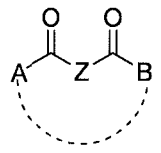
Claims

1. A compound according to Formula (I)

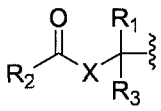


(I)

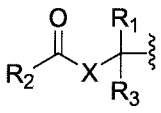
or a pharmaceutically acceptable salt thereof, where the dotted bond denotes an optional bond between A and B to form a cyclic structure, and wherein

Z is selected from $-CH_2-CH_2-$ or $>CH(CH_3)$,

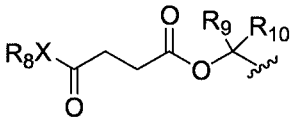
A and B are independently different or the same and are selected from -OR, -O-R', -NHR'', -SR''' or –OH, both A and B are not –OH, wherein R is



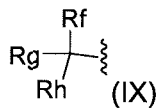
R' is selected from the formula (II), (V) or (IX) below:



(II)

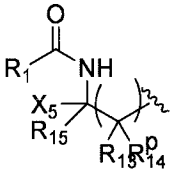


(V)

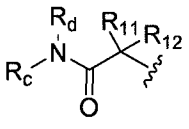


(IX)

R', R'' and R''' are independently different or identical and is selected from formula (VII-VIII) below:

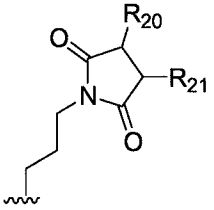


(VII)



(VIII)

R_1 and R_3 are independently different or identical and are selected from H, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, O-acyl, O-alkyl, N-acyl, N-alkyl, Xacyl, CH_2Xalkyl, $CH_2CH_2CH_2OC(=O)CH_2CH_2COX_6R_8$ or



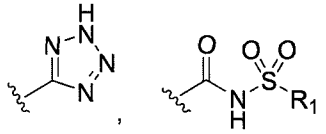
X is selected from O, NH, NR_6, S,

R_2 is selected from Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, $C(O)CH_3$, $C(O)CH_2C(O)CH_3$, $C(O)CH_2CH(OH)CH_3$,

p is an integer and is 1 or 2,

R_6 is selected from H, alkyl, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, acetyl, acyl, propionyl, benzoyl, or formula (II), or formula (VIII)

X_5 is selected from -H, -COOH, $-C(=O)XR_6$,$CONR_1R_3$ or one of the formulas



R_9 is selected from H, Me, Et or $O_2CCH_2CH_2COXR_8$,

R_{10} is selected from Oacyl, NHalkyl, NHacyl, or $O_2CCH_2CH_2CO\ X_6R_8$,

X_6 is O or NR_8, and R_8 is selected from H, alkyl, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, acetyl, acyl, propionyl, benzoyl, or formula (II), or formula (VIII),

R_{11} and R_{12} are independently the same or different and are selected from H, alkyl, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, acetyl, acyl, propionyl, benzoyl, acyl, -CH_2Xalkyl, -CH_2Xacyl, where X is selected from O, NR_6 or S,

R_{13}, R_{14} and R_{15} are independently different or identical and are selected from H, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, -COOH, O-acyl, O-alkyl, N-acyl, N-alkyl, Xacyl, CH_2Xalkyl

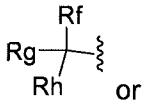
R_c and R_d are independently CH_2Xalkyl, CH_2Xacyl, where X = O, NR_6 or S, and alkyl is e.g. H, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, and acyl is e.g. formyl, acetyl, propionyl, isopropionyl, byturyl, tert-butyryl, pentanoyl, benzoyl or the like,

R_f , Rg and Rh are independently selected from Xacyl, -CH_2Xalkyl, -CH_2X-acyl and R_9,

alkyl is selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, nonyl or decyl, and acyl is selected from formyl, acetyl, propionyl, butyryl pentanoyl, benzoyl and the like,

R_{20} and R_{21} are independently different or identical and are selected from H, lower alkyl, i.e. C_1-C_4 alkyl or R_{20} and R_{21} together may form a C_4-C_7 cycloalkyl or an aromatic group, both of which may optionally be substituted with halogen, hydroxyl or a lower alkyl, or

