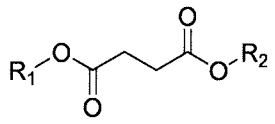
Claims

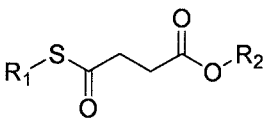
1. A succinate prodrug for use in the treatment or prevention of lactic acidosis.

2. A succinate prodrug 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.

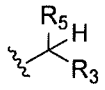
3. A succinate prodrug for use in the treatment or prevention of a drug-induced side-effect selected from lactic acidosis and side-effects related to defect, inhibition or malfunction in aerobic metabolism upstream of complex I.

4. A succinate prodrug for use according to any one of claims 1-3, wherein the compound has Formula (A) or (A1)

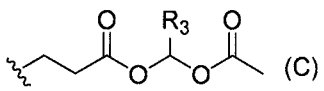

(A)


(A1)

wherein R_1 and R_2 are same or different and selected from formula (B)

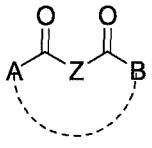

(B)

and wherein the drug-induced mitochondrial side effect is Complex I inhibition and wherein R_3 is selected from H, or optionally substituted C_1-C_3 alkyl such as e.g. methyl, ethyl, propyl or iso-propyl and wherein R_5 is $-OC(=O)R_a$, wherein R_a is methyl or formula (C)


(C)

5. A succinate prodrug for use according to claim 4, wherein R_1 and R_2 are same or different and selected from formula (B), wherein R_3 is H or methyl and R_a is methyl or formula (C).

6. A protected succinate prodrug for use according to any of claims 1-4, wherein the compound is given by Formula (I)

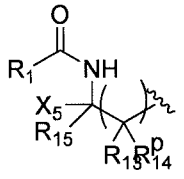


(I)

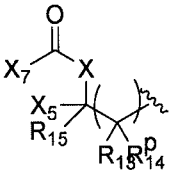
or a pharmaceutically acceptable salt thereof, wherein the dotted bond between A and B denotes an optional bond so as to form a ring closed structure, and wherein

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

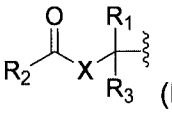
A is selected from -SR, -OR and NHR, and R is



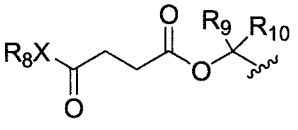
or



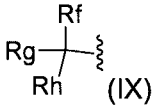
B is selected from -O-R', -NHR'', -SR''' or -OH; and R' is selected from the formula (II) to (IX) below:



(II)

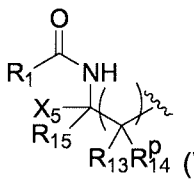


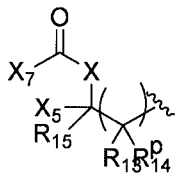
(V)

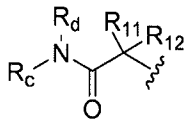


(IX)

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,

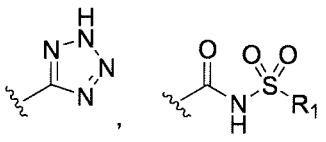
X is selected from O, NH, NR_6, S,

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 R_{13} and R_{14} or R_{13} and R_{15} may bridge to form a cyclic system,

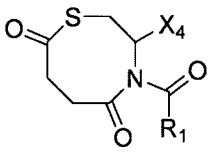
R_f , R_g and R_h are independently different or identical and are selected from Xacyl, -CH_2Xalkyl, -CH_2X-acyl and R_9,

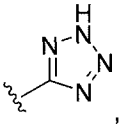
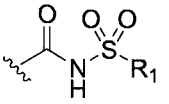
alkyl is selected from Me, Et, propyl, i-propyl, butyl, iso-butyl, t-butyl,

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

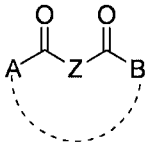
acyl and/or alkyl may be optionally substituted, and

