinase or c-jun-N-terminal kinases; TPA; NDA antagonists; beta-interferons; growth factors; glutamate inhibitors; and/or as part of a cell therapy. Exemplary N-NOS inhibitors include 4-(6-amino-pyridin-2-yl)-3-methoxyphenol 6-[4-(2-dimethylamino-ethoxy)-2-methoxy -phenyl]-pyridin-2-yl-amine, 6-[4-(2-15 dimethylamino-ethoxy)-2,3 -dimet-hyl-phenyl]-pyridin-2-yl-amine, 6-[4-(2-pyrrolidinylethoxy-)-2,3 -dimethyl-p-henyl]-pyridin-2-yl-amine, 6-[4-(4-(n-methyl)pi peridinyloxy)-2,3-dimethyl-p-henyl]-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-3 -methoxy -phenyl]pyridin-2-yl-amine, 6-[4-(2-pyrrolidinyl-ethoxy)-3 -methoxy -phenyl]-pyridin-2-yl-amine, 6-{ 4-[2-(6, 7 -dimethoxy-3,4-dihydro-1h-isoquinolin-2-yl)-ethoxy]-3-methoxy-phenyl }-pyridin-2-yl-amine, 6-{3-methoxy-4-[2-(4-phenethyl-piper-azin-1-yl)-ethoxy]-phenyl}pyridin-2-yl-amine, 6-{3-methoxy-4-[2-(4-methyl-piperazin-1-yl)-

ethoxy]-phenyl}pyridin-2-yl-amine, 6-{ 4-[2-(4-dimethylamin-o-piperidin-1-yl)-ethoxy]-3-methoxyphenyl}-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-3 -ethoxy -phenyl]-pyridin-2-yl-amine, 6-[4-(2-pyrrolidinyl-ethoxy)-3-ethoxy-phenyl]-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-2-isopropyl-phenyl]-pyridin-2-yl-amine, 4-(6-amino-pyridin-yl)-3-cyclopropyl-phenol 6-[2-cyclopropyl-4-(2-dimethy -lamino-ethoxy)-phenyl]-pyridin-2-ylamine, 6-[2-cyclopropyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-yl-amine, 3-[3-(6-amino-pyridin-2yl)-4-cycl-opropyl-phenoxy]-pyrrolidine-1-carboxylic acid tert-butyl ester 6-[2-cyclopropyl-4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 4-(6-30 amino-pyridin-2-yl)-3 -cyclobutyl-phenol 6-[2-cyclobutyl-4-(2-dimethylamino-ethoxy)-phenyl]-pyridin-2-yl-amine, 6-[2-cyclobutyl-4-(2-pyrrolid-in-1-yl-ethoxy)-phenyl]-pyridin-2-yl-amine, 6-[2-cyclobutyl-4-(1-methyl-pyr -rolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 4-(6-amino-pyri din-2-yl)-3 -cy -cl openty 1-phenol 6-[2-cycl openty 1-4-(2-dimethy laminoethoxy)-phenyl]-pyrid -in-2-yl-amine, 6-[2-cyclopentyl-4-(2-pyrrolidin-1 yl-ethoxy)-phenyl]-pyridin-2-y 1-amine, 3 -[4-(6-amino-pyridin-2yl)-3 -methoxy -phenoxy]-pyrrolidine-1-carboxylic acid tert butyl ester 6-[4-(1-methyl-pyrrolidin-3-yl-oxy)-2-metho-xy-phenyl]-5 pyridin-2-yl-amine, 4-[4-(6-amino-pyridin-2yl)-3-methoxy-phenoxy-]-piperidine-1-carboxylic acid tert butyl ester 6-[2-methoxy-4-(1-methyl-p-iperidin-4-yl-oxy)-phenyl]pyridin-2-yl-amine, 6-[4-(allyloxy)-2-methoxy-ph-enyl]-pyridin-2-yl-amine, 4-(6-aminopyridin-2-yl)-3-methoxy-6-allyl-phenol 12 and 4-(6-amino-pyridin-2-yl)-3-methoxy-2-allyl-phenol 13 4-(6-amino-pyridin-2-yl)-3-methoxy-6-propyl-phenol 6-[4-(2-dimethylamino-ethoxy)-2-methoxy -5-propyl-phenyl]-pyridin-yl-amine, 6-[2-isopropyl-4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-isopropyl-4-(pi peridin-3 -yl-oxy)phenyl]-pyridin-2-yl-amine, 6-[2-isopropyl-4-(1-methyl-azetidin-3 -yl-oxy)-phenyl]pyridin-2-yl-amine, 6-[2-isopropyl-4-(1-methyl-piperidin-4-yl-oxy)-phenyl]-pyridin-2-ylamine, 6-[2-isopropyl-4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amin-e 6-[2- isopropyl-4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-isopropyl-4-(2-methyl-2-aza-bicyclo[2.2.1]hept-5-yl-oxy)-phenyl]-p-yridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-2-methoxy -phenyl]-pyridin-2-yl-amine, 6-{ 4-[2-(benzyl-methylamino)-ethoxy]-2-methoxy-phenyl }-pyridin-2-yl-amine, 6-[2-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-yl-amine, 2-(6-amino-pyridin-2-yl)-5-(2-dimethylamino-ethoxy)-phenol 2-[4-(6-amino-pyridin-2-yl)-3-methoxy-phenoxy]-acetamide 6-[4-(2-amino-ethoxy)-2-methoxy-phenyl]-pyridin-2-yl-amine, 6-{ 4-[2-(3,4-dihydro-1hisoquinolin-2-yl)-ethoxy]-2-methoxy -phenyl} -pyrid-in-2-yl-amine, 2-[4-(6-amino-pyridin-2-yl)-3 -methoxy -phenoxy]-ethanol 6-{ 2-methoxy -4-[2-(2,2, 6,6-tetramethy 1-pi peridin-1-yl)ethoxy]-phenyl }-py-ridin-2-yl-amine, 6-{ 4-[2-(2,5-dimethyl-pyrrolidin-1-yl)-ethoxy]-2- methoxy-phenyl }-pyridin-2-yl-amine, 6-{ 4-[2-(2,5-dimethyl-pyrrolidin-1-yl)-ethoxy]-2-methoxy-phenyl }-pyridin-2-yl-amine, 2-[4-(6-amino-pyridin-2-yl)-3-methoxy-phenoxy]-1-(2,2,6,6-tetramethyl-piperidin-1-yl)-ethanone 6-[2-methoxy-4-(1-methyl-pyrrolidin-2-ylmethoxy)-phenyl]-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-2-propoxy -phenyl]pyridin-2-yl-amine, 6-{ 4-[2-(benzyl-methyl-amino)-ethoxy]-2-propoxy-phenyl }-pyridin-2-yl-amin-e 6-[4-(2-ethoxy-ethoxy)-2-methoxy-phenyl]-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-2-isopropoxy-phenyl]-pyridin-2-yl-amine, 6-[4-(2-ethoxy-ethoxy)-2-isopropoxy -phenyl]-pyridin-2-yl-amine, 6-[2-methoxy -4-(3 -methyl-butoxy)-phenyl]-pyri din-2-y 1-amine, 6-[4-(2-dimethy lamino-ethoxy)-2-ethoxy-pheny 1] -pyri din-2-y 1-amine, 6-{ 4-[2-(benzyl-methyl-amino)-ethoxy]-2-ethoxy-phenyl }-pyridin-2-yl-amine, 6-[2-ethoxy -4-(3 -methyl-butoxy)-phenyl]-pyridin-2-yl-amine, 1-(