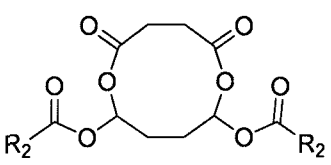
R_{20} and R_{21} may be

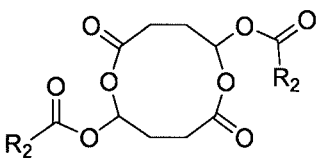


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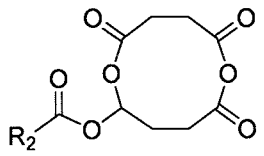
CH_2X-acyl, F, CH_2COOH, CH_2CO_2alkyl, and

when there is a cyclic bond present between A and B the compound is



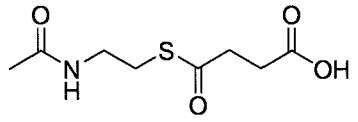
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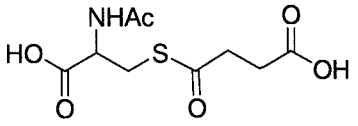
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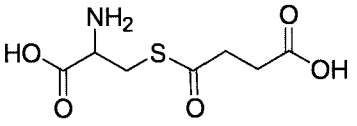


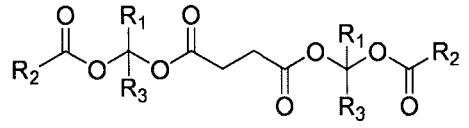
and acyls and alkyls may be optionally substituted,

with the proviso that the compound is not any one of

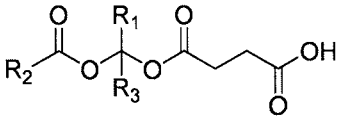




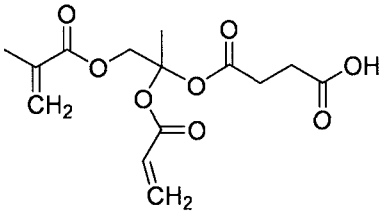


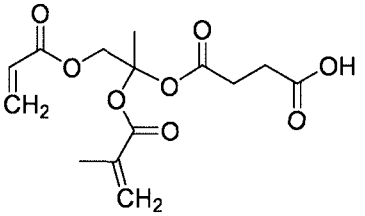


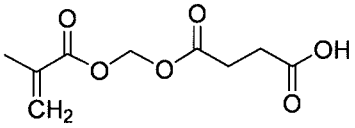
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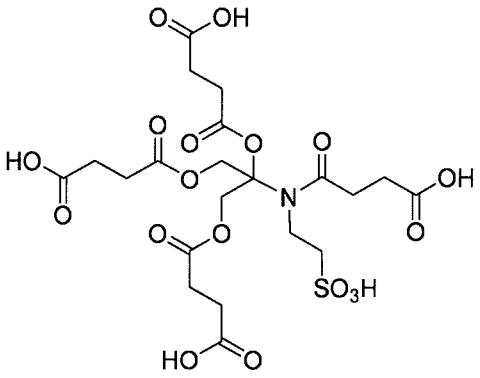


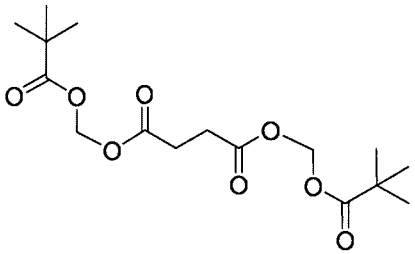
wherein R_2 is Me, Et, i-Pr, t-Bu or cycloalkyl and R_3 is H and R_1 is Me, Et, n-Pr and iso-Pr,

