



(51) International Patent Classification:

A61P 1/16 (2006.01)

C07H 19/06 (2006.01)

A61P 25/00 (2006.01)

(21) International Application Number:

PCT/US2021/061053

(22) International Filing Date:

30 November 2021 (30.11.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/119,764

01 December 2020 (01.12.2020) US

(71) Applicant: **WELLSTAT THERAPEUTICS CORPORATION** [US/US]; 14200 Shady Grove Road, Suite 600, Rockville, MD 20850 (US).

(72) Inventors: **GARCIA GARCIA, Rolando Alejandro**; 2 Martins Landing Court, Germantown, MD 20874 (US). **SAYDOFF, Joel A.**; 986 Bel Air Drive E., Vista, CA 98204 (US). **SIMPSON, David Michael**; 6611 Sulky Lane, North Bethesda, MD 20852 (US). **VON BORSTEL, Reid Warren**; 10017 Sorrel Avenue, Potomac, MD 20854 (US).

(74) Agent: **KREISLER, Lewis, J.**; Wellstat Management Company, LLC, 14200 Shady Grove Road, Suite 600, Rockville, MD 20850 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: 5'-O-PHENYLACETYLURIDINE AND THERAPEUTIC USE

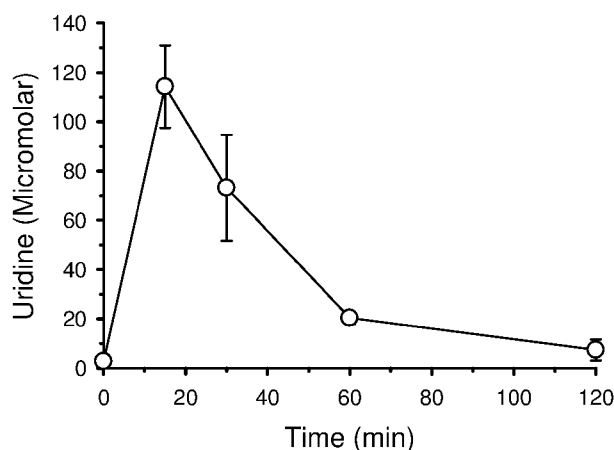


FIG. 1

(57) Abstract: 5' -O-Phenylacetyluridine effectively delivers both phenylacetate and uridine to a subject. It can be used to treat hepatic encephalopathy and genetic disorders of the hepatic nitrogen cycle.



Published:

— *with international search report (Art. 21(3))*

5'-O-PHENYLACETYLRIDINE AND THERAPEUTIC USE

BACKGROUND OF THE INVENTION

Phenylacetate and its precursor phenylbutyrate have important therapeutic applications, exploiting the activity of phenylacetate as an ammonia scavenger for elimination of excess ammonia in conditions such as hepatic encephalopathy and genetic disorders of the nitrogen cycle. Furthermore, additional activities of phenylacetate as a molecular chaperone to mitigate protein misfolding in the endoplasmic reticulum, and as an inhibitor of histone deacetylation have been harnessed for therapeutic benefit in various other diseases and disease models.

In conditions such as hepatic encephalopathy, excess ammonia is not the sole factor in disease pathogenesis and progression, as neuroinflammation and diminished mitochondrial function are also involved. The pyrimidine nucleoside uridine has broad anti-inflammatory activity, both systemically and in the brain, and provides support for cells, including neurons, with defective mitochondrial electron transport and oxidative phosphorylation. Oral 2',3',5'-tri-O-acetyluridine increases plasma uridine more effectively than oral uridine itself, in part because of the dose-limiting side effects of oral uridine.

SUMMARY OF THE INVENTION

This invention provides the compound 5'-O-Phenylacetyluridine. It provides a method of treating or preventing a condition selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle in a subject comprising administering to the subject an amount of a compound of this invention effective to treat the disorder. This invention also provides a compound of this invention for use in treating or preventing, or for the manufacture of a medicament for treating or preventing a condition selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle. And it

provides a pharmaceutical composition comprising a compound of this invention and a pharmaceutically acceptable carrier.

The compound 5'-O-Phenylacetyluridine (PAU), when administered orally has been found to increase plasma uridine more effectively than uridine itself. And to deliver phenylacetate into the bloodstream more effectively than phenylbutyrate, a precursor that is favored over phenylacetate as a drug due to the unpleasant odor of phenylacetate, and which is approved by FDA for use as an ammonia scavenger.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Plasma uridine in mice after oral administration of 5'-phenylacetyluridine

FIG. 2: Plasma uracil in mice after oral administration of 5'-phenylacetyluridine

FIG. 3: Plasma uridine + uracil in mice after oral administration of 5'-phenylacetyluridine

DETAILED DESCRIPTION OF THE INVENTION

As used herein the transitional term “comprising” is open-ended. A claim utilizing this term can contain elements in addition to those recited in such claim. Thus, for example, the claims can read on treatment regimens that also include other therapeutic agents or therapeutic virus doses not specifically recited therein, as long as the recited elements or their equivalent are present.