6-amino-3 -azabicyclo[3.1.0]hex-3-yl)-2-[4-(6-amino-pyridin-2-yl)-3-et-hoxy-phenoxy]-ethanone 6-[2-5 ethoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-py-ridin-2-yl-amine, 3 -{ 2-[4-(6-aminopyridin-2-yl)-3-ethoxy-phenoxy]-ethyl }-3-aza-bicyclo[3.1.0]hex-6-yl-amine, 1-(6-amino-3-aza-bicyclo[3 .1.0]hex-3-yl)-2-[4-(6-amino-pyridin-2-yl)-3-methoxy-phenoxy]-ethanone 3-{ 2-[4-(6-amino-pyridin-2-yl)-3-methoxy-phenoxy]-ethyl }-3-aza-bicyclo[3. -1.0]hex-6-ylamine,6-[2-isopropoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-py-ridin-2-yl-amine, 6-{ 4-[2-(benzyl-methyl-amino)-ethoxy]-2-isopropoxy-phenyl-}-pyridin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-2-methoxy -5-propyl-phen-yl]-pyridin-2-yl-amine, 6-[5-allyl-4-(2-dimethylamino-ethoxy)-2-methoxy -phe-nyl]-pyridin-2-yl-amine, 6-[5-allyl-2-methoxy -4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-yl-amine, 6-[3 -allyl-4-(2-dimethylaminoethoxy)-2-methoxy-phenyl]-pyridin-2-yl-amine, 6-[2-methoxy-4-(pyrrolidin-3-yl-oxy)-phenyl]-p-yridin-2-yl-amine, 6-[2-methoxy -4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-ethoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-isopropoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-methoxy -4-(pi peridin-4-yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-methoxy -4-(2,2,6, 6-tetramethylpiperidin-4-yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-isopropoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 3-[4-(6-amino-pyridin-2-yl)-3-methoxy-phenoxy]-azetidine-1-carboxylic acid tert-butyl ester 6-[4-(azetidin-3-yl-oxy)-2-methoxy-phenyl]-pyridin-2-ylamine, 6-[2-methoxy-4-(1-methyl-azetidin-3 -yl-oxy)-phenyl]-pyridin-2-y-1-amine, 6-[2-isopropoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-isopropoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-methoxy -4-(pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[2-methoxy-4-(1-methyl-pyrrolidin-3-yl-oxy)-phenyl]pyridin-2-yl-amine, 6-[2-methoxy -4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyridin-2-ylamine, 6-[2-methoxy -4-(2-methyl-2-aza-bicyclo[2.2.1]hept-5-yl-oxy)-phenyl]-pyrid-in-2-yl-amine, 6-[2-methoxy-4-(1-methyl-piperidin-4-yl-oxy)-phenyl]-pyridin-2-yl-amine, 6-[4-(1-ethyl-pi peridin-4-yl-oxy)-2-methoxy -phenyl]-pyridin-2-yl-amine, 6-[5-allyl-2-methoxy- 4-(1-methyl-pyrrolidin-3-yl-oxy)-phenyl]-pyr-idin-2-yl-amine, 6-[4-(2-dimethylaminoethoxy)-2,6-dimethyl-phenyl]-pyridin-2-yl-amine, 6-[2,6-dimethyl-4-(3-piperidin-1-ylpropoxy)-phenyl]-pyridin-2-yl-amine, 6-[2,6-dimethyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-y-1-amine, 6-{ 2,6-dimethyl-4-[3-(4-methyl-piperazin-1-yl)-propoxy]phenyl}-py-ridin-2-yl-amine, 6-[2,6-dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-yl-amine, 6-{ 4-[2-(benzyl-methyl-amino)-ethoxy]-2,6-dimethyl-phenyl }-p-yridin-2-ylamine, 2-[4-(6-amino-pyridin-2-yl)-3,5-dimethyl-phenoxy]-acetamide 6-[4-(2-amino-5 ethoxy)-2,6-dimethyl-phenyl]-pyridin-2-yl-amine, 6-[2-isopropyl-4-(2-pyrrolidin-1-ylethoxy)-phenyl]-pyridin-2-yl-amine, 2-(2, 5-dimethyl-pyrrolidin-1-yl)-6-[2-isopropyl-4-(2-pyrrolidin-1-yl-etho-xy)-phenyl]-pyridine 6-{ 4-[2-(3,5-dimethyl-piperidin-1-yl)-ethoxy]-2-isopr -opy 1-pheny 1} -pyri din-2-y 1-amine, 6-[4-(2-dimethy 1 amino-ethoxy)-2-i sop ropy 1-phenyl]-pyridin-2-y 1-amine, 6-[2-tert-butyl-4-(2-dimethy lamino-ethoxy)-phen-yl]-pyridin-2-yl-amine, 6-[2-tert-butyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl-]-pyridin-2-yl-amine, 6-[4-(2-pyrrolidinyl-ethoxy)-2, 5-dimethyl-phenyl]-pyr-idin-2-yl-amine, 6-[4-(2-dimethylaminoethoxy)-2,5-dimethyl-phenyl]-pyridin-2-yl-amine, 6-[4-(2-(4-phenethylpiperazin-1-yl)ethoxy)-2,5-dimethyl-pheny -1]-pyridin-2-yl-amine, 6-[2-cyclopropyl-4-(2-dimethylamino-1-methyl-ethoxy)-phenyl]-pyridin-2-yl-amine, 6-[cyclobutyl-4-(2-dimethylamino-1-methyl-etho-xy)-phenyl]-pyridin-2-yl-amine, 6-[4-(allyloxy)-2-cyclobutyl-phenyl]-pyridin-2-ylamine, 2-allyl-4-(6-amino-pyridin-2-yl)-3 -cyclobutyl-phenol and 2-allyl-4-(6-aminopyridin-2-yl)-5-cyclobutyl-phenol4-(6-amino-pyridin-2yl)-5-cyclobutyl-2-propyl-

phenol 4-(6-amino-pyridin-2yl)-3-cyclobutyl-2-propyl-phenol 6-[2-cyclobutyl-4-(2-dimethylamino-1-methyl-ethoxy)-5-propyl-phenyl]-pyri -din-2-yl-amine, 6-[2-cyclobutyl-4-(2-dimethylamino-1-methyl-ethoxy)-3-propy-1-phenyl]-pyridin-2-yl-amine, 6-[2-cyclobutyl-4-(2-dimethylamino-ethoxy)-5-propyl-phenyl]-pyridin-2-y 1-amine, 6-[2-cyclobutyl-4-(2-dimethylamino-ethox -y)-3 -propyl-phenyl]-pyridin-2-yl-amine, 6-[2-cyclobutyl-4-(1-methyl-pyrroli -din-3-yl-oxy)-5-propyl-phenyl]-pyridin-2-yl-amine, 6-[cyclobutyl-4-(1-methy -1-pyrrolidin-3 -yl-oxy)-3 -propyl-phenyl]-pyridin-2-yl-amine, 2-(4-benzyloxy -5-hydroxy-2-methoxy-phenyl)-6-(2,5-dimethyl-pyrrol-1-yl)-p-yridine 6-[4-(2-dimethylamino-ethoxy)-5-ethoxy-2-methoxy-phenyl]-pyridin-2-yl-amine, 6-[5-ethyl-2-methoxy -4-(1-methyl-piperidin-4-yl-oxy)-phenyl]-pyr -idin-2-yl-amine, 6-[5-ethyl-2-methoxy-4-(piperidin-4-yl-oxy)-phenyl]-pyridi-n-2-yl-amine, 6-[2,5-dimethoxy-4-(1-methyl-pyrrolidin-3 -yl-oxy)-phenyl]-pyr -idin-2-yl-amine, 6-[4-(2-dimethylamino-ethoxy)-5-ethyl-2-methoxy -phenyl]-py -ridin-2-yl-amine.

[00272] Exemplary NMDA receptor antagonist include (+)-(IS, 2S)-1-(4-hydroxy-phenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-pro-panol, (1 S, 2S)-1-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxy -4-pheny 1 pi peri -dino)-!-propanol, (3 R, 4 S)-3 -(4-(4-fluoropheny 1)-4-hydroxypiperidin-1-yl-)-chroman-4,7-diol, (lR *, 2R *)-1-(4-hydroxy-3-methylphenyl)-2-(4-(4-fluoro-phenyl)-4-hydroxypiperidin-1-yl)-propan-1-ol-mesylate or a pharmaceutically acceptable acid addition salt thereof

[00273] Exemplary dopamine agonists include ropininole; L-dopa decarboxylase inhibitors such as carbidopa or benserazide, bromocriptine, dihydroergocryptine, etisulergine, AF-14, alaptide, pergolide, piribedil; dopamine DI receptor agonists such as A-68939, A-77636, dihydrexine, and SKF-38393; dopamine D2 receptor agonists such as carbergoline, lisuride, N-0434, naxagolide, PD-118440, pramipexole, quinpirole and ropinirole; dopamine/beta-adrenegeric receptor agonists such as DPDMS and dopexamine; dopamine/5-HT uptake inhibitor/5-HT-IA agonists such as roxindole; dopamine/opiate receptor agonists such as NIH-10494; alpha 2-adrenergic antagonist/dopamine agonists such as terguride; alpha 2-adrenergic antagonist/dopamine D2 agonists such as ergolines and talipexole; dopamine uptake inhibitors such as GBR-12909, GBR-13069, GYKI-52895, and NS-2141; monoamine oxidase-B inhibitors such as selegiline, N-(2-butyl)-N-methylpropargylamine, N-methyl-N-(2-pentyl)propargylamine, AGN-1133, ergot derivatives, lazabemide, LU-53439, MD-280040 and mofegiline; and COMT inhibitors such as CGP-28014.

[00274] Exemplary acetyl cholinesterase inhibitors include donepizil, 1-(2-methyl-lHbenzimida-zol-5-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(2-phenyl-lH-benzimidazol-5-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-pr-opanone; 1-(1-ethyl-2-methyllH-benzimidazol-5-yl)-3-[1-(phenylmethyl)-4-p-iperidinyl]-1-propanone; 1-(2-methyl-6-benzothiazolyl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(2-methyl-6-benzothiazolyl)-3-[1-[(2-methyl-4-thiazolyl)methyl]-4-piperidinyl]-1-propanone; 1-(5-methyl-benzo[b]thie-n-2-yl)-3-[l-(phenylmethyl)4-piperidinyl]-1-propanone; 1-(6-methyl-benzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-prop-anone; 1-(3,5-dimethylbenzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(benzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(benzofuran-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-pro-panone; 1-(1-phenylsulfonyl-6-methyl-indol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-methyl-indol-2-yl)-3-[1-(phenylmethyl)-4-piper-idinyl]-1-propanone; 1-(1-