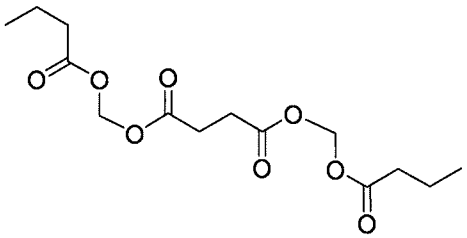


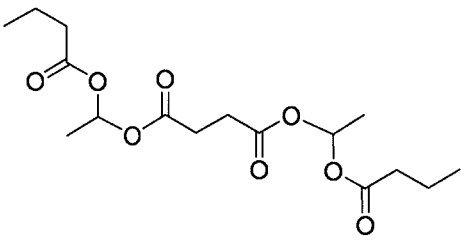


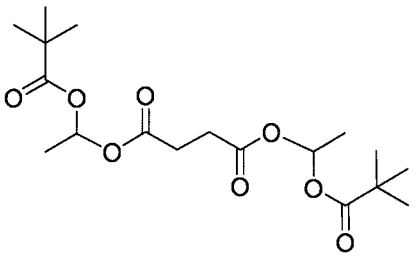


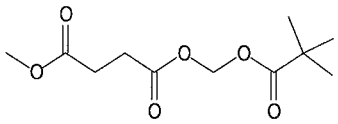


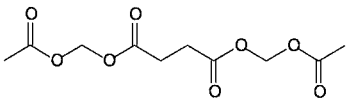


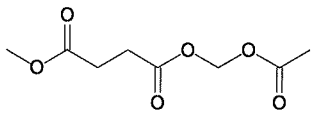


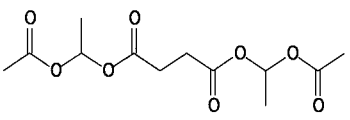


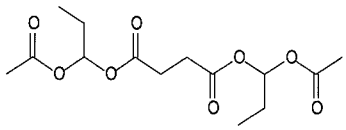


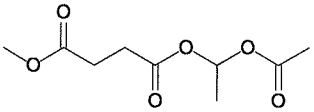


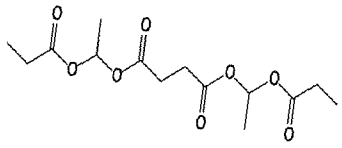


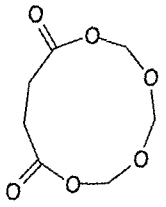


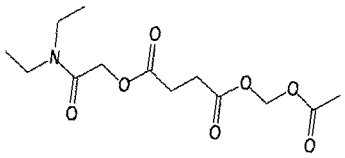


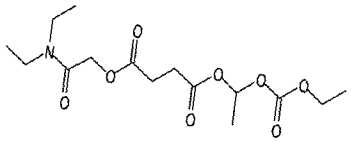


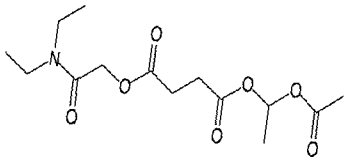


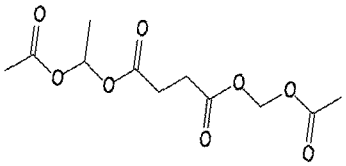


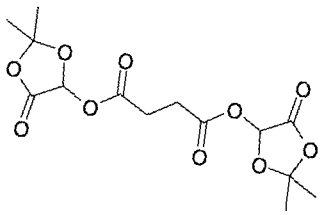


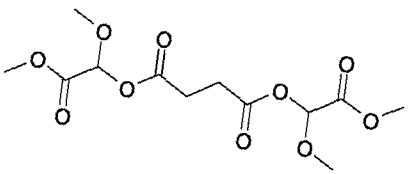


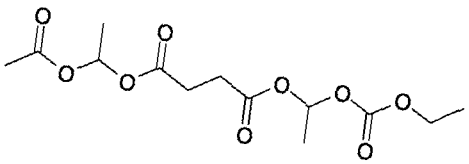


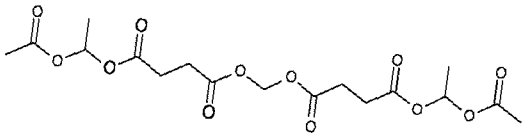


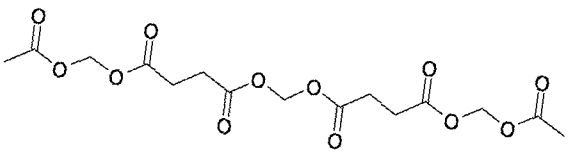


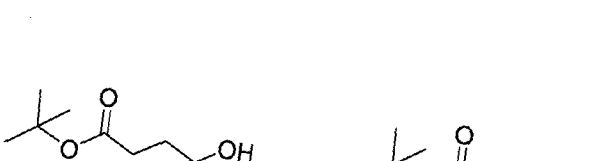


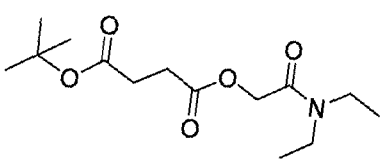


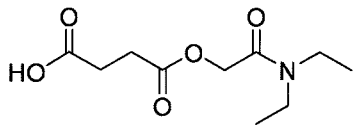


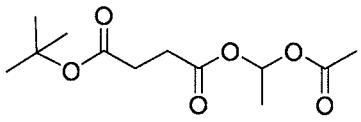


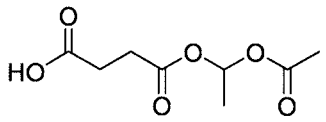


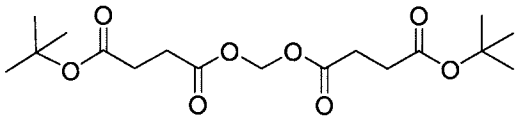


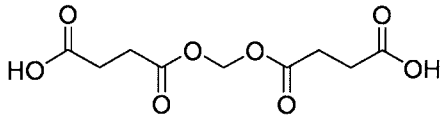


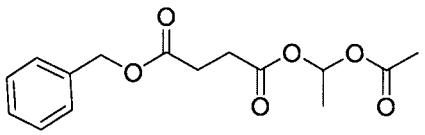


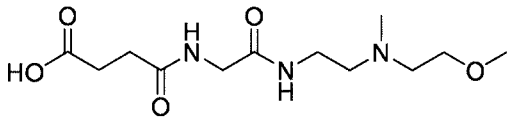




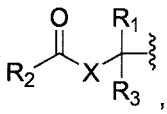








2. A compound according to claim 1, wherein Z is selected from $-CH_2-CH_2-$ or $>CH(CH_3)$, A is -selected from -O-R, wherein R is

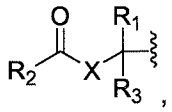


B is selected from -O-R', -NHR'', -SR''' or -OH; wherein R' is selected from the formula (II), (V) or (IX) above, R', R'' and R''' are independently different or identical and are selected from formula (VII) or (VIII) above.

