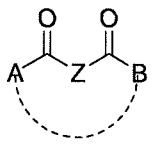
Claims

1. A compound according to the invention is given by Formula (I)

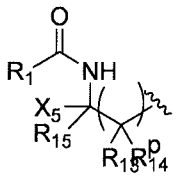


(I)

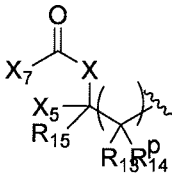
or a pharmaceutically acceptable salt thereof, wherein the dotted bond between A and B denotes an optional bond so as to form a ring closed structure, and wherein

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

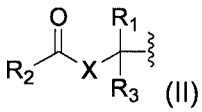
A is selected from -SR, -OR and NHR, and R is



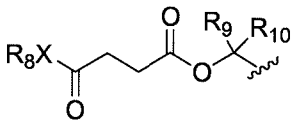
or



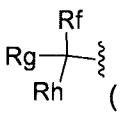
B is selected from -O-R', -NHR'', -SR''' or -OH; and R' is selected from the formula (II) to (IX) below:



(II)

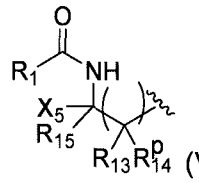


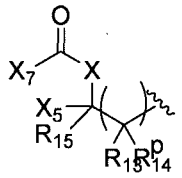
(V)

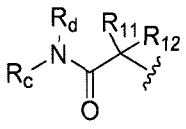


(IX)

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


(VII) or




(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_2X-acyl, F, CH_2COOH, CH_2CO_2alkyl,

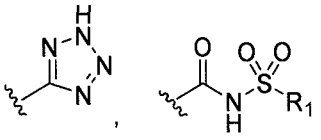
X is selected from O, NH, NR_6, S,

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, 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, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, -COOH, -$C(=O)XR_6$, , $CONR_1R_3$ or is formula



X_7 is selected from R_1, $-NR_1R_3$,

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

R_{10} is selected from Oacyl, NHalkyl, NHacyl, or $O_2CCH_2CH_2COX_6R_8$

X_6 is selected from O, NR_8, NR_6R_8, wherein R_6 and R_8 are independently different or identical and are 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 different or identical and are selected from H, Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl, acetyl, propionyl, benzoyl, -CH_2Xalkyl, -CH_2Xacyl, where X is O, NR_6 or S,

R_c and R_d are independently different or identical and are selected from CH_2Xalkyl, CH_2Xacyl, where X = 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;

Substituents on R13 and R14 or R13 and R15 may bridge to form a cyclic system,

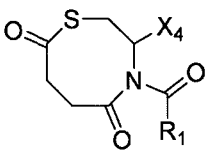
R_f , R_g and R_h are independently different or identical and are selected from Xacyl, -CH_2Xalkyl, -CH_2X-acyl and R_9,

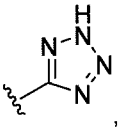
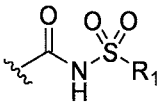
alkyl is selected from Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl,

acyl is selected from formyl, acetyl, propionyl, isopropionyl, byturyl, tert-butyryl, pentanoyl, benzoyl,

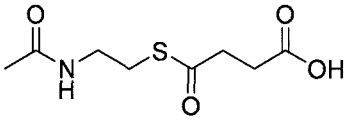
acyl and/or alkyl may be optionally substituted, and

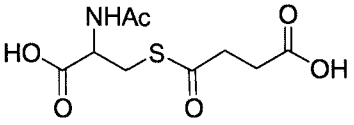
when the dotted bond between A and B is present, the compound according to formula (I) is

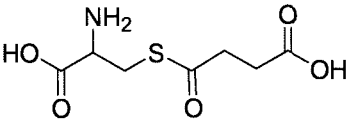


wherein X_4 is selected from –COOH, -C(=O)XR_6,  , 

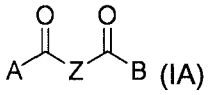
with the proviso that the compound is not

 or





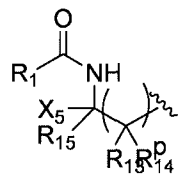
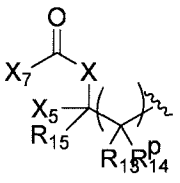
2. A compound according to claim 1 having Formula (IA)

 (IA)

or a pharmaceutically acceptable salt thereof, wherein thereof, wherein

Z is $–CH_2-CH_2-$,

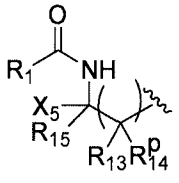
A is selected from -SR, -OR and NHR, and R is