phenylsulfonyl-5-amino-indol-2-yl)-3-[1-(phenylm-ethyl)-4-piperidinyl]-1-propanone; 1-(5-amino-indol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; and 1-(5-acetylamino-indol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-quinolyl)-3-[1-(pheny lmethyl)-4-piperidinyl]-1-propanone; 1-(5-indolyl)-3-[1-(phenylmethyl)-4-piperidiny-1]-1-propanone; 1-(5-benzthienyl)-3-[1-(phenylmethyl)-4-piperidinyl] -1-propanone; 1-(6-quinazolyl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-benzoxazolyl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(5 -benzofurany 1)-3 -[1-(phenylmethyl)-4-piperidinyl] -1-propanone; 1-(5-methyl-benzimidazol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propa-none; 1-(6-methylbenzimidazol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(5-chlorobenzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidin-yl]-1-propanone; 1-(5-azaindol-2-yl)-, 3-[1-(phenylmethyl)4-piperidinyl]-1-p-ropanone; 1-(6-azabenzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(1H-2-oxo-pyrrolo[2',3 ',5,6]benzo[b]thieno-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-methyl-benzothiazol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-methoxy-indol-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone; 1-(6-methoxy-benzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-pro-panone; 1-(6-acetylamino-benzo[b]thien-2-yl)-3-[1-(phenylmethyl)-4-piperid-inyl]-1-propanone; 1-(5-acetylamino-benzo[b]thien-2-yl)-3-[1-(pheny lmethy 1-)-4-pi peri diny 1]-1-propanone; 6-hydroxy-3-[2-[1-(pheny lmethy 1)-4-piperidin-yl]ethyl]-1 ,2-benzisoxazole; 5-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1 ,2-benzisoxazole; 6-methoxy-3 [2-[1 (phenylmethyl)-4-piperidinyl]et-hyl]-1 ,2-benzi soxazol e; 6-acetami de-3 -[2-[1-(pheny lmethy 1)-4-pi peri diny 1]-ethy 1] -1 ,2-benzisoxazole; 6-amino-3-[2-[1-(phenymethyl)-4-piperidinyl]ethy-l]-1 ,2-benzisoxazole; 6-(4-morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidin-yl]ethyl]-1 ,2-benzisoxazole; 5, 7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidi -nyl]ethyl]-6H -pyrrolo[4,5-f]-1 ,2-benzisoxazol-6-one; 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1 ,2-benzisothiazole; 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethenyl]-1 ,2-benzisoxazole; 6-phenylamino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1 ,2,-benzisoxaz-ole; 6-(2-thiazoly)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1 ,2-benzis-oxazole; 6-(2-oxazolyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1 ,2-be-nzisoxazole; 6-pyrrolidinyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1, -2-benzisoxazole; 5, 7 -dihydro-5,5-dimethyl-3-[2-[1-(phenylmethyl)-4-piperid-inyl]ethyl]-6H -pyrrolo[4,5-f]-1 ,2-benzisoxazole-6-one; 6,8-dihydro-3 -[2-[1-(phenylmethyl)-4-pi peridinyl]ethyl]-7H -pyrrolo[5, 4-g]-1 ,2-benzisoxazole-7 -one; 3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-5,6, -8-trihydro-7H-isoxazolo[4,5-g]-uinolin-7-one; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine, 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylp-iperidine, 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine, 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine, 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, 1-cyclohexymethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, 1-(m-florobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpi peri dine, 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine, and 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine.

[00275] Exemplary calcium channel antagonists include diltiazem, omega-conotoxin GVIA, methoxyverapamil, amlodipine, felodipine, lacidipine, and mibefradil.

[00276] Exemplary GABA-A receptor modulators include clomethiazole; IDDB; gaboxadol(4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol); ganaxolone (3-alpha-hydroxy-3-betamethy 1-5 -alpha-pregnan-20-one); fengabine (2-[(buty limino)-(2-chl oropheny 1)methy 1] -4- chlorophenol); 2-(4-methoxyphenyl)-2,5,6, 7,8,9-hexahydro-pyrazolo[4,3-c]cinnolin-3-one; 7 -cyclobutyl-6-(2-methyl-2H-1 ,2,4-triazol-3-ylmethoxy)-3-phenyl-1 ,2,4-triazolo[4,3-b]pyridazine; (3-fluoro-4-methylphenyl)-N-({ -1-[(2-methylphenyl)methyl]-benzimidazol-2-yl }methyl)-N-pentylcarboxamide; and 3-(aminomethyl)-5-methylhexanoic acid.

[00277] Exemplary potassium channel openers include diazoxide, flupirtine, pinacidil, levcromakalim, rilmakalim, chromakalim, PC0-400 and SKP-450 (2-[2"(1 ", 3 "dioxolone)-2-methyl]-4-(2'-oxo-1 '-pyrrolidinyl)-6-nitro-2H-1-benzopyran).

[00278] Exemplary AMPA kainate receptor antagonists include 6-cyano-7 -nitroquinoxalin-2,3-di-one (CNQX); 6-nitro-7-sulphamoylbenzo[f]quinoxaline-2,3-dione (NBQX); 6,7-dinitroquinoxaline-2,3-dione (DNQX); 1-(4-aminophenyl)-4-methyl-7,8-m-ethylenedioxy-5H-2,3-benzodiazepine hydrochloride; and 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f]quinoxaline.

[00279] Exemplary sodium channel antagonists include ajmaline, procainamide, flecainide and riluzole.

[00280] Exemplary matrix-metalloprotease inhibitors include 4-[4-(4-fluorophenoxy)benzenesulfonylamino]tetrahydropyran-4-carboxylic acid hydroxy amide; 5-Methyl-5-(4-(4'-fluorophenoxy)-phenoxy)-pyrimidine-2,4,6-trione; 5-n-Butyl-5-(4-(4'fluorophenoxy)-phenoxy)-pyrimidine-2,4,6-trione and prinomistat.

[00281] Exemplary inhibitors of p38 MAP kinase and c-jun-N-terminal kinases include pyridyl imidazoles, such as PD 169316, isomeric PD 169316, SB 203580, SB 202190, SB 220026, and RWJ 67657. Others are described in US Patent 6,288,089, and incorporated by reference herein.

[00282] In an exemplary embodiment, a combination therapy for treating or preventing MS comprises a therapeutically effective amount of a compound of the present invnetion and/or activity of a sirtuin protein and one or more of Avonex® (interferon beta-1a),Tysabri® (natalizumab), orFumaderm® (BG-12/0ral Fumarate).

[00283] In another embodiment, a combination therapy for treating or preventing diabetic neuropathy or conditions associated therewith comprises a therapeutically effective amount of a compopund of the invention and one or more of tricyclic antidepressants (TCAs) (including, for example, imipramine, amytriptyline, desipramine and nortriptyline), serotonin reuptake inhibitors (SSRis) (including, for example, fluoxetine, paroxetine, sertralene, and citalopram) and antiepileptic drugs (AEDs) (including, for example, gabapentin, carbamazepine, and topimirate).

[00284] In another embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of blood coagulation disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include a compound of the invention and/or activity of a sirtuin protein and one or more anti-coagulation or anti-thrombosis agents. For example, one or more compounds of the invention can be combined with an effective amount of one or more of: aspirin, heparin, and oral Warfarin that inhibits Vit Kdependent factors, low molecular weight heparins

that inhibit factors X and II, thrombin inhibitors, inhibitors of platelet GP IIbiiia receptors, inhibitors of tissue factor (TF), inhibitors of human von Willebrand factor, inhibitors of one or more factors involved in hemostasis (in particular in the coagulation cascade). In addition, compounds of the invention can be combined with thrombolytic agents, such as t-PA, streptokinase, reptilase, TNK-t-PA, and staphylokinase.

[00285] In one embodiment, compounds of the present invention may be administered as a combination therapy for treating or preventing a metabolic disorder, for example, antidiabetic agents. Exemplary anti-diabetic agents include, for example, an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase IB inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a peroxisome proliferator -activated receptor -γ (PP AR - γ) ligand such as trogli tazone, rosagli tazone, pioglitazone or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide wherein the amounts of the first and second compounds result in a therapeutic effect. Other antidiabetic agents include a glucosidase inhibitor, a glucagon-like peptide-I (GLP-1), insulin, a PPAR α/ γ dual agonist, a meglitinide and an αP2 inhibitor. In an exemplary embodiment, an anti-diabetic agent may be a dipeptidyl peptidase IV (DP-IV or DPP-IV) inhibitor, such as, for example LAF237 from Novartis (NVP DPP728; 1-[[[2-[(5-cyanopyridin-2-yl)amino] ethyl]amino]acetyl]-2- cyano-(S)- pyrrolidine) or MK-04301 from Merck (see e.g., Hughes et al., Biochemistry 38: 11597-603 (1999)).

[00286] In certain embodiments, one or more compounds of the present invention may be administered alone or in combination with other compounds useful for treating or preventing inflammation. Exemplary anti-inflammatory agents include, for example, steroids (e.g., cortisol, cortisone, fludrocortisone, prednisone, 6-alpha-methylprednisone, triamcinolone, betamethasone or dexamethasone), nonsteroidal antiinflammatory drugs (NSAIDS (e.g., aspirin, acetaminophen, tolmetin, ibuprofen, mefenamic acid, piroxicam, nabumetone, rofecoxib, celecoxib, etodolac or nimesulide). In another embodiment, the other therapeutic agent is an antibiotic (e.g., vancomycin, penicillin, amoxicillin, ampicillin, cefotaxime, ceftriaxone, cefixime, rifampinmetronidazole, doxycycline or streptomycin). In another embodiment, the other therapeutic agent is a PDE4 inhibitor (e.g., roflumilast or rolipram). In another embodiment, the other therapeutic agent is an antihistamine (e.g., cyclizine, hydroxyzine, promethazine or diphenhydramine). In another embodiment, the other therapeutic agent is an anti-malarial (e.g., artemisinin, artemether, artsunate, chloroquine phosphate, mefloquine hydrochloride, doxycycline hyclate, proguanil hydrochloride, atovaquone or halofantrine). In one embodiment, the other therapeutic agent is drotrecogin alfa. Further examples of anti-inflammatory agents include, for example, aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alclometasone, alfentanil, algestone, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amcinonide, amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antrafenine, apazone, beclomethasone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen,