3. A compound according to claim 1 or 2, wherein Z is $-CH_2CH_2-$ and A is –OR.

4. A compound according to any of the preceding claims, wherein A is –OR, and B is selected from -OR', -NHR'', -SR''' or -OH; and R', R', R'' and R''' being as described above.

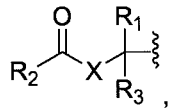
5. A compound according to any of the preceding claims, wherein A is selected from -O-R, wherein R is



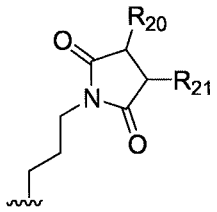
and R_1 or R_3 is $CH_2CH_2CH_2OC(=O)CH_2CH_2COX_6R_8$, and B is –OR' or -OH.

6. A compound according to any of claims 1-4, wherein A is –OR, and B is –OH or –OR', and wherein R' is selected from formula (VII) or formula (VIII) as defined above.

7. A compound according to any of claims 1-4, wherein A is selected from -O-R, wherein R is



and R_1 or R_3 is

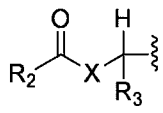


and B is –OR' or –OH.

8. A compound according to any of the preceding claims, wherein Z is $-CH_2CH_2-$.

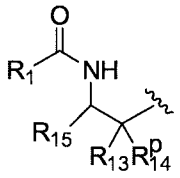
9. A compound according to any of the preceding claims, wherein Z is $-CH_2CH_2-$ and A is –OR and B is –OH.

10. A compound according to any of the preceding claims, wherein A is –OR and R is formula (II):



(II).

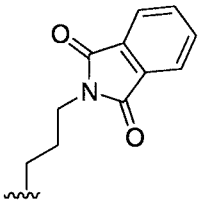
11. A compound according to any of the preceding claims, wherein formula (VII) is



(VII)

12. A compound according to any of the preceding claims, wherein at least one of R_f, R_g, R_h in formula (IX) is –H or alkyl, with alkyl as defined herein.