Abbreviations:

PAU or 5'-PAU: 5'-O-Phenylacetyluride, also known as 5'-phenylacetyluridine

PA: Phenylacetate

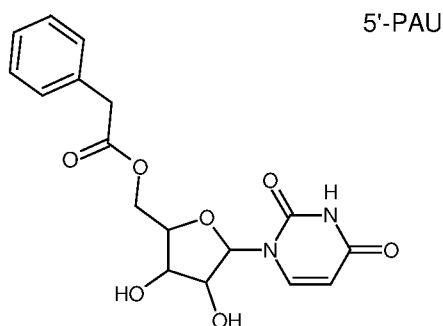
PB: Phenylbutyrate

NaPB: Sodium phenylbutyrate

DMF: Dimethylformamide

TLC: Thin-layer chromatography

DMSO:	Dimethyl sulfoxide
HPMC:	Hydroxypropylmethyl cellulose
LPS:	Lipopolysaccharide
TNF:	Tissue necrosis factor



Molecular Formula = C₁₇H₁₈N₂O₇

Formula Weight = 362.33402

LogP = 0.51 +/- 0.61

In addition to providing therapeutic benefits derived from concurrent delivery of uridine and phenylacetate, there are important safety factors achieved by using uridine in combination with phenylacetate because the uridine can attenuate the metabolic imbalances caused by phenylacetate or its precursor phenylbutyrate.

In accordance with the method, the compound for use, the use, and the pharmaceutical composition of this invention any conventional disorder characterized by the potential for benefit imparted by phenylacetate and uridine in a mammalian subject can be treated or prevented. Such conditions are selected based on any of several known activities and mechanisms of action of phenylacetate or its precursor phenylbutyrate, in which broad tissue-neuroprotective and tissue protective activity imparted by therapeutic doses of uridine are also indicated. In one embodiment, Hepatic Encephalopathy is treated with 5'-phenylacetyluridine, with the phenylacetate moiety scavenging excessive circulating and tissue ammonia associated with this condition, and uridine providing direct neuroprotective activity against neuroinflammation and mitochondrial dysfunction that also characterize hepatic encephalopathy. Hepatic encephalopathy at all stages of severity, from acute crisis to minimal clinical symptoms, is treated with 5'-phenylacetyluridine. For severe hepatic encephalopathy, doses ranging 1 up to 9 grams per square meter of body surface area of phenylacetyluridine are administered once to

three times per day, with the dose selected depending on severity of ammonia overload in a particular patient.

Right ventricular failure and pulmonary artery remodeling in pulmonary hypertension involves pathologic metabolic remodeling affecting the heart and pulmonary artery, with excessive aerobic glycolysis, similar to the Warburg effect in many cancers. Phenylacetate inhibits pyruvate carboxylase, partially mitigating pathological aerobic glycolysis. Furthermore, uridine improves inotropy in pressure-overloaded myocardium. Therefore, as a single agent, or in combination with uridine triacetate for modulating uridine/phenylacetate ratios, 5'-phenylacetyluridine provides more complete protection of the right ventricle in pulmonary hypertension than either agent alone; right ventricular failure is the primary cause of death in people with primary pulmonary hypertension. For treatment of pulmonary hypertension, doses of 5'-phenylacetyluridine ranging from 1 to 5 grams per square meter of body surface area are administered one to three times per day.

In accordance with this invention the compound can be administered to any mammalian subject. In one embodiment the mammalian subject is a human subject. In accordance with this invention, any conventional route of administration can be utilized. Preferably the compound is administered orally. The skilled practitioner can titrate to optimize the dosage for a particular patient. Typically the compound is administered orally to a human patient in a dose of from 1 to 5 grams per square meter of body surface area. Usually the dose is administered 1 to 3 times per day.

PB is generally administered to patients as a sodium salt (Buphenyl®) at doses of 5-25 g/day. Since sodium comprises 12% sodium weight/weight and therefore a 10 g/day NaPB treatment would result in 1.2 g of sodium intake. The recommended daily intake of sodium is 2.3 g and excessive sodium intake is associated with increased incidence of hypertension, myocardial infarction and stroke (Strazzullo, D'Elia et al. 2009; Frieden and Briss 2010). One object of this invention is to provide a biologically active derivative of PB in a form which does not add excessive sodium intake. This is accomplished by means of ester linkage with uridine.