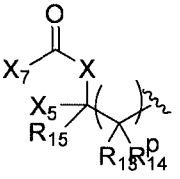
or

B is selected from -O-R', -NHR'', -SR''' or -OH; and

R', R'' and R''' are independently different or identical and is selected from one or the formulas below:


(VII)

or



R_1 and R_3 are independently different or identical and are selected from H, Me, Et, propyl, O-Me, O-Et, O-propyl,

X is selected from O, NH, S,

p is an integer and is 1,

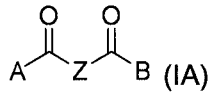
R_6 is selected from H, Me, Et,

X_5 is selected from -H, Me, Et, -COOH, $-C(=O)XR_6$, , $CONR_1R_3$

X_7 is selected from R_1, $-NR_1R_3$,

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, wherein alkyl and acyl are as defined herein before.

3. A compound according to claim 1 or 2 having Formula (IA)

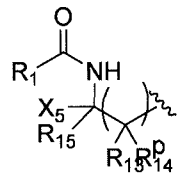


(IA)

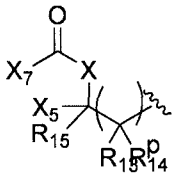
or a pharmaceutically acceptable salt thereof, wherein

Z is $-CH_2-CH_2-$,

A is selected from -SR, -OR and NHR, and R is

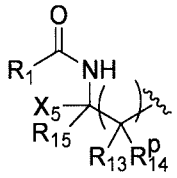


or



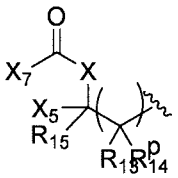
B is selected from -O-R', -NHR'', -SR''' or -OH; and

R', R'' and R''' are independently different or identical and is selected from one or the formulas below:



(VII)

or



R_1 and R_3 are independently different or identical and are selected from H, Me, Et, propyl, O-Me, O-Et, O-propyl,

X is selected from O, NH, S,

p is an integer and is 1,

R_6 is selected from H, Me, Et,

X_5 is selected from -H, Me, Et, -COOH, $-C(=O)OR_6$, , $CONR_1R_3$,

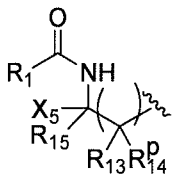
X_7 is selected from R_1, $-NR_1R_3$,

R_{13}, R_{14} and R_{15} are independently different or identical and are selected from H, Me, Et, -COOH.

4. A compound according to any one of the preceding claims, wherein Z is $-CH_2CH_2-$ and A is -SR.

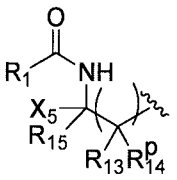
5. A compound according to any one of the preceding claims, wherein Z is $-CH_2CH_2-$, A is -SR, and B is OH or SR'''.

6. A compound according to any one of the preceding claims, wherein Z is $-CH_2CH_2-$, A is -SR, B is OH or SR''', where R''' is

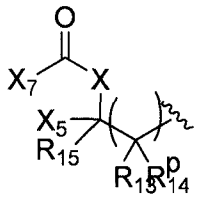


7. A compound according to any one of the preceding claims, wherein Z is $-CH_2CH_2-$ and A is SR and B is OH.

8. A compound according to any one of claims 1-6, wherein Z is $-CH_2CH_2-$, A is SR, B is OH or SR''', where R''' is

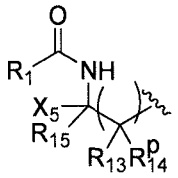


9. A compounds according to any one of claims 1-3, wherein Z is $-CH_2CH_2-$, A is NR, B is OH and R is

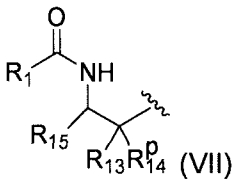


and X is S.

10. A compound according to any of the preceding claims, wherein R and/or R''' is

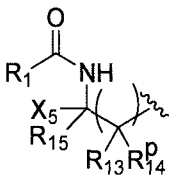


and p=1 and X_5 is –H such that formula (VII) is

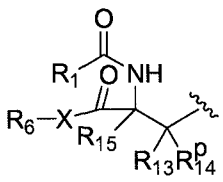


(VII)

11. A compound according to any of claims 1-9, wherein R and/or R''' is

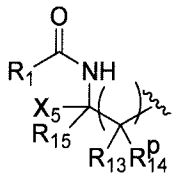


and p=1 and X_5 is $COXR_6$ such that formula (VII) is

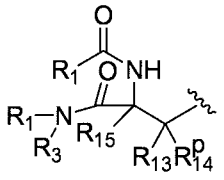


(VII)