betamethasone, betamethasone-17-valerate, bezitramide, .alpha.-bisabolol, bromfenac, pbromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, budesonide, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butorphanol, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chloroprednisone, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clobetasol, clocortolone, clometacin, clonitazene, clonixin, clopirac, cloprednol, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cortisone, cortivazol, cropropamide, crotethamide, cyclazocine, deflazacort, dehydrotestosterone, desomorphine, desonide, desoximetasone, dexamethasone, dexamethasone-21-isonicotinate, dexoxadrol, dextromoramide, dextropropoxyphene, deoxycorticosterone, dezocine, diampromide, diamorphone, diclofenac, difenamizole, difenpiramide, diflorasone, diflucortolone, diflunisal, difluprednate, dihydrocodeine, dihydrocodeinone-enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, enoxolone, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, fluazacort, flucloronide, flufenamic acid, flumethasone, flunisolide, flunixin, flunoxaprofen, fluocinolone acetonide, fluocinonide, fluocinolone acetonide, fluocortin butyl, fluocortolone, fluoresone, fluorometholone, fluperolone, flupirtine, fluprednidene, fluprednisolone, fluproquazone, flurandrenolide, flurbiprofen, fluticasone, formocortal, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, halcinonide, halobetasol, halometasone, haloprednone, heroin, hydrocodone, hydrocortamate, hydrocortisone, hydrocortisone acetate, hydrocortisone succinate, hydrocortisone hemisuccinate, hydrocortisone 21-lysinate, hydrocortisone cypionate, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoflupredone, isoflupredone acetate, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levallorphan, levorphanol, levophenacyl-morphan, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, mazipredone, meclofenamic acid, medrysone, mefenamic acid, meloxicam, meperidine, meprednisone, meptazinol, mesalamine, metazocine, methadone, methotrimeprazine, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methylprednisolone suleptnate, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, mometasone, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, nalorphine, !-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paramethasone, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenomorphan, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirazolac, piritramide, piroxicam, pirprofen, pranoprofen, prednicarbate, prednisolone, prednisone, prednival,

prednylidene, proglumetacin, proheptazine, promedol, propacetamol, properidine, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, proxazole, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylic acid, salicylsulfuric acid, salsalate, salverine, simetride, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tixocortol, tolfenamic acid, tolmetin, tramadol, triamcinolone, triamcinolone acetonide, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac.

[00287] In an exemplary embodiment, compounds of the present invention may be administered with a selective COX-2 inhibitor for treating or preventing inflammation. Exemplary selective COX-2 inhibitors include, for example, deracoxib, parecoxib, celecoxib, valdecoxib, rofecoxib, etoricoxib, lumiracoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, tert-butyl 1 benzyl-4-[(4-oxopiperidin-1-yl} sulfonyl]piperidine-4-carboxylate, 4-[5-(phenyl)-3-(trifluoromethyl)-1 H -pyrazol-1-y 1]benzenesulfonamide, salts and prodrugs thereof.

MATERIALS AND METHODS

Example 1, Preparation of 1'5'-dinicotinate 2'3'-acetonide **4**

(3aR,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-d][1,3]dioxol-4-ol (prepared according to Kim E, K; Krishnamurthy R; *Chem. Commun.*, 2015; 51**,** 5618-5621, and references therein) (1 g, 5.26 mmol, 1 eq) was dissolved in dry dichloromethane (DCM) (40 mL) in a 100 mL round bottom flask (RBF) under nitrogen. Pyridine-3-carbonyl chloride hydrochloride (2.06 g, 16.24 mmol, 2.2 eq) was added in one portion and cooled to 0 ^{o}C, then triethyl amine (TEA) (3.66 ml, 26.29 mmol, 5.0 eq) was added dropwise and the mixture allowed to warm to room temperature (RT) and stirred for 24 hrs. The mixture was then washed with H_2O (50 mL), $NaHCO_3$ (50 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography using an increasing gradient of 60 % EtOAc in Petroleum. Ether to 100 % EtOAc over 2L on a biotage purification system to provide 1.65 g (78 %) of a α/β mix of 1'5'-dinicotinate 2'3'-acetonide **4** as a yellow solid.

^{1}H-NMR (400MHz, MeOD) δ ppm: 9.18 (0.15H, dd, *J*= 2.3, 0.9 Hz, Ar (α)), 9.15 (0.15H, dd, *J*= 2.3, 0.9 Hz, Ar, (α)), 9.04 (0.35H, dd, *J*= 2.3, 0.9 Hz, Ar, (β)), 9.01 (0.35H, dd, *J*= 2.3, 0.9 Hz, Ar, (β)), 8.77-8.80 (0.3H, m, Ar), 8.71-8.74 (0.7H, m, Ar, (β)), 8.42-8.47 (0.3H, m, Ar), 8.28-8.33 (0.7H, m, Ar, (β)), 7.58-7.63 (0.3H, m, Ar), 7.51 (0.7H, m, Ar, (β)), 6.53 (0.3H, d, *J*= 4.3 Hz, H-1α), 6.42 (0.7H, s, H-1β), 5.05-5.10 (1.7H, m, H-2α, H-2β, H-3β), 4.97 (0.3H, d, *J*= 7.0, 3.3 Hz, H-3α), 4.71-4.75-4.78

(0.3H, m, H-4α), 4.71-4.71 (0.7H, m, H-4β), 4.55-4.65 (0.6H, m, H-5α), 4.49-4.56 (1.4H, m, H-5β), 1.53 (2.1H, s, CH_3 (β)), 1.40 (2.1H, s, CH_3 (β)), 1.38 (1.8H, s, CH_3 (α)).

^{13}C NMR (125 MHz, MeOD) δ ppm: 165.9 (C=O, α), 165.7 (C=O, β), 164.9 (C=O, β), 164.6 (C=O, α), 154.5 (Ar, α), 154.4 (Ar, β), 154.3 (Ar, α), 154.2 (Ar, β), 151.4 (Ar, α), 151.3 (Ar, β), 151.2 (Ar, α), 151.1 (Ar, β), 139.1 (Ar, α), 139.0 (Ar, α), 139.0 (Ar, β), 138.9 (Ar, β), 127.7 (Ar, α), 127.6 (Ar, β), 127.4 (2 x Ar, β), 117.1 (C-$(CH_3)_2$, α), 114.4 (C-$(CH_3)_2$, β), 105.1 (C-1β), 99.4 (C-1α), 87.0, 86.6, (C-2β or C-3β and C-4β), 83.0 (C-3α), 82.6 (C-2β or C-3β), 81.9 (C-4α), 81.8 (C-3α), 66.3 (C-5β), 66.0 (C-5α), 26.8 (C-$(CH_3)_2$, β), 26.5 (C-$(CH_3)_2$, α), 25.5 (C-$(CH_3)_2$, α), 25.1 (C-$(CH_3)_2$, β).

Example 2, Preparation of 1'2' 3'-O-acetate, 5'-O-nicotinate **5**

[(2R,3R,4R)-4,5-diacetoxy-2-(hydroxymethyl)tetrahydrofuran-3-yl] acetate (prepared according to Kim E, K; Krishnamurthy R; *Chem. Commun.*, 2015; 51, 5618-5621, and references therein) (3.45 g, 12.49 mmol, 1 eq) was dissolved in dry dichloromethane (DCM) (60 mL) in a 250 mL round bottom flask RBF under nitrogen. Pyridine-3-carbonyl chloride hydrochloride (2.89 g, 16.24 mmol, 1.3 eq) was added in one portion and cooled to 0 °C, then triethyl amine (TEA) (8.70 ml, 62.45 mmol, 5.0 eq) was added dropwise and the mixture allowed to warm to room temperature (RT) and stirred for 24 hrs. The mixture was then washed with H_2O (50 mL), $NaHCO_3$ (50 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography using an increasing gradient of 30 % EtOAc in Petroleum Ether to 50 % EtOAc in Petroleum. Ether over 2.5L on a biotage purification system to provide 3.0 g (63 %) of an α/β mix of 1'2' 3'-O-acetate, 5'-O-nicotinate **5** as an off-white solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 9.24-9.27 (1H, m, Ar, α and β), 8.80-8.84 (1H, m, Ar, α and β), 8.29-8.35 (1H, m, Ar, α and β), 7.41-7.46 (1H, m, Ar, α and β), 6.46 (0.45H, d, *J*= 4.4 Hz, H-1α), 6.46 (0.55H, s, H-1β), 5.30-5.51 (2H, m, H-2α, H-2β, H-3α, H-3β), 4.44-4.65 (3H, m, H-4α, H-4β, H-5α, H-5β), 2.15, 2.14, 2.11, 2.08, 2.02 (9H, s, 6 x C=O-CH_3, α and β).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 170.2, 169.7, 169.6, 169.4, 168.9 (6 x C=O-CH_3, α and β), 164.7, 164.6 (2 x C=O, Nicotinate, α and β), 153.8, 153.7, 151.0, 137.2, 137.1, 125.6, 125.4, 123.5, 123.4 (5 x Ar, Nicotinate, α and β), 98.2 (C-1β), 94.0 (C-1α), 81.6, 79.2 (C-4α, C-4β), 74.2, 70.4, 70.0, 69.8 (C-2α, C-2β, C-3α, C-3β), 64.2, 63.9 (C-5α, C-5β), 21.0, 20.9, 20.5, 20.4, 20.3 (6 x C=O-CH_3, α and β).

