2’,3’-DIACETYLURIDINE SUBSTITUTED WITH ACETOACETYL AT THE 5’ POSITION

Oral delivery of uridine for therapeutic purposes is limited by its poor bioavailability, approximately 7% in both humans and mice. Ester prodrugs of uridine have been found to improve its bioavailability, though only one, 2’,3’,5,-tri-O-acetyluridine (or uridine triacetate) has been found adequate to deliver sufficient uridine for clinical purposes. The bioavailability of oral uridine triacetate has been measured at approximately 50% (Ashour 1996). There is therefore room for improvement in the efficiency of uridine delivery, which is important in that relatively large doses of uridine are required for it therapeutic applications.

SUMMARY ~~OF THE INVENTION~~

~~This invention~~In one aspect, the present disclosure provides ~~the~~ a compound, 5’-O-(Acetoacetyl)-2’,3’-di-O-acetyluridine. It provides a method of treating or preventing a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject, comprising administering to the subject an amount of a compound of this ~~invention~~disclosure effective to treat the disorder. This ~~invention~~disclosure also provides a compound of this ~~invention~~disclosure for use in treating or preventing, or for the manufacture of a medicament for treating or preventing, a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject. In another aspect, the present disclosure provides use of the compound as described herein in the manufacture of a medicament for treating a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject. In another aspect, the present disclosure provides the compound as described herein for use in therapy. And it provides a pharmaceutical composition comprising a compound of this ~~invention~~disclosure and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound as described herein in an amount effective to treat or prevent a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject and a pharmaceutically acceptable carrier. ~~This invention~~In another aspect, the present disclosure also provides a method for producing 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine, comprising the steps of: (a) mixing 2',3'-O-isopropylideneuridine and 2,2,6-trimethyl-4H-1,3-dioxin-4-one in dimethylformamide under conditions to produce 5'-O-acetoacetyl-2',3'-O-isopropylideneuridine; (b) mixing the 5'-O-acetoacetyl-2',3'-O-isopropylideneuridine from step (a) with aqueous acetic acid under conditions to produce crude 5'-O-Acetoacetyluridine; (c) dissolving the crude 5'-O-Acetoacetyluridine from step (b) in a mixture of dichloromethane and pyridine, and

then adding acetic anhydride and stirring for several days; (d) to the mixture resulting from step (c), switch the solvent to ethyl acetate and neutralize with saturated $NaHCO_3$ to yield crude 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine. This ~~invention~~disclosure also provides 5'-O-Acetoacetyluridine as a crude intermediate and as an isolated compound. In another aspect, the present disclosure provides a compound, 5'-O-Acetoacetyluridine.

The acetate substituents improve absorption from the gastrointestinal tract into the circulation, and are rapidly removed by nonspecific esterase activity. Acetate is a benign metabolite, but is pharmacologically and therapeutically neutral. The finding that the introduction of an acetoacetyl substituent at the 5' position improves uridine bioavailability sufficiently for therapeutic purposes in addition to having beneficial pharmacological activity in disorders for which uridine delivery is also indicated~~,~~, yielding dual therapeutic activity in a single molecule, is an important advance.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Plasma [uridine + uracil] in mice after oral administration of uridine prodrugs

UTA = uridine triacetate (2',3',5'-tri-O-acetyluridine)

Tri-AcAcU = 2',3',5'-tri-O-(acetoacetyl)uridine

AcAcDAU = 5'-O-(acetoacetyl)-2',3'-di-O-acetyluridine

DA-HU = 2',3'-di-O-acetyl-5'-O-heptanoyluridine

FIGURE 2. Plasma uridine in mice after oral administration of uridine prodrugs

Tri-AcAcU = 2',3',5'-tri-O-(acetoacetyl)uridine

AcAcDAU = 5'-O-(acetoacetyl)-2',3'-di-O-acetyluridine

DA-HU = 2',3'-di-O-acetyl-5'-O-heptanoyluridine

FIGURE 3: Plasma uridine in mice after oral administration of uridine prodrugs

UTA = uridine triacetate (2',3',5'-tri-O-acetyluridine)

CLAIMS

What is claimed is:

1. A compound, 5'-O-(Acetoacetyl)-2',3'-di-O-acetyluridine.

2. ~~A method of~~Use of the compound of claim 1 in the manufacture of a medicament for treating a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject~~, comprising administering to the subject an amount of the compound of claim 1 effective to treat the disorder~~.

3. The ~~method~~ use of claim 2, wherein the disorder is a neurological disorder.

4. The ~~method~~ use of claim 3, wherein the neurological disorder is selected from the group consisting of a genetic neurodegenerative disease, an age-related neurodegenerative disorder, and a traumatic or ischemic brain injury.

5. The ~~method~~ use of claim 4, wherein the neurological disorder is a genetic neurodegenerative disease.

6. The ~~method~~ use of claim 5, wherein the genetic neurodegenerative disease is selected from the group consisting of:
Down Syndrome Dementia,
Huntington's Disease, and
Amyotrophic lateral sclerosis.

7. The ~~method~~ use of claim 4, wherein the neurological disorder is an age-related neurodegenerative disorder.

8. The ~~method~~use of claim 7, wherein the age-related neurodegenerative disorder is selected from the group consisting of:

Parkinson's Disease, and
senile dementia.