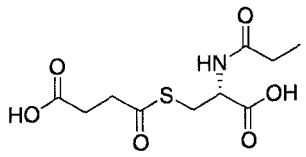
12. A compound according to any of claims 1-9, wherein R and/or R''' is

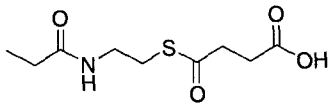

(VII)

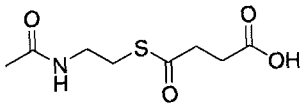
and p=1 and X_5 is $CONR_1R_3$ such that formula (VII) is

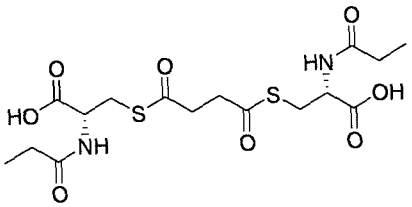

(VII)

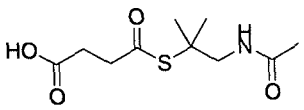
13. A compound according to any one of the preceding claims, wherein the compound is selected from:

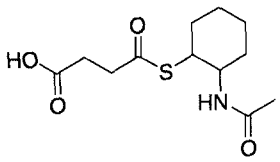


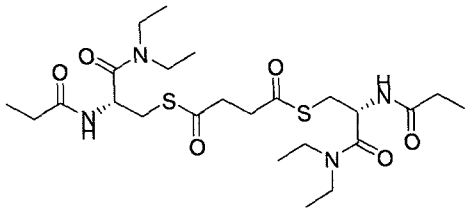


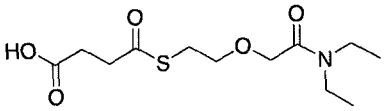


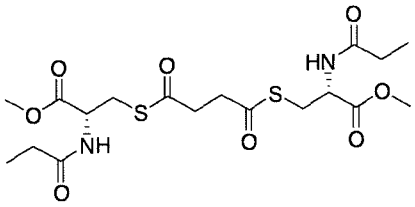


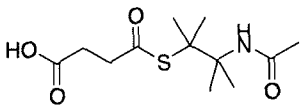


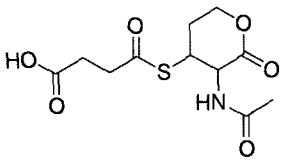


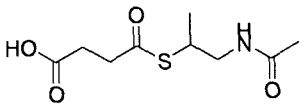


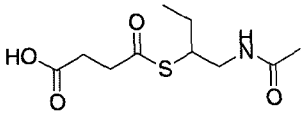


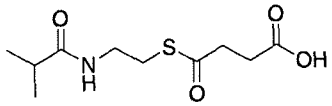


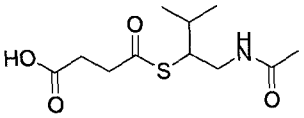


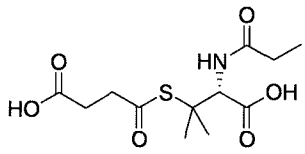


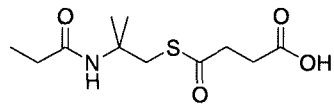


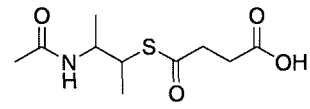


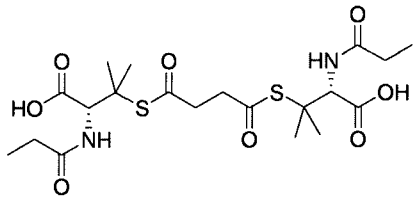


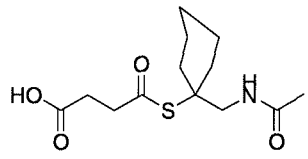


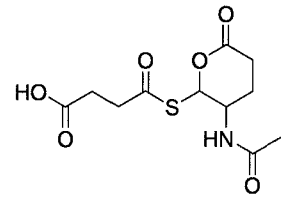


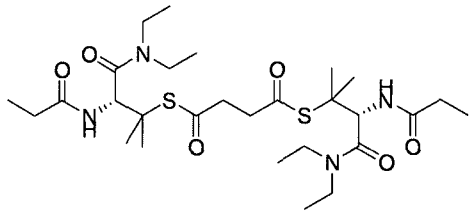


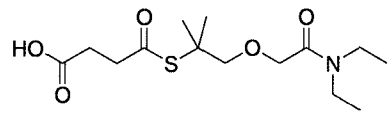


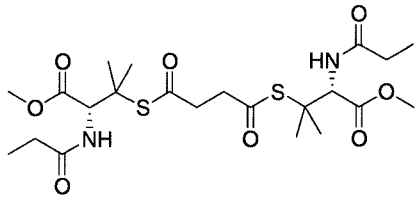