Example 3, Preparation of cyclic –NAR triflate salt (acetonide protected) **3**

2'3'-*O,O*-acetonide triflate salt **3** was prepared as follows: 1'5' dinicotinate 2'3' acetonide **4** (115 mg, 0.29 mmol, 1eq) was added to a 35mL Polytetrafluoroethylene (PTFE) milling vessel and equipped with a 0.8cm PTFE milling ball. DCM (19 µl, 0.29 mmol, 1eq) followed by TMSOTf (52µl, 0.29 mmol, 1eq) was added (molar equivalent "solvent-assisted"). The reactants were shaken in a Retsch MM400

mixer mill at 30 Hz for 5 mins. The desired product was present along with nicotinic acid by-product of the cyclization.

^{1}H-NMR (MeOD, 400MHz) - δ 9.21 (s, IH, aromatic), 8.83-8.87 (m, IH, aromatic), 8.66 (dt, H-1, J-8.0, 1.7 Hz, aromatic), 7.82-7.84 (m, 1H, aromatic), 6.37 (s, 1H, H-1(anomeric)), 5.05 (d, 1H, J=6.0Hz, H-2), 4.99 (d, 1H, J=6.0Hz, H-3), 4.65-4.71 (m, 2H, H-4, H-5), 4.40-4.46 (m, 1H, H-5'), 1.46 (s, 3H, acetonide), 1.33 (s, 3H, acetonide).

^{13}C-NMR (MeOD, 125MHz) - δ 164.2 (CH_2O-C=O), 150.4, 147.9, 146.4, 143.8, 127.3, (aromatic), 121.8 (q, *J*=395.7 Hz, CF_3), 114.5 (acetonide), 105.5 (C-1 (anomeric)), 87.4 (C-4), 86.5 (C-2), 82.3 (C-3), 66.8 (C-5), 26.7 (CH_3-actetonide), 25.0 (CH_3-acetonide).

HMRS (ES, M^+) calculated for $C_{14}H_{16}NO_5$ 278.1028; found 278.1008.

Example 4, Preparation of cyclic –NAR triflate salt (diacetate) **6**
Same procedure as above starting from 1'2' 3'-O-acetate, 5'-O-nicotinate **5**

^{1}H-NMR (MeOD, 400MHz) - δ 9.50 (s, IH, aromatic), 9.21 (d, IH, *J*=6.5 Hz, aromatic), 9.07 (d, 1H, *J*=8.3 Hz, aromatic), 8.21 (dd, 1H, *J*=8.2, 6.4 Hz, aromatic), 6.46 (d, 1H, *J*=4.8 Hz, H-1(anomeric)), 5.48 (dd, 1H, *J*=5.3, 4.8 Hz, H-2), 5.29 (dd, 1H, *J*=5.3, 4.9 Hz, H-3), 5.07 (ABX, J_{ab}=13.3 Hz, J_{ax}= 3.3 Hz, 1H, H-5), 4.98 (ABX, J_{ab}=13.3 Hz, J_{bx}=1.7 Hz, 1H, H-5'), 4.83-4.86 (m, 1H, H-4), 2.07 (s, 3H, C=OC<u>H</u>$_3$), 2.03 (s, 3H, C=OC<u>H</u>$_3$).

HMRS (ES, M^+) calculated for $C_{15}H_{16}NO_7$ 322.0927; found 322.0892.

Example 5: Preparation of cyclic –NARH (diacetate) 1A

$NaHCO_3$ (208 mg, 2.48 mmol, 5 eq) was dissolved in minimal H_2O followed by the addition of sodium dithionite (85%, 203 mg, 0.99 mmol, 2 eq). Cyclic–NAR triflate salt (diacetate) (190 mg, 0.50 mmol, 1 eq) was dissolved in minimal THF and added into the solution and stirred for 3 hrs. Additional $NaHCO_3$ and dithionite (1:1 mol: mol) was added until saturation of the solution and a deep yellow colour resulted. The mixture was extracted with EtOAc (3 x 50 mL) and the organic layer extracted with brine until the fluorine peak representing the triflate counterion was absent by ^{19}F-NMR. The organic layer was then dried over $MgSO_4$, filtered and concentrated under high vacuum to afford cyclic-NARH diacetate **1A** as a yellow oil.

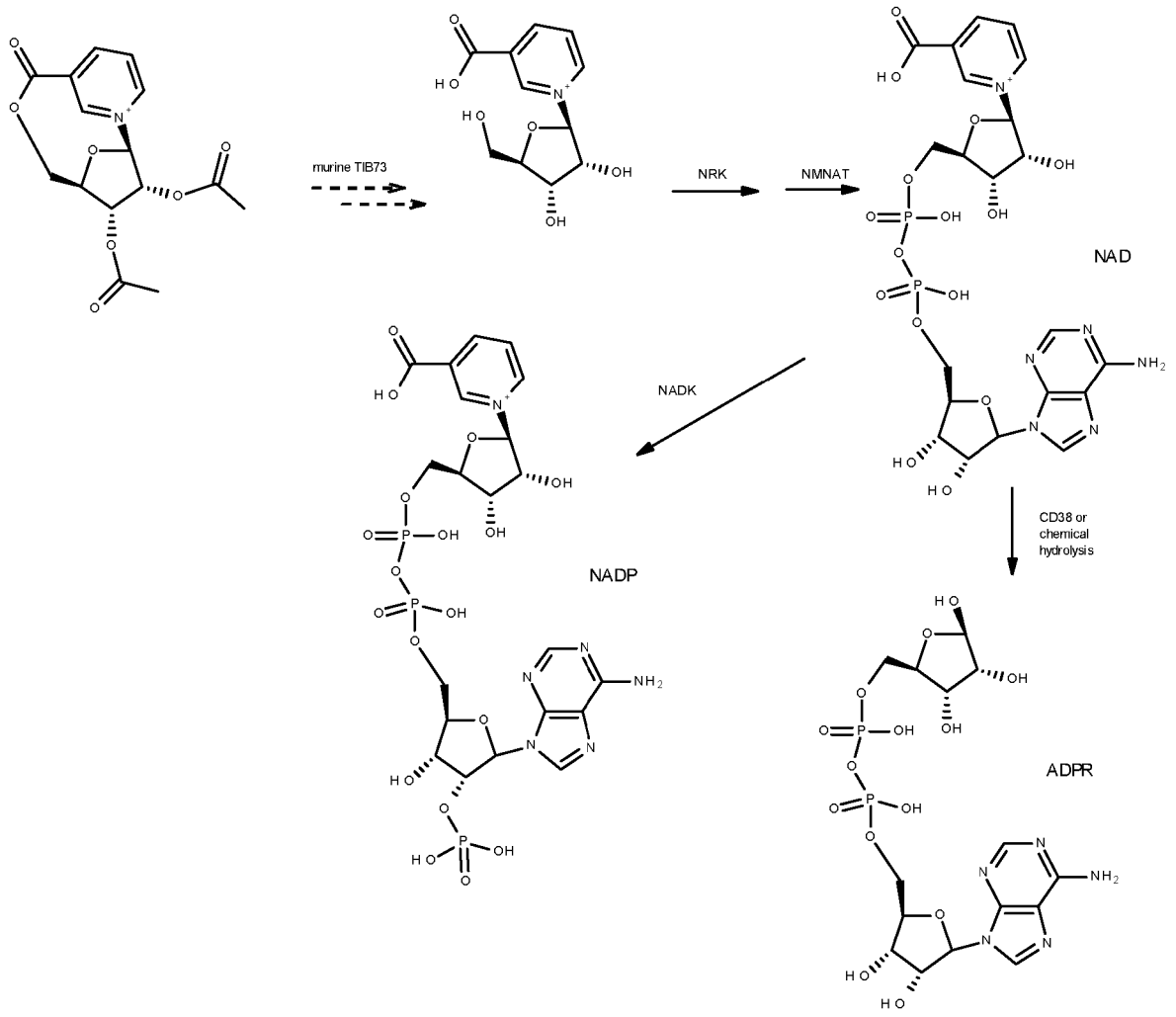
^{1}H-NMR (400MHz, MeOD) δ ppm: 7.23-7.25 (1H, m, N-<u>H</u>C=C-C=O), 5.91 (dq, *J*=8.2, 1.6 Hz, 1H, N-<u>H</u>C=CH), 5.14 (1H, dd, *J*=5.3, 2.3 Hz, H-2 or H-3), 4.89-4.97 (2H, m, H-1, H-2 or H-3), 4.72-4.76 (2H, m, H-5, N-HC=C<u>H</u>), 4.09-4.12 (1H, m, H-4), 3.87 (1H, dd, *J*=12.8, 1.3 Hz, H-5'), 2.98-3.01 (2H, m, N-HC=CH-C<u>H</u>$_2$), 1.99 (s, 3H, OAc), 1.95 (s, 3H, OAc).

^{13}C NMR (125 MHz, MeOD) δ ppm: 171.5, 171.2, 168.5 (2 x O-C=O-CH_3, O=C-O-C), 136.2 (N-HC=C-C=O), 130.9 (N-HC=CH), 105.1 (N-HC=CH), 102.3 (N-HC=C-C=O), 92.3 (C-1), 81.0 (C-4), 71.6, 71.3 (C-2, C-3), 63.9 (C-5), 23.6 (N-HC=CH-CH_2), 20.5, 20.3 (2 x O-C=O-CH_3).

HMRS (ES, M+H^+) calculated for $C_{15}H_{17}NO_7$ 324.1083; found 324.1091.