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,  , 

7. A compound for use according to any of claims 1-3 having Formula (I)

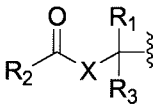


(I)

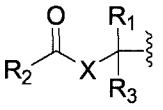
or a pharmaceutically acceptable salt thereof, where the dotted bond denotes an optional bond between A and B to form a cyclic structure, and wherein

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

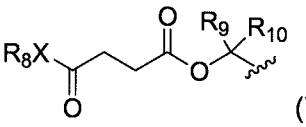
A and B are independently different or the same and are selected from -OR, -O-R', -NHR'', -SR''' or –OH, both A and B are not –OH, wherein R is



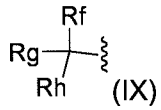
R' is selected from the formula (II), (V) or (IX) below:



(II)

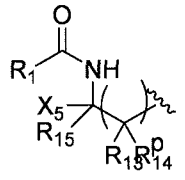


(V)



(IX)

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

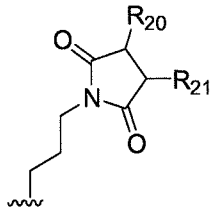


(VII)



(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



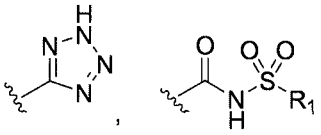
X is selected from O, NH, NR_6, S,

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,

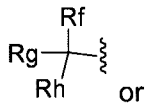
R_f , Rg and Rh are independently selected from Xacyl, $-CH_2Xalkyl$, $-CH_2X$-acyl and R_9,

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

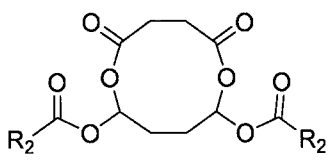
R_{20} and R_{21} may be



or

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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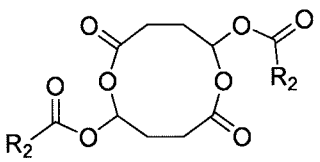

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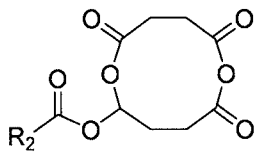

and acyls and alkyls may be optionally substituted.

8. A combination of a drug substance and a succinate prodrug 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, 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.

9. A combination according to claim 8, wherein the succinate prodrug has the formula as defined in any one of claims 4-7.

10. A combination according to claim 8 or 9, wherein the drug substance is as defined herein.

11. A combination according to any one of claims 8-10, wherein the drug substance is an anti-diabetic substance.

12. A combination according to any of claims 8-11, wherein the anti-diabetic substance is metformin.

13. A composition comprising a drug substance and a succinate prodrug, 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.

14. A composition according to claim 13, wherein the succinate prodrug is used for prevention or alleviation of 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.

15. A composition according to claim 13 or 14 wherein the succinate prodrug has the formula as defined in claim 4 or 5.

16. A composition according to any one of claims 13-15, wherein the drug substance is as defined herein.

17. A composition according to any one of claims 13-16, wherein the drug substance is an anti-diabetic substance.

18. A composition according to any one of claims 13-17, wherein the anti-diabetic substance is metformin.

19. 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, and

ii) a second container comprising a succinate prodrug, 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.

20. A kit according to claim 19, wherein the succinate prodrug has the formula as defined in any one of claims 4-7.

21. A kit according to claim 19 or 20, wherein the drug substance is as defined herein.

22. A kit according to any one of claims 19-21, wherein the drug substance is an anti-diabetic substance.

23. A kit according to any one of claims 19-22, wherein the anti-diabetic substance is metformin.

24. Use of an effective amount of a succinate prodrug 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 in a subject.

25. Use of an effective amount of a succinate prodrug 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 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.

26. The use according to claim 24 or 25, wherein the succinate prodrug has the formula as defined in any one of claims 4-7.

27. The use according to any one of claims 25-26, wherein the drug substance is as defined herein.

28. The use according to any one of claims 25-27, wherein the drug substance is an anti-diabetic substance.

29. The use according to claim 28, wherein the anti-diabetic substance is metformin.