9. The ~~method~~use of claim 8, wherein the senile dementia is selected from the group consisting of Alzheimer's Disease and vascular dementia.

10. The ~~method~~use of claim 4, wherein the neurological disorder is a traumatic or ischemic brain injury.

11. The ~~method~~use of claim 10, wherein the traumatic or ischemic brain injury is selected from the group consisting of:
secondary injury following traumatic brain injury,
secondary injury following hypoxic-ischemic encephalopathy,
secondary injury following birth asphyxia
secondary injury following ischemic stroke,
secondary injury following hemorrhagic stroke,
secondary injury following cardiac arrest, and
secondary injury following drowning.

12. The ~~method~~use of claim 2, wherein the disorder is a neuromuscular disorder.

13. The ~~method~~use of claim 12, wherein the neuromuscular disorder is selected from the group consisting of:
age-related sarcopenia,
Muscle disuse atrophy,
muscular dystrophy,
myotonic dystrophy,
chronic fatigue syndrome, and
Friedreich's Ataxia.

14. The ~~method~~use of claim 2, wherein the disorder is a heart failure.

15. The ~~method~~use of claim 14, wherein the heart failure is selected from the group consisting of:

dilated cardiomyopathy,

right ventricular failure,

acute heart failure, and

chronic heart failure.

16. The ~~method~~use of claim 2, wherein the disorder is a primary genetic mitochondrial disease.

17. The ~~method~~use of claim 16, wherein the primary genetic mitochondrial disease is selected from the group consisting of:

MELAS (Mitochoncrial Encephalomyopathy with Lactic Acidemia and stroke-like episodes),

MERRF (Myoclonus, epilepsy, and myopathy with ragged red fibers),

NARP,

NARP/MILS (Neurogenic muscular weakness, ataxia, retinitis pigmentosa/Maternally inherited Leigh syndrome),

LHON (Lebers hereditary optic neuropathy) “Mitochondrial blindness”,

KSS (Kearns-Sayre Syndrome),

PMPS (Pearson Marrow-Pancreas Syndrome),

PEO (Progressive external ophthalmoplegia),

CPEO (Chronic progressive external ophthalmoplegia),

Leigh Syndrome,

MNGIE (Mitochondrial neurogastrointestinal encephalopathy syndrome),

Alpers syndrome,

Multiple mtDNA deletion syndrome,

MtDNA depletion syndrome,

Mitochondrial Complex I deficiency,

Mitochondrial Complex II (SDH) deficiency,

Mitochondrial Complex III deficiency,

Mitochondrial Complex IV (Cytochrome c oxidase) deficiency,
Mitochondrial Complex V deficiency,
Adenine Nucleotide Translocator (ANT) deficiency,
Pyruvate dehydrogenase (PDH) deficiency,
Multiple mitochondrial DNA deletion syndromes,
Barth syndrome,
Mitochondrial myopathy,
Mitochondrial epilepsy, and
Mitochondrial renal tubular acidosis.

18. The ~~method~~use of claim 2, wherein the mammalian subject is a human subject.

19. The ~~method~~use of claim 2, wherein the compound is to be administered orally.

20. The ~~method~~use of claim 19, wherein the compound is to be administered in a dose of from one to three g/m^2.

21. The ~~method~~use of claim 20, wherein the dose is to be administered two or three times per day.

22. The compound of claim 1 for use in therapy.

~~22. The compound of claim 1 for use in treating or preventing a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject.~~

~~23. The compound of claim 1 for use in the manufacture of a medicament for treating or preventing a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject.~~

~~24~~23. A pharmaceutical composition comprising the compound of claim 1 in an amount effective to treat or prevent a disorder characterized by cerebral metabolic energy failure or diminished mitochondrial energy reserve capacity in a mammalian subject and a pharmaceutically acceptable carrier.

~~25~~24. A method for producing 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine, comprising the steps of:

(a) mixing 2',3'-O-isopropylideneuridine and 2,2,6-trimethyl-4H-1,3-dioxin-4-one in dimethylformamide under conditions to produce 5'-O-acetoacetyl-2',3'-O-isopropylideneuridine;

(b) mixing the 5'-O-acetoacetyl-2',3'-O-isopropylideneuridine from step (a) with aqueous acetic acid under conditions to produce crude 5'-O-Acetoacetyluridine;

(c) dissolving the crude 5'-O-Acetoacetyluridine from step (b) in a mixture of dichloromethane and pyridine, and then adding acetic anhydride and stirring for several days;

(d) to the mixture resulting from step (c), switch the solvent to ethyl acetate and neutralize with saturated $NaHCO_3$ to yield crude 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine.

~~26~~25. The method of claim ~~25~~24, wherein step (a) is performed at a temperature of from 90 °C to 110 °C.

~~27~~26. The method of claim ~~25~~24, wherein step (b) is performed at a temperature of from room temperature to 75 °C.

~~28~~27. The method of claim ~~27~~26, wherein step (b) is performed at a temperature of about 65 °C.

~~29~~28. The method of claim ~~25~~24, wherein step (c) is performed at about room temperature.

~~30~~29. The method of claim ~~25~~24, further comprising purifying the crude 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine from step (d) to yield purified 5'-O-Acetoacetyl-2',3'-di-O-acetyluridine.

~~31~~30. A compound, 5’-O-Acetoacetyluridine.