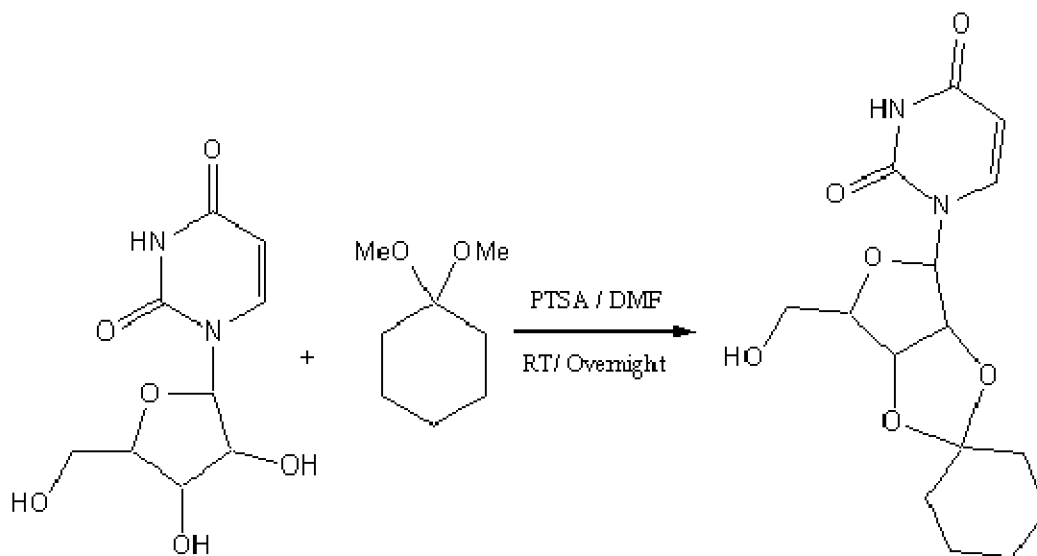
Glutamine depletion due to PB represents an additional metabolic compromise in mammals that do not have a urea cycle disorder or excessive levels of ammonia. Glutamine depletion and resulting loss of ammonia can lead to a depletion of pyrimidines (uridine and cytidine) because pyrimidine synthesis requires glutamine. Pyrimidine synthesis can be altered by levels of glutamine or dietary protein (Monks, Chisena et al. 1985; Nelson, Qureshi et al. 1993; Zaharevitz, Grubb et al. 1993). The use of a uridine ester-linked PB-related derivative provides uridine and thus prevents uridine depletion.

The invention will be better understood by reference to the following examples, which illustrate but do not limit the invention described herein.

EXAMPLES

EXAMPLE 1: Preparation of 5'-O-Phenylacetyluridine

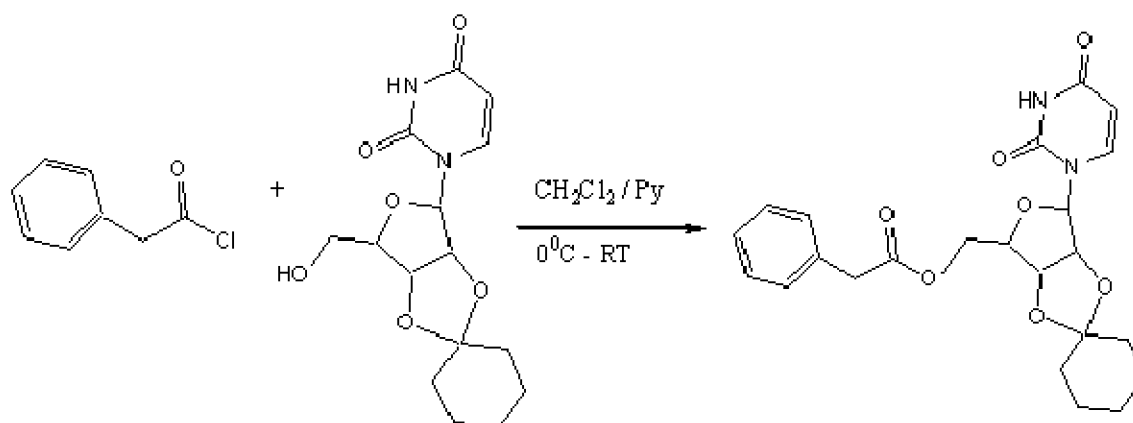
1. Preparation of 2',3'-O-Cyclohexylideneuridine



Uridine (50g, 205 mmols) was dissolved in anhydrous DMF (250 mL) and a catalytic amount of *para*-toluenesulfonic acid (1.8 grams) was added while stirring under argon at room temperature. After 20 minutes, 31 mL, or 2.0 equivalents, of 1,1-dimethoxycyclohexane was added. The