Example 6, *in vitro* study of lactones in TIB73 (murine cell lines)

The lactone **6** (Example 4) was incubated with TIB73 murine hepatocyte cells for 24hrs. The measurements were performed on the same number of cells and normalised. Over the course of the assay, cyclic NAR diacetate was converted to an active form, proposed to be NAR by deacetylation carried out by non-specific cellular esterases and hydrolysis of the lactone. NAR is then converted to NAD intracellularly via NAMN and NAAD.



Figures 1-4 show that a modest increase in NAD and its phosphorylated NADP was observed over this period. However ADPR, the hydrolysed form of NAD, which can only be produced by the cells from NAD via a range of hydrolases (e.g. CD38) and transferases, such as sirtuin and PARP enzymes was produced in very substantial amount. Of note, Substantial ADPR cannot be produced from the lactone unless NAD is produced from that precursor and NAD becomes more abundant in

cells. Therefore this preliminary cell assay supports the hypothesis that cyclic NAR diacetate **6** enters the murine hepatocyte cells TIB73 and contributes to the NAD metabolome of these cells.

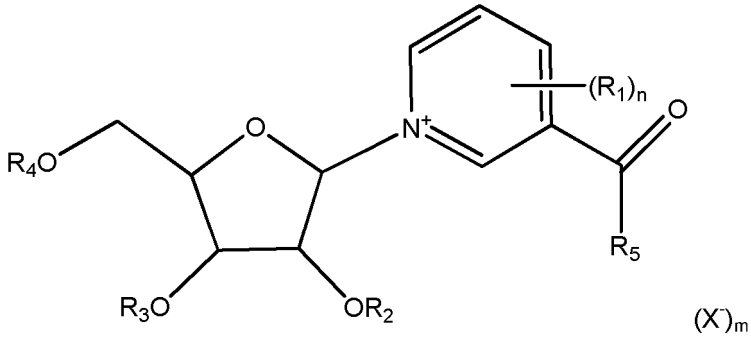
Example 7, *in vitro* study of lactones and NR/NAR like compounds in TIB73 (murine cell lines)

The lactone **6** (Example 4), NR, NAR, TA-NR (triacetate NR) and TA-NAR (triacetate NAR) were incubated with TIB73 murine hepatocyte cells for 24hrs. Figure 5 shows that the lactone **6**, NR, NAR. TA-NR and TA-NAR, which are all NR/NAR like compounds, are responsible for an NAD increase in cells and that the cyclic lactone shares similar properties in terms of raising NAD level in cells, in a similar manner to NR. As discussed above, NR has found its place in science, nutraceuticals and pharmaceuticals potential for its ability of raising NAD in cells. The present invention therefore provides a new scaffold which has a similar ability to NR in raising NAD intracellularly but has the advantages described above.

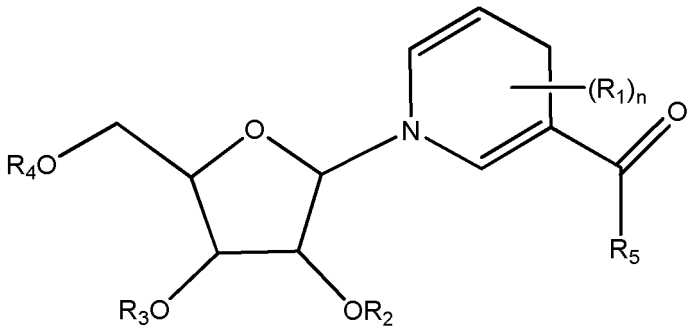
Not wishing to be bound by theory, the timeline indicates that while the NAD boost take place for the lactone **6**, NR and NAR, the cyclic lactone has a different kinetic profile to NR and therefore is likely to increase NAD concentration in cells with a different profile, resulting in different pharmacology (cyclic lactone is a precursor to NAR). NAR releases NAD with a different profile to that of NR and the lactone **6**. The triacetate derivatives demonstrate that triesters are also able to increase NAD levels.

Claims:

1. A method of making a compound of structural formula V or VA:



V or



VA

wherein:

X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate;

each R_1 is independently halide, -CN, $-NO_2$, optionally substituted $(C_1$-$C_8)$aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$;

R_2 and R_3 are each independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted $(C_1$-$C_8)$aliphatic, optionally substituted $(C_3$-$C_8)$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or

R_2 and R_3 join together to form an optionally substituted ring;

R_4 is hydrogen, -

R_5 is $-(Y)_oR''$;

each Y is independently –O-, –S-, or –N-;

each R is independently hydrogen, optionally subsitituted $(C_1$-$C_8)$aliphatic, optionally substituted $(C_3$-$C_8)$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, or optionally substituted heterocycloalky;

each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

R'' is hydrogen, optionally substituted (C_1-C_8) aliphatic, optionally substituted aryl, optionally substituted primary or secondary amino, or optionally substituted azido;

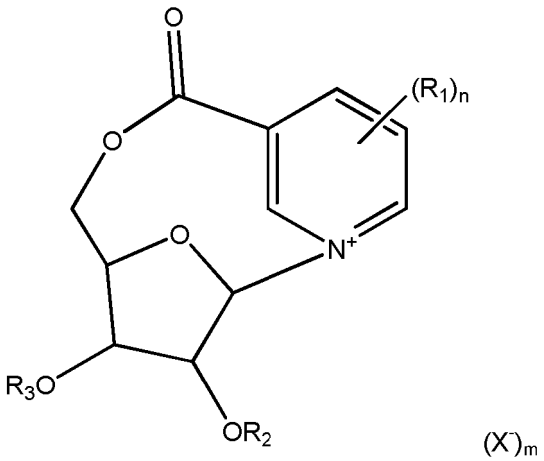
n is 0-4;

m is 0 or 1; and

o is 0 or 1;

the method comprising the steps of:

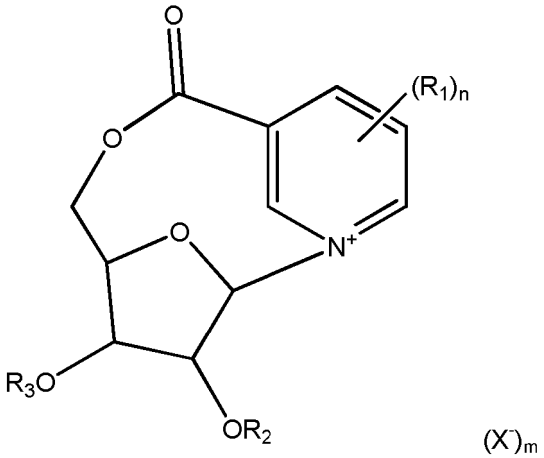
i) decyclizing a compound of structural formula I:



I

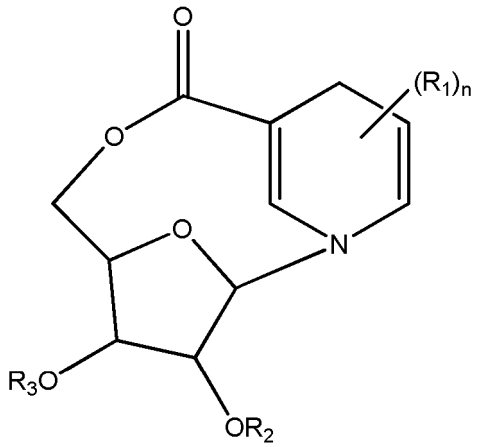
to give the compound of structural formula V; or

i) reducing a compound of structural formula I:



I

to give a compound of structural formula IA:



IA;

and

ii) decyclizing a compound of structural formula IA to give a compound of structural formula VA.

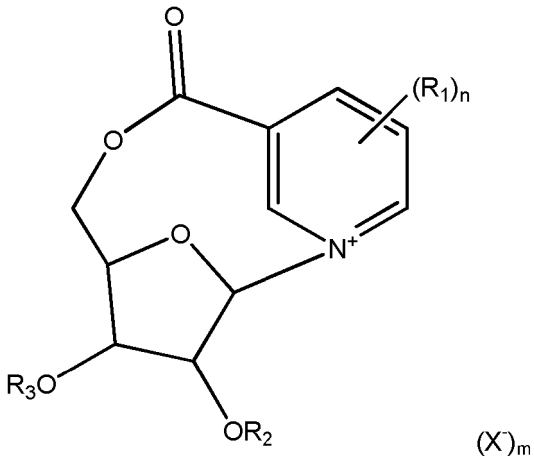
2. The method of Claim 1, wherein the decylizing step takes place in the presence of i) ammonia, potassium carbonate, potassium hydroxide or an amine and ii) an alcohol or water.

3. The method of Claim 2, wherein the alcohol is methanol, ethanol or isopropanol.

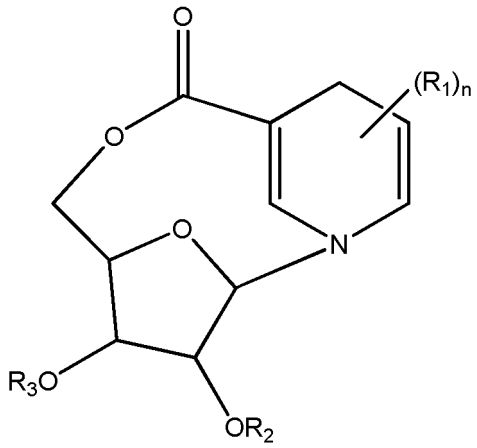
4. The method of Claim 1, wherein the decyclizing step takes place in the presence of i) ammonia, potassium carbonate, potassium hydroxide or an amine and ii) an alcohol comprising an alkoxide version of the alcohol in catalytic amount; or water.