13. A compound according to any of the preceding claims, wherein A is –OR and R_1 or R_3 is



or R_1 or R_3 is $CH_2CH_2CH_2OC(=O)CH_2CH_2COX_6R_8$.

14. A compound according to any of claims 1-13 for use in medicine.

15. A compound according to any of claim 1-13, for use in cosmetics.

16. A compound according to any of claims claim 1-13 for use in the treatment of or prevention of metabolic diseases, or in the treatment of diseases of mitochondrial dysfunction or disease related to mitochondrial dysfunction, treating or suppressing of mitochondrial disorders, stimulation of mitochondrial energy production, treatment of cancer and following hypoxia, ischemia, stroke, myocardial infarction, acute angina, an acute kidney injury, coronary occlusion and atrial fibrillation, or to avoid or counteract reperfusion injuries.

17. A compound according for use according to claim 16, wherein the medical use is prevention or treatment of drug-induced mitochondrial side-effects.

18. A compound for use according to claim 17, wherein the prevention or drug –induced mitochondrial side-effects relates to drug interaction with Complex I, such as e.g. metformin-Complex I interaction.

19. A compound according to claim 17, wherein diseases of mitochondrial dysfunction involves e.g. mitochondrial deficiency such as a Complex I, II, III or IV deficiency or an enzyme deficiency like e.g. pyruvate dehydrogenase deficiency.

20. A compound for use according to any of claims 16-19, wherein the diseases of mitochondrial dysfunction or disease related to mitochondrial dysfunction are selected from Alpers Disease (Progressive Infantile Poliodystrophy, Amyotrophic lateral sclerosis (ALS), Autism, Barth syndrome (Lethal Infantile Cardiomyopathy), Beta-oxidation Defects, Bioenergetic metabolism deficiency, Carnitine-Acyl-Carnitine Deficiency, Carnitine Deficiency, Creatine Deficiency Syndromes (Cerebral Creatine Deficiency Syndromes (CCDS) includes: Guanidinoaceteate Methyltransferase Deficiency (GAMT Deficiency), L-Arginine:Glycine Amidinotransferase Deficiency (AGAT Deficiency), and SLC6A8-Related Creatine Transporter Deficiency (SLC6A8 Deficiency), Co-Enzyme Q10 Deficiency Complex I Deficiency (NADH dehydrogenase (NADH-CoQ reductase deficiency), Complex II Deficiency (Succinate dehydrogenase deficiency), Complex III Deficiency (Ubiquinone-cytochrome c oxidoreductase deficiency), Complex IV Deficiency/COX Deficiency (Cytochrome c oxidase deficiency is caused by a defect in Complex IV of the respiratory chain), Complex V Deficiency (ATP synthase deficiency), COX Deficiency, CPEO (Chronic Progressive External Ophthalmoplegia Syndrome), CPT I Deficiency, CPT II Deficiency, Friedreich's ataxia (FRDA or FA), Glutaric Aciduria Type II, KSS (Kearns-Sayre Syndrome), Lactic Acidosis, LCAD (Long-Chain Acyl-CoA Dehydrogenase Deficiency), LCHAD, Leigh Disease or Syndrome (Subacute Necrotizing Encephalomyelopathy), LHON (Leber's hereditary optic neuropathy), Luft Disease, MCAD (Medium-Chain Acyl-CoA Dehydrogenase Deficiency), MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Strokelike Episodes), MERRF (Myoclonic Epilepsy and Ragged-Red Fiber Disease), MIRAS (Mitochondrial Recessive Ataxia Syndrome), Mitochondrial Cytopathy, Mitochondrial DNA Depletion, Mitochondrial Encephalopathy including: Encephalomyopathy and Encephalomyelopathy, Mitochondrial Myopathy, MNGIE (Myoneurogastointestinal Disorder and Encephalopathy, NARP (Neuropathy, Ataxia, and Retinitis Pigmentosa), Neurodegenerative disorders associated with Parkinson's, Alzheimer's or Huntington's disease, Pearson Syndrome, Pyruvate Carboxylase Deficiency, Pyruvate Dehydrogenase Deficiency, POLG Mutations, Respiratory Chain Deficiencies, SCAD (Short-Chain Acyl-CoA Dehydrogenase Deficiency), SCHAD, VLCAD (Very Long-Chain Acyl-CoA Dehydrogenase Deficiency).