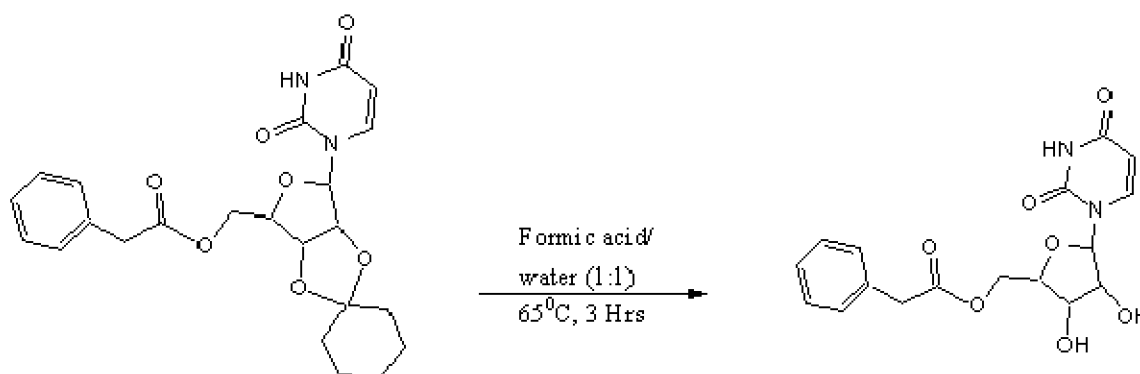
reaction mixture was stirred at room temperature under argon overnight. The reaction was checked by TLC (EtOAc, $R_f = 0.2$) for completion and 250 mL of methanol was added and then evaporated twice. The crude reaction mixture was purified by flash chromatography using silica gel and ethyl acetate to yield 33 grams of the desired product (50% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 1.34 – 1.69 (m, 10H), 3.55 (broad s, 2H) 4.03 – 4.05 (m, 1H), 4.73 (d, 1H, $J = 3.6$ Hz), 4.86 – 4.88 (m, 1H), 5.06 (s, OH), 5.61 (d, 1H, $J = 8.1$ Hz), 5.82 (dd, 1H, $J = 2.6, 7.0$ Hz), 7.76 – 7.80 (m, 1H), 11.35 (s, NH)

2. Preparation of 2',3'-O-Cyclohexylidene-5'-O-phenylacetyluridine



Under argon, 2',3'-O-cyclohexylideneuridine (26.0 g, 84.4 mmol) was dissolved in 250 mL of anhydrous CH_2Cl_2 , 125 mL of pyridine was added, and the mixture was cooled to 0°C . Then, phenylacetyl chloride (16 mL, 1.2 eq) was added dropwise over 30 minutes. The reaction mixture was stirred at 0°C for 4 hrs. and at room temperature for another 4 hrs. Completion of the reaction was verified by TLC (EtOAc, $R_f = 0.6$). The reaction was quenched with methanol and evaporated to dryness. The residue was dissolved in EtOAc (500 mL) and washed with 0.1 N HCl, 0.05 N HCl, water, saturated NaHCO_3 , and finally with water. The crude product was purified by flash chromatography using silica gel and 50% EtOAc/hexane to give 30 g of the desired product (85% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 1.33 – 1.69 (m, 10H), 3.69 (s, 2H), 4.19 – 4.24 (m, 3 H), 4.73 – 4.74 (m, 1H), 4.88 (dd, 1H, $J = 2.2, 6.6$ Hz), 5.61 (d, 1H, $J = 8.1$ Hz), 5.77 (d, 1H, $J = 1.9$ Hz), 7.24 – 7.32 (m, 5H), 7.60 (d, 1H, $J = 8.1$ Hz), 11.42 (s, NH).

3. Preparation of 5'-O-Phenylacetyluridine



2',3'-O-Cyclohexylidene-5'-O-phenylacetyluridine (32.80 g, 77.1 mmols) was dissolved in 300 mL of a 1:1 mixture of formic acid and water. The reaction mixture was heated at 65-70 °C for 4 hrs. differs from reaction figure TLC (ethyl acetate) confirmed the consumption of the starting material. Water and formic acid were removed by evaporation under vacuum. The crude product was dissolved in water (250 mL) and evaporated to dryness twice. Purification by flash chromatography using silica gel and ethyl acetate yielded 15.1 grams (56%) of the desired product. Attempts to recrystallize the product from solvents ethyl acetate/hexane, ethyl ether/hexane, methanol/hexane, ethanol/ hexane, ethanol/ ethyl ether, acetone/hexane, ethanol/ ethyl ether, methanol/ethyl ether were unsuccessful. Analysis by LC-MS showed that 92% of the total absorbance of light at λ_{230} corresponded to the product. ^1H NMR (400 MHz, DMSO- d_6) δ 3.71 (ABq, 2H), 3.85 – 4.05 (m, 3H), 4.15 – 4.30 (m, 2H), 5.28 (d, OH, J = 5.1 Hz), 5.43 (d, OH, J = 6.5 Hz), 5.61 (d, 1H, J = 8.1 Hz), 5.72 (d, 1H, J = 5.1 Hz), 7.24 – 7.31 (m, 5H), 7.46 (d, 1H, J = 8.1 Hz), 11.35 (s, NH). Melting point 55 – 57 °C

EXAMPLE 2: Plasma uridine and uracil pharmacokinetics after oral administration of 5'-O-phenylacetyluridine (PAU)

Chemical(s): HPMC (Hydroxypropylmethyl cellulose; SIGMA-Aldrich: cat# H3785, CAS 9004-65-3), 5'-O-Phenylacetyluridine (PAU, lot 432-132)

Vehicle: Aqueous HPMC (0.75%) was used as a suspending vehicle for oral administration.