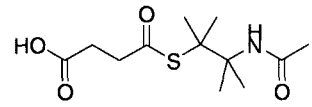


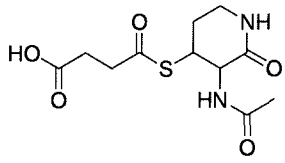


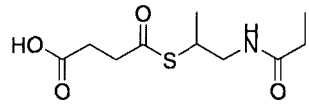


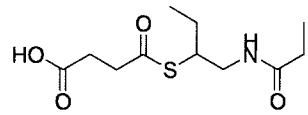


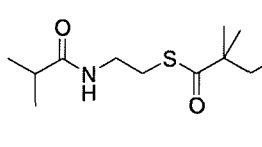


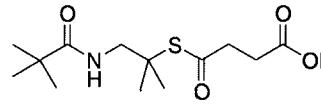


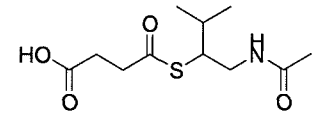


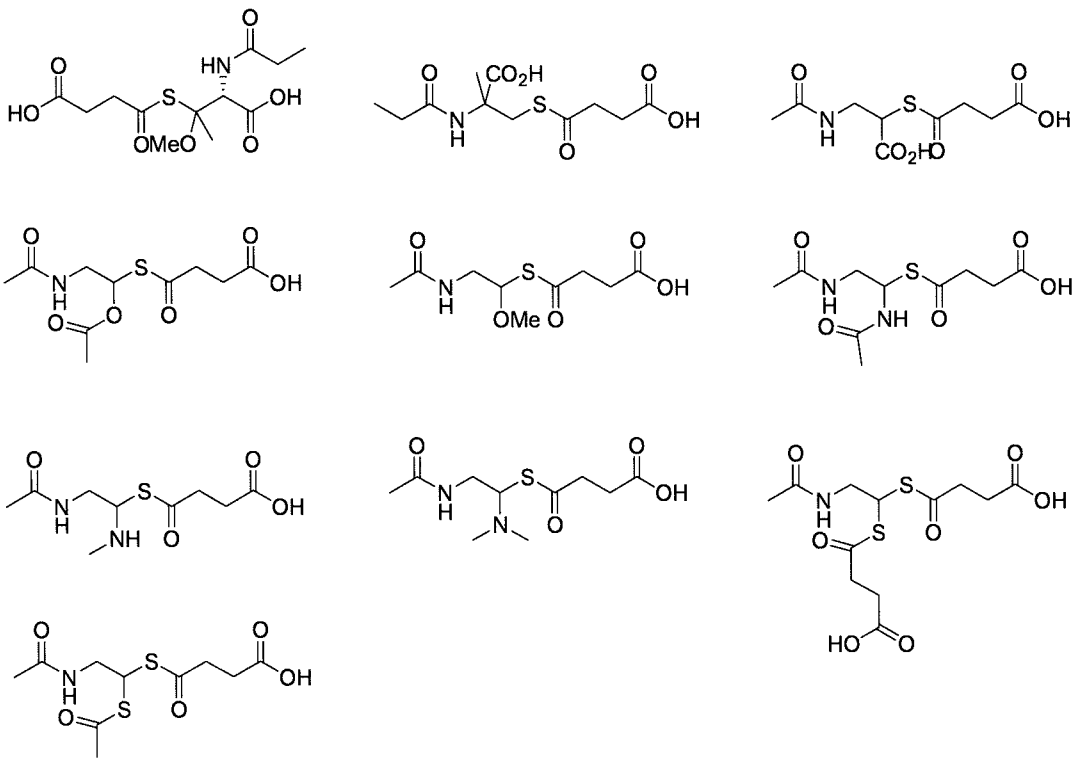












14. A compound according to any of claims 1-13 for use in medicine.

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

16. A compound according to any of claims 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 14, 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 16, wherein diseases of mitochondrial dysfunction or disease related to 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 diseases of mitochondrial dysfunction or disease related to mitochondrial dysfunction as defined in any of claims 19-21 in a subject.

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) 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 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 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 drug substance is an anti-diabetic substance, which is metformin.

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