5. The method of any one of Claims 1-4, wherein the reducing step takes place in the presence of i) a solvent selected from dichloromethane, 1,2-dichloroethane, n-butyl acetate, chloroform, ethyl acetate, or any combination thereof, and ii) aqueous sodium dithionite or sodium borohydride.

6. A compound represented by structural formula I or IA:



I



IA;

wherein:

X^- is halide, nitrate, sulfate, acetate, citrate, succinate, aspartate, ascorbate, carbonate, carbamate, formate, gluconate, lactate, malate, phosphate, benzoate, alkyl bromide, alkyl sulfate, alkyl phosphate, diphosphate, triflate, or trifluoroacetate;

each R_1 is independently halide, -CN, $-NO_2$, optionally substituted (C_1-C_8)aliphatic, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^a{}_2$, $-C(O)NR^a{}_2$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^a{}_2$, $-C(O)ONR^a{}_2$, $-OC(O)NR^a{}_2$, $-C(O)NR^aC(O)OR^a$, $-C(=NR^a)R^a$, $-C(=NR^a)NR^a{}_2$, $-NR^aC(=NR^a)NR^a{}_2$, $-OC(O)R^a$, $-OC(O)OR^a$, $-NR^aC(O)OR^a$, $-NR^aSO_2R^a$, $-NR^aSO_2NR^a{}_2$, $-SR^a$, $-S(O)R^a$, $-SO_2R^a$, $-C(O)OSO_2R^a$, $-C(O)OS(O)R^a$, $-C(O)OSR^a$, $-OSO_2R^a$, or $-SO_2NR^a{}_2$;

each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted aralkyl, and optionally substituted heterocycloalkyl; or

R_2 and R_3 join together to form an optionally substituted ring;

each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

each R' is independently hydrogen, (C_1-C_8)aliphatic, (C_3-C_8)cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl;

n is 0-4; and

m is 0 or 1.

7. The compound of Claim 6, wherein:

X^- is triflate, fluoride, chloride, bromide, or iodide;

each R_1 is independently halide, -CN, $-NO_2$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-OR^a$, $-NR^a{}_2$, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^a{}_2$;

each R_2 and R_3 are independently hydrogen, -C(O)R', -C(O)OR', -C(O)NHR', or (C_1-C_8)alkyl; or

R_2 and R_3 join together to form an optionally substituted ring;

each R^a is independently hydrogen, optionally substituted (C_1-C_8)aliphatic, optionally substituted aryl, or optionally substituted heteroaryl; and

each R' is independently hydrogen, or (C_1-C_8)alkyl.

8. The compound of Claim 7, wherein:

X^- is chloride;

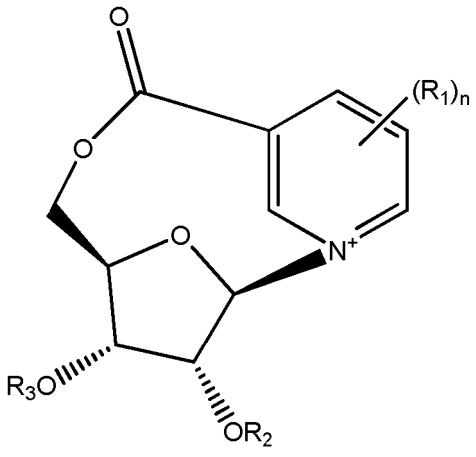
each R_2 and R_3 are -C(O)R'; or

R_2 and R_3 join together to form a ring substituted with R*;

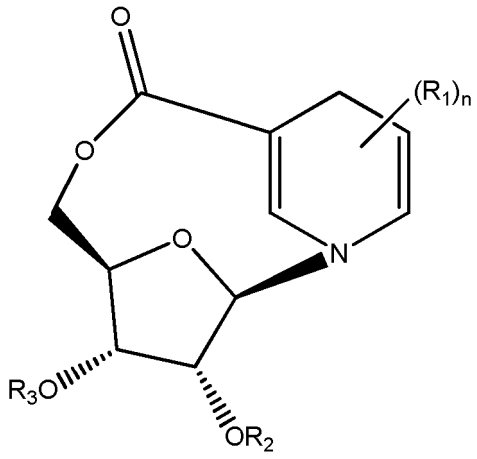
each R' is (C_1-C_8)alkyl; and

R* is (C_1-C_6) alkyl.

9. The compound of any one of Claims 6-8, wherein the compound of structural formula I or IA is:

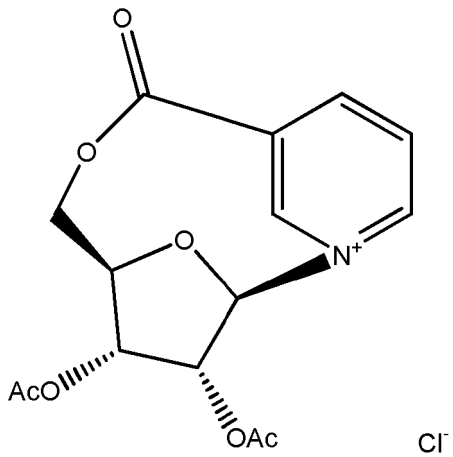


1 or

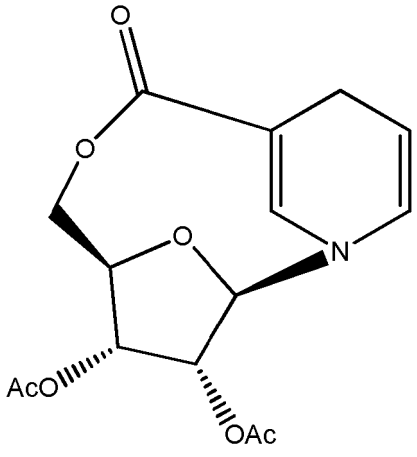


1A .

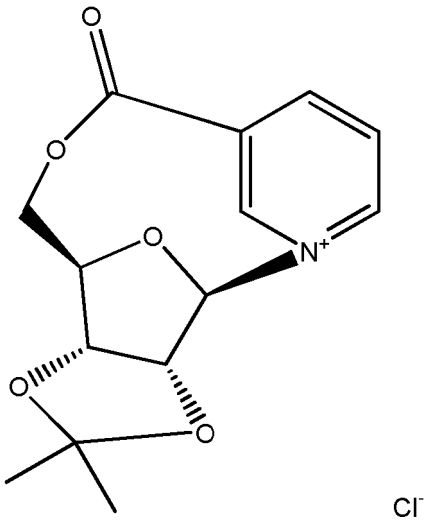
10. The compound of any one of Claims 6-8, wherein the compound of structural formula I or IA is:



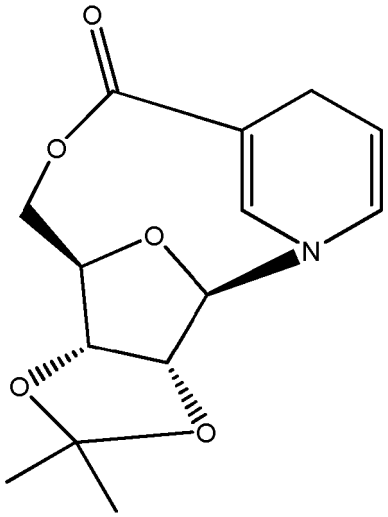
2,



2A,



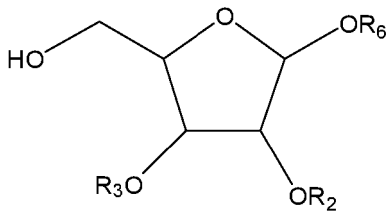
3, or



3A.

11. A method of producing the compound of structural formula I or IA of any one of Claims 6-10, comprising the steps of:

i) contacting a compound of structural formula II:

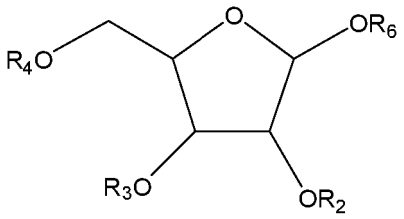


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a_2$, -SR^a ,-SO_2R^a, -SO_2OR^a or -O-P(=O)-$(OR^a)_2$;

with nicotinoyl halide or nicotinoyl anhydride, each of which is optionally substituted with R_1, in the presence of a base, to form a compound of structural formula III:



III

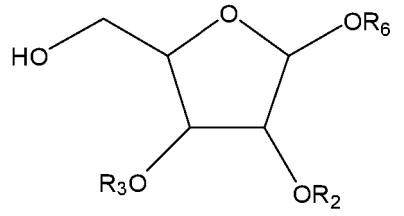
wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$;

R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1);or

contacting a compound of structural formula II:

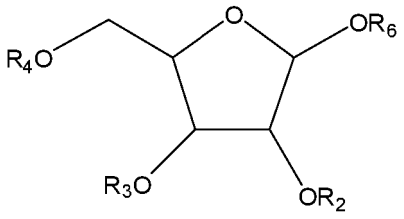


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NR^a{}_2$, -SR^a , -SO_2R^a, SO_2OR^a, or -O-P(=O)-$(OR^a)_2$;

with nicotinic acid, optionally substituted with R_1 in the presence of a coupling agent to generate compound of formula III:



III

wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$;

R_6, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1); and

ii) cyclizing the compound of formula III in the presence of Lewis Acid to form the compound of formula I; and
iii) optionally reducing the compound of formula I to give the compound of formula IA.

12. The method of Claim 11, wherein the Lewis Acid is $SnCl_4$, $TiCl_4$, $GeCl_4$, trimethylsilyl trifluoromethanesulfonate or substituted pyridinium triflate.