Dosing Formulation: PAU was added to 0.75% HPMC and homogenized to eliminate clumps. The suspension were made up to the desired volume and concentration and sonicated to disaggregate any small leftover clumps into fine particles. Suspensions were stored at 4°C until use. Suspensions were used within 24 hrs of preparation.

Dosing: Mice received a dose of 587 mg/Kg PAU (molar equivalent to 400 mg/kg uridine) gavaged at 0.02 ml/g body weight.

Animals: Female CD-1 mice.

(Remainder of page intentionally blank.)

Species	Strains	Gender	Number	Age and Weight Range at Shipment	Vendor	Diet and Housing
Mouse	CD-1	Females	9	~ 26-30 g	Envigo	Harlan Teklad 2016, ad libitum, housed 5/cage

The general initial layout for the experiment involved gavaging groups of 6 mice with PAU and obtaining blood samples at several times points thereafter (3 mice were bled for 2 time points (15 and 60 minutes), and another 3 mice were bled for the other 2 time points (30 and 120 minutes). Each experiment included an HPMC (vehicle only) time point with 3 mice to establish a baseline for blood uridine.

Group No.	No. of Animals	Bleeding Time After Dosing
PAU	6	15, 30, 60, & 120 min
HPMC	3	-

Blood samples were collected into plasma separation tubes, which were centrifuged immediately after blood collection, and aliquots of plasma were frozen for subsequent processing. Plasma was later deproteinated, and uridine and uracil were quantified by liquid chromatography using UV absorbance detection and mass spectrometry.

Delivery of uridine into the bloodstream was assessed by monitoring plasma uridine and the sum of uridine and uracil [uridine + uracil], as uracil is the first product in enzymatic degradation of uridine. Mice convert administered uridine to uracil more rapidly and extensively than do humans, so that uridine + uracil provides a better index for translation of dosing and pharmacokinetics to humans than does measurement of uridine alone.

Plasma uridine, uracil and [uridine + uracil] concentrations after administration of PAU are shown in Figures 1, 2 and 3 respectively.

The delivery of phenylacetate into the bloodstream after oral administration of PAU was also assessed. Sodium phenylbutyrate is used in clinical practice as an ammonia scavenger in hepatic encephalopathy or genetic nitrogen cycle disorders, or as a chaperone or histone deacetylase inhibitor. It is predominantly metabolized to phenylacetate via beta-oxidation in the liver, and phenylacetate mediates the therapeutic benefits of phenylbutyrate. PAU was administered orally at a dose equimolar to 200 mg/kg sodium phenylbutyrate. Female BALB/c mice (n= 3-5 group) were given test compounds p.o. and after 30 minutes were retro-orbitally bled to obtain plasma. The table summarizing the comparative bioavailability of PAU and sodium phenylbutyrate derivatives indicates the maximum concentration (C_{Max}) obtained in serum after equimolar oral administration of these compounds as an index of bioavailability. An equimolar dose of uridine was used as a comparator for efficiency of delivery of uridine into the circulation by oral administration of PAU.

Table 1. Plasma concentrations of uridine, PB and respective metabolites after oral administration of sodium phenylbutyrate or PAU

Compound	Uridine	Uracil	PB	PA
NaPB	NA	NA	26	401
PAU	76	159	<1	1281
Uridine	10	24	NA	NA

Plasma concentrations units are micromoles/liter (μM)

NaPB = sodium phenylbutyrate

PB = phenylbutyrate

PA = phenylacetate

PAU = 5'-O-Phenylacetyluridine

Oral PAU was substantially more effective than an equimolar dose of oral sodium phenylbutyrate for raising plasma phenylacetate concentrations, yielding a >3-fold higher

concentration of circulating phenylacetate at 30 minutes after administration. Furthermore, PAU elevated plasma uridine and uracil better than did and equimolar dose of oral uridine.

EXAMPLE 3: Anti-inflammatory effects of 5'-O-Phenylacetyluridine (PAU)

Injection of bacterial cell wall constituent lipopolysaccharide (LPS) has been used as a model of inflammation. The inflammatory cascade can lead to cellular and organ damage when unchecked. Tissue necrosis factor α (TNF α) is strongly induced during inflammation and attenuating this response can be protective in numerous diseases including rheumatoid arthritis, psoriasis, vasculitis and Alzheimer's disease.