21. A compound for use according to claim 20, wherein the mitochondrial dysfunction or disease related to mitochondrial dysfunction is attributed to complex I dysfunction and selected from Leigh Syndrome, Leber's hereditary optic neuropathy (LHON), MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers).

22. A composition comprising a compound of Formula (I) as defined according any of claims 1-13 and one or more pharmaceutically or cosmetically acceptable excipients.

23. Use of a composition as defined in claim 22 in the manufacture of a medicament for the treatment of or prevention of metabolic diseases, or in the treatment of diseases of mitochondrial dysfunction or disease related to mitochondrial dysfunction as defined in any of claims 20-21.

24. The use according to claim 23 wherein the medicament is administered parenterally, orally, topically (including buccal, sublingual or transdermal), via a medical device (e.g. a stent), by inhalation or via injection (subcutaneous or intramuscular)

25. The use according to any of claims 23-24, wherein the medicament is administered as a single dose or a plurality of doses over a period of time, such as e.g. one daily, twice daily or 3-5 times daily as needed.

26. A compound according to any of claims 1-13 for use in the treatment or prevention of lactic acidosis.

27. A compound according to any of claims 1-13 for use in the treatment or prevention of a drug-induced side-effect selected from lactic acidosis and side-effects related to Complex I defect, inhibition or malfunction.

28. A compound according to any of claims 1-13 for use in the treatment or prevention of a drug-induced side-effect selected from lactic acidosis and side-effects related to defect, inhibition or mal-function in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and drugs that affect the levels of glucose or other Complex I-related substrates).

29. A combination of a drug substance and a compound according to any of claims 1-13 for use in the treatment and/or prevention of a drug-induced side-effect selected from i) lactic acidosis, ii) side-effects related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and drugs that affect the levels of glucose or other Complex-I-related substrates), wherein

i) the drug substance is used for treatment of a disease for which the drug substance is indicated, and

ii) the succinate prodrug is used for prevention or alleviation of the side effects induced or inducible by the drug substance, wherein the side-effects are selected from lactic acidosis and side-effects related to a Complex I defect, inhibition or malfunction.

30. A composition comprising a drug substance and a compound according to any of claims 1-13, wherein the drug substance has a potential drug-induced side-effect selected from i) lactic acidosis, ii) side-effects related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and even drugs that affect the levels of glucose or other Complex-I-related substrates).

31. A kit comprising:

i) a first container comprising a drug substance, which has a potential drug-induced side-effect selected i) from lactic acidosis, ii) and side-effects related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and even drugs that affect the levels of glucose or other substrates), and

ii) a second container comprising a compound according to any of claims 1-13, which has the potential for prevention or alleviation of the side effects induced or inducible by the drug substance, wherein the side-effects are selected from i) lactic acidosis, ii) side-effects related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and even drugs that affect the levels of glucose or other substrates).

32. Use of an effective amount of a compound according to any of claims 1-13 in the manufacture of a medicament for the treatment and/or prevention of a drug-induced side-effect selected from i) lactic acidosis, ii) side-effect related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis,

beta-oxidation, pyruvate metabolism and even drugs that affect the levels of glucose or other substrates) in a subject.

33. Use of an effective amount of a compound according to any of claims 1-13 in the manufacture of a medicament for the treatment, prevention or alleviation of a drug-induced side-effect selected from i) lactic acidosis, ii) side-effect related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I (indirect inhibition of Complex I, which would encompass any drug effect that limits the supply of NADH to Complex I, e.g. effects on Krebs cycle, glycolysis, beta-oxidation, pyruvate metabolism and even drugs that affect the levels of glucose or other substrates) in a subject, who is suffering from a disease that is treated with a drug substance, which potentially induce a side-effect selected from i) lactic acidosis, ii) side-effect related to a Complex I defect, inhibition or malfunction, and iii) side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of Complex I, such as in dehydrogenases of Kreb's cycle, pyruvate dehydrogenase and fatty acid metabolism.

34. The use according to claim 33, wherein the drug substance is an anti-diabetic substance.

35. The use according to any one of claims 33-34, wherein the anti-diabetic substance is metformin.

36. A compound according to any of claims 1-13, for use in the treatment of absolute or relative cellular energy deficiency.