13. The method of Claim 11, wherein the Lewis Acid is a metal based Lewis Acid.

14. The method of Claim 13, wherein the metal based Lewis Acid is a silicon based Lewis Acid.

15. The method of Claim 13 or 14, wherein the metal based Lewis Acid is trimethylsilyl trifluoromethanesulfonate.

16. The method of any one of Claims 11-15, wherein:
R_2 and R_3 are -C(O)R'; and
each R' is independently hydrogen, $(C_1$-$C_8)$aliphatic, $(C_3$-$C_8)$cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, or heterocycloalkyl.

17. The method of Claim 16, wherein R_2 and R_3 are -C(O)CH_3.

18. The method of any one of Claims 11-15, wherein R_2 and R_3 join together to form an optionally substituted ring.

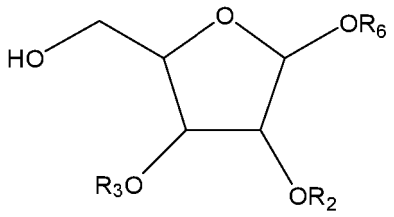
19. The method of Claim 18, wherein R_2 and R_3 join together to form –C$(CH_3)_2$-.

20. The method of any one of Claims 11-19, wherein the cyclization step ii) comprises milling the compound of formula III.

21. The method of any one of Claims 11-19, wherein the cyclization step ii) comprises cyclizing the compound of formula III in the presence of an organic solvent.

22. The method of Claim 21, wherein the organic solvent is dichloroethane (DCE), acetonitrile or dichloromethane (DCM).

23. The method of any one of Claims 11-22, comprising the step of:
i) milling a compound of structural formula II:

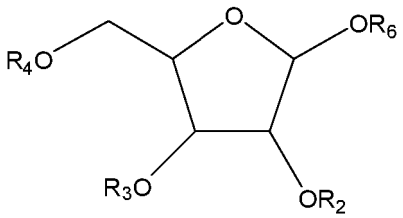


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a ,-SO_2R^a, SO_2OR or -O-P(=O)-$(OR^a)_2$;

with nicotinoyl halide or nicotinoyl anhydride, each of which is optionally substituted with R_1, in the presence of a base for between 1 minutes to 60 minutes at between 5 to 30 Hz, to form a compound of structural formula III:



III

wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -NR^a_2, -$C(O)NR^a_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a_2$, -$C(O)ONR^a_2$, -$OC(O)NR^a_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a_2$, -$NR^aC(=NR^a)NR^a_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a_2$;

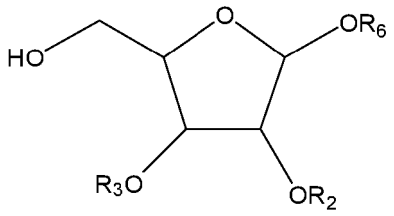
R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1).

24. The method of any one of Claims 11-23, wherein the base is trialkylamine, imidazole, pyridine, or DMAP.

25. The method of any one of Claims 11-23, comprising the step of:

i) contacting a compound of structural formula II:

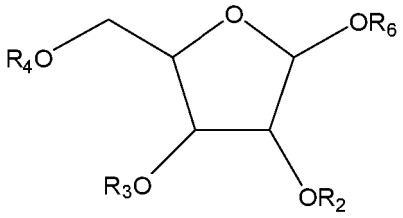


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a ,-SO_2R^a, SO_2OR or -O-P(=O)-$(OR^a)_2$;

with nicotinoyl halide or nicotinoyl anhydride, each of which is optinally substituted with R_1, in the presence of a base and a solvent for between 1 minutes to 60 minutes at between 5 to 30 Hz, to form a compound of structural formula III:



III

wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -NR^a_2, -$C(O)NR^a_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a_2$, -$C(O)ONR^a_2$, -$OC(O)NR^a_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a_2$, -$NR^aC(=NR^a)NR^a_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a_2$;

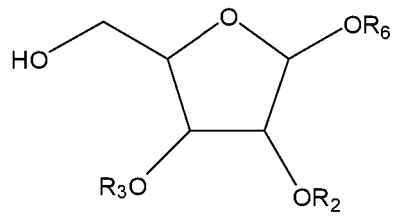
R_6 is -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1).

26. The method of Claim 25, wherein the base is trialkyl amine, imidazole, pyridine, or DMAP.

27. The method of any one of Claims 11-22, comprising the steps of:

i) milling a compound of structural formula II:

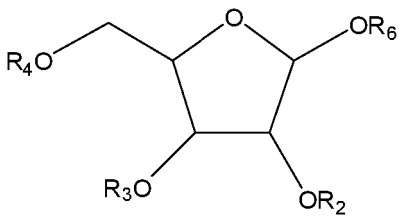


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a , -SO_2R^a, SO_2OR, or -O-P(=O)-$(OR^a)_2$;

with nicotinic acid, optionally substituted with R_1, in the presence of a coupling agent for between 1 minutes to 60 minutes at between 5 to 30 Hz to generate compound of formula III:



III

wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$;

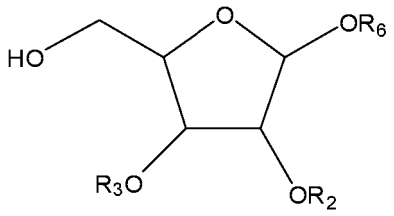
R_6, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1).

28. The method of any one of Claims 11-22 or 26, wherein the coupling agent is HOBT, HATU, HBTU, DCI, or DCC.

29. The method of any one of Claims 11-22, comprising the steps of:

i) contacting a compound of structural formula II:

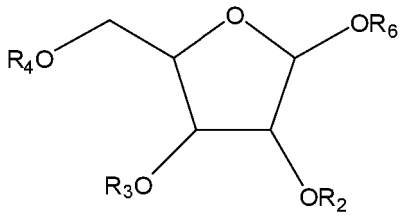


II

wherein:

R_6 is –H, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, -$OC(O)NHR^a$, -SR^a , -SO_2R^a, SO_2OR, or -O-P(=O)-$(OR^a)_2$;

with nicotinic acid, optionally substituted with R_1, in the presence of a coupling agent and a solvent for between 1 minutes to 60 minutes at between 5 to 30 Hz to generate compound of formula III:



III

wherein:

each R_1 is independently halide, -CN, -NO_2, optionally substituted (C_1-C_8)aliphatic, -OR^a, -$C(O)R^a$, -$C(O)OR^a$, -$NR^a{}_2$, -$C(O)NR^a{}_2$, -$NR^aC(O)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^a{}_2$, -$C(O)ONR^a{}_2$, -$OC(O)NR^a{}_2$, -$C(O)NR^aC(O)OR^a$, -$C(=NR^a)R^a$, -$C(=NR^a)NR^a{}_2$, -$NR^aC(=NR^a)NR^a{}_2$, -$OC(O)R^a$, -$OC(O)OR^a$, -$NR^aC(O)OR^a$, -$NR^aSO_2R^a$, -$NR^aSO_2NR^a{}_2$, -SR^a, -$S(O)R^a$, -SO_2R^a, -$C(O)OSO_2R^a$, -$C(O)OS(O)R^a$, -$C(O)OSR^a$, -OSO_2R^a, or -$SO_2NR^a{}_2$;

R_6, -OR^a, -$OC(O)R^a$, -$OC(O)OR^a$, or -$OC(O)NHR^a$; and

R_4 is –CO(pyridyl optionally substituted with R_1).

30. The method of Claim 29, wherein the coupling agent is HOBT, HATU, HBTU, DCI or DCC.

31. A compound of any one of Claims 6-10, for use as a medicament.

32. A compound of any one of Claims 6-10, for use in the treatment of aging, stress, cardiovascular disease, cell death, cancer, metabolic disorder, neuronal disease, blood coagulation disorder, weight control, inflammatory disease, flushing, viral infection, fungal infection, dietary deficiency of vitamin B3, pellagra, pellagra-like condition, vitamin B3 deficiency, or a mitochondrial disease or disorder.

Intellectual Property Office

Application No:	GB1614214.3	**Examiner:**	Dr S. David Evans
Claims searched:	1-32	**Date of search:**	27 June 2017

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A,E	-	WO 2017/079195 A (MITOBRIDGE INC) see the whole document
A,E	-	WO 2017/011788 A (UNIV CORNELL) see the entire document
A,E	-	WO 2016/149395 A (CHROMADEX INC) see the whole document
A	-	WO 2007/061798 A (CORNELL RES FOUNDATION INC) see the entire document
A	-	WO 2015/186068 A (GLAXOSMITHKLINE IP NO 2 LTD) see the whole document
A	-	WO 2015/186114 A (GLAXOSMITHKLINE IP NO 2 LTD) see the entire document
A	-	WO 2015/014722 A (UNIV BELFAST) see the entire document

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

C07H

The following online and other databases have been used in the preparation of this search report

CAS-ONLINE, WPI, EPODOC

Intellectual Property Office

International Classification:

Subclass	Subgroup	Valid From
C07H	0019/048	01/01/2006
A61K	0031/4353	01/01/2006
A61K	0031/4425	01/01/2006
A61P	0003/00	01/01/2006
A61P	0003/02	01/01/2006
A61P	0003/04	01/01/2006
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A61P	0025/28	01/01/2006
A61P	0029/00	01/01/2006
A61P	0031/10	01/01/2006
A61P	0031/12	01/01/2006
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C07H	0019/23	01/01/2006
C07H	0019/24	01/01/2006