Female BALB/c mice 41 weeks of age (n = 7-8/group) were treated with Vehicle (0.75% HPMC) or PAU p.o. and 30 minutes later LPS (2.5 mg/kg i.p.) was administered. One hour after LPS, mice were sacrificed and blood was collected for measurement of plasma TNF α .

Table 2: Effect of PAU on plasma TNF α changes due to LPS

Treatment	TNF α (pg/ml) $\pm$ SEM
Vehicle	15,981 $\pm$ 2,951
PAU (165 mg/kg)	10,068 $\pm$ 2,583
PAU (331 mg/kg)	7,034 $\pm$ 1,236 +

+ Indicate p < .05 compared to Vehicle control.

PAU provides significant anti-inflammatory effect in the LPS-induced elevation of plasma TNF α .

CLAIMS

What is claimed is:

1. A compound, 5'-O-Phenylacetyluridine.
2. A method of treating or preventing a condition in a mammalian subject, wherein the condition is selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle, comprising administering to the subject an effective amount of the compound of claim 1, thereby treating or preventing the condition.
3. The method of claim 2, wherein the administration is oral.
4. The method of claim 3, wherein the mammalian subject is a human subject.
5. The method of claim 4, wherein the administration is oral.
6. The method of claim 5, wherein the effective amount is from 1 to 5 grams per square meter of body surface area, administered one, two or three times daily.
7. The compound of claim 1 for use in treating or preventing a condition in a mammalian subject, wherein the condition is selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle.
8. The compound for use of claim 7, wherein the compound is administered orally to the mammalian subject.
9. The compound for use of claim 7, wherein the mammalian subject is a human subject.

10. The compound for use of claim 9, wherein the compound is administered orally to the human subject.

11. The compound for use of claim 10, wherein the compound is administered in a dose of from 1 to 5 grams per square meter of body surface area, administered one, two or three times daily.

12. The compound of claim 1 for use in the manufacture of a medicament for treating or preventing a condition in a mammalian subject, wherein the condition is selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle.

13. The compound for use of claim 12, wherein the medicament is formulated for oral administration to the mammalian subject.

14. The compound for use of claim 12, wherein the mammalian subject is a human subject.

15. The compound for use of claim 14, wherein the medicament is formulated for oral administration to the human subject.

16. The compound for use of claim 15, wherein the medicament is formulated for administration of the compound in a dose of from 1 to 5 grams per square meter of body surface area, administered one, two or three times daily.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of claim 1 in an amount effective to treat or prevent a condition in a mammalian subject, wherein the condition is selected from the group consisting of hepatic encephalopathy and a genetic disorder of the hepatic nitrogen cycle.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition is formulated for oral administration to the mammalian subject.

19. The pharmaceutical composition of claim 17, wherein the mammalian subject is a human subject.

20. The pharmaceutical composition of claim 19, wherein the pharmaceutical composition is formulated for oral administration to the human subject.

21. The pharmaceutical composition of claim 20, formulated for administration of the compound in a dose of from 1 to 5 grams per square meter of body surface area, administered one, two or three times daily.

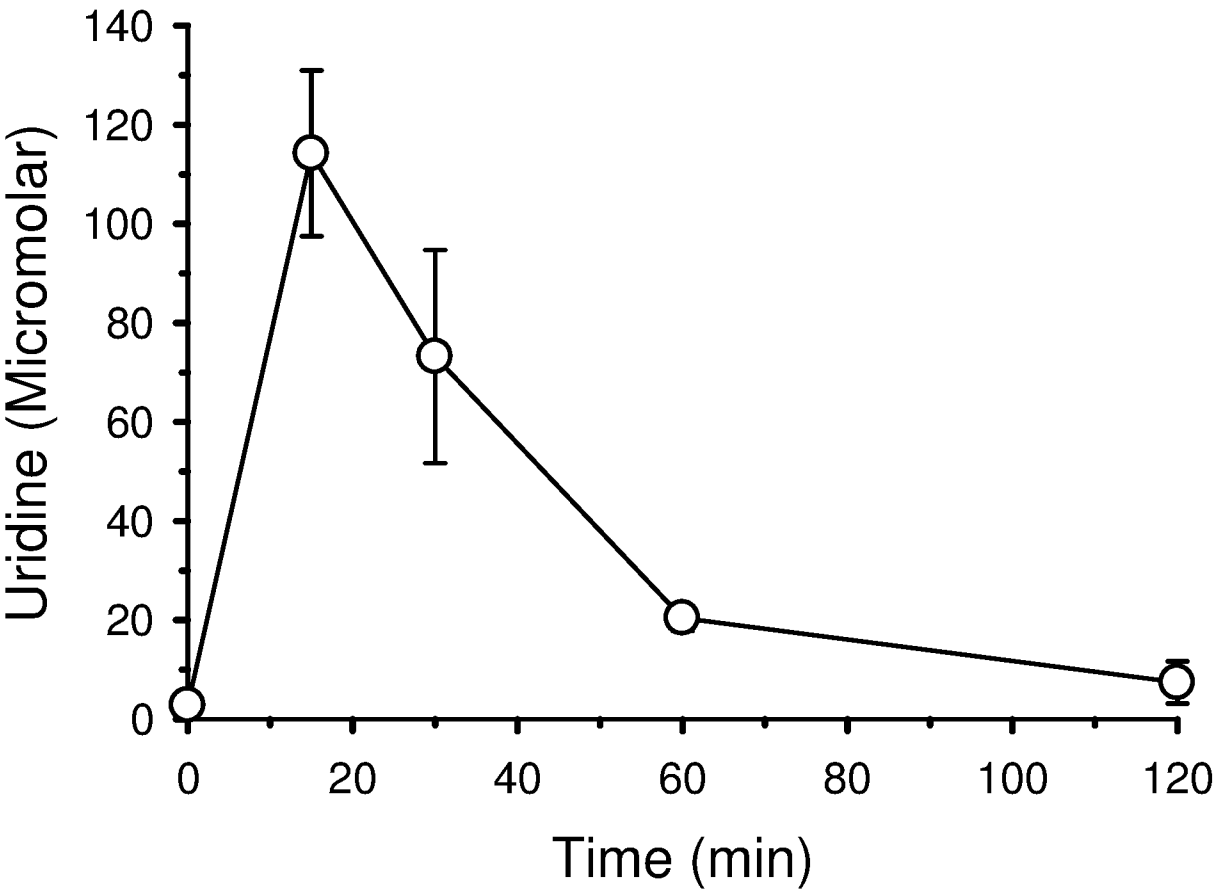


FIG. 1
1/3

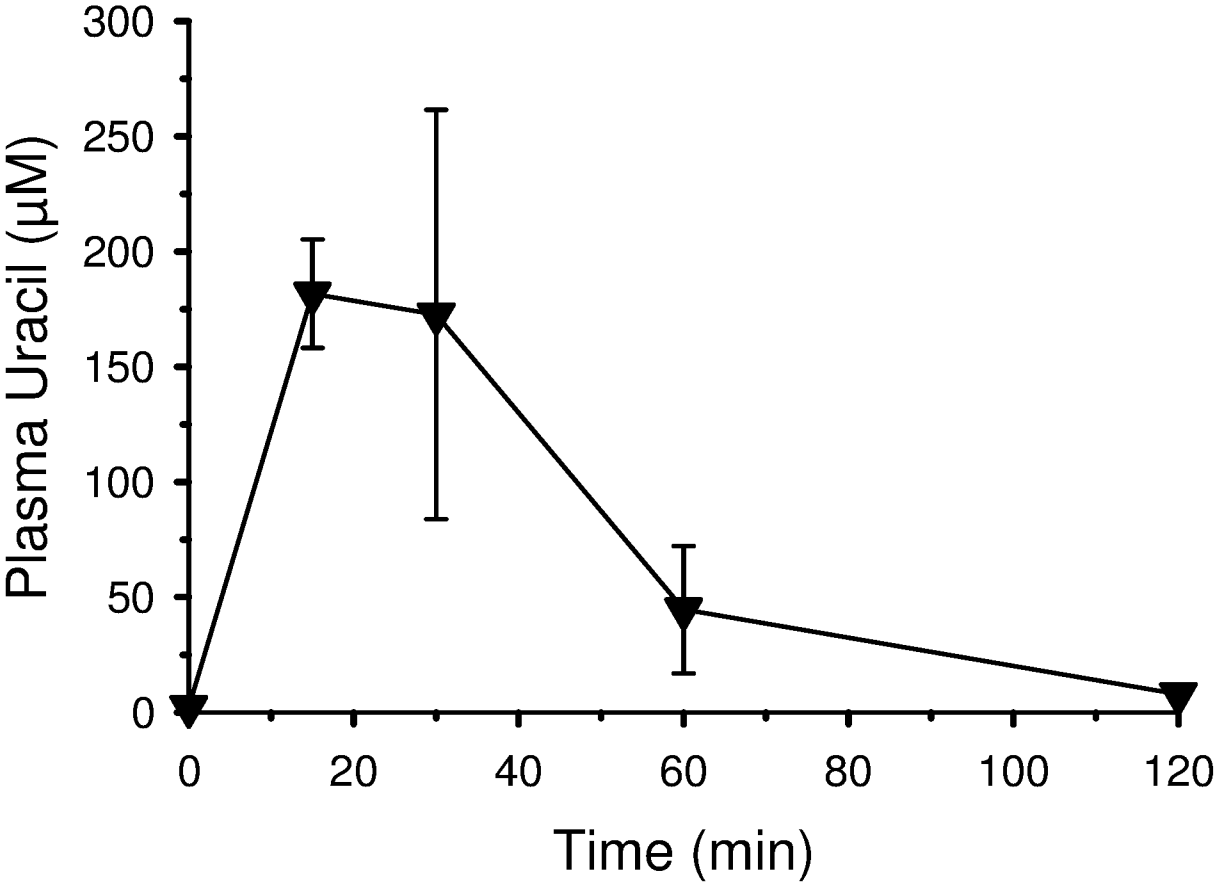


FIG. 2
2/3

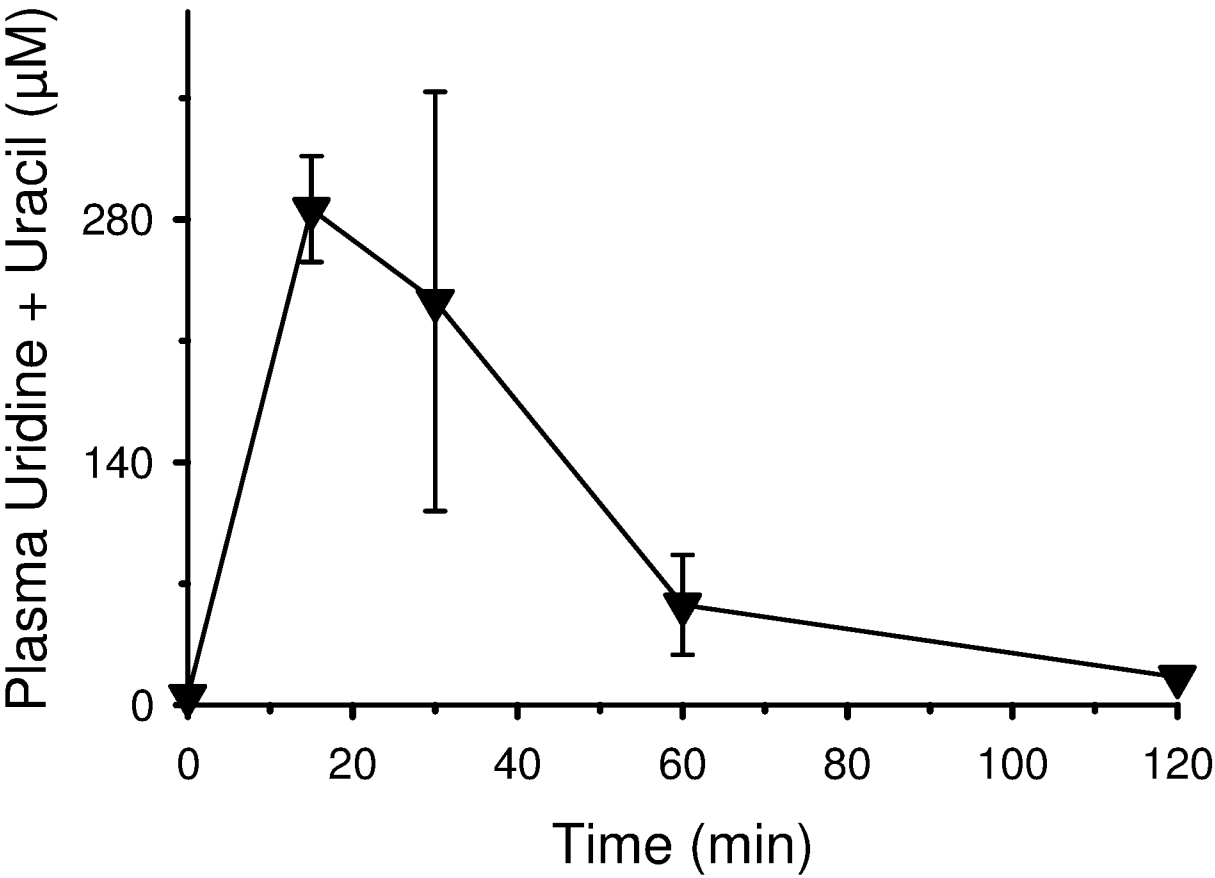


FIG. 3
3/3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/061053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 1/16; A61P 25/00; C07H 19/06 (2022.01)

CPC - A61P 1/16; A61P 25/00; C07H 19/06 (2022.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, Substance Record for SID 47237025. Modify Date: 22 June 2015 [retrieved on 14 January 2022]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/47237025 >. entire document	1-21
A	US 5,585,512 A (YAMAZAKI et al) 17 December 1996 (17.12.1996) entire document	1-21
A	US 9,566,257 B2 (JALAN et al) 14 February 2017 (14.02.2017) entire document	1-21

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 January 2022

Date of mailing of the international search report

FEB 07 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300