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(71) Applicant: NEW YORK UNIVERSITY [US/US]; 70 Washington Square South, New York, NY 10012 (US).

(72) Inventors: PACOLD, Michael; c/o New York University, 70 Washington Square South, New York, NY 10012 (US). BANH, Robert; c/o New York University, 70 Washington Square South, New York, NY 10012 (US). SHI, Guangbin; c/o New York University, 70 Washington Square South, New York, NY 10012 (US). SPILLIER, Quentin; c/o New York University, 70 Washington Square South, New York, NY 10012 (US).

(74) Agent: GROMOVA, Anna V. et al.; Troutman Pepper Hamilton Sanders LLP, 70 Linden Oaks, Suite 210, Rochester, NY 14625 (US).

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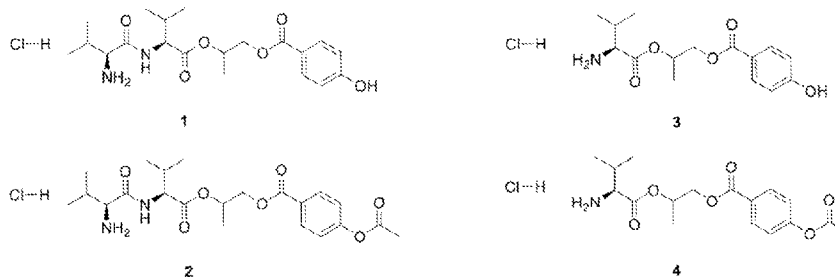
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(54) Title: 4-HYDROXYBENOZATE ESTERS FOR TREATMENT OF HPDL DEFICIENCY AND OTHER DEFICIENCIES OF COQ10 HEADGROUP SYNTHESIS

FIGURE 1



(57) Abstract: The present invention relates to compositions and methods for the treating 4- hydroxyphenylpyruvate dioxygenase-like (HPDL)-related diseases or disorders. Compositions and dosage forms comprising the compounds of the present invention are disclosed.



4-HYDROXYBENOZATE ESTERS FOR TREATMENT OF HPDL DEFICIENCY AND OTHER DEFICIENCIES OF COQ10 HEADGROUP SYNTHESIS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Application Nos. 63/662,587, filed on June 21, 2024, and 63/526,421, filed on July 12, 2023, the disclosure of each of which is incorporated by reference herein in its entirety.

FIELD OF INVENTION

[0002] The present invention relates to compositions and methods for the treating 4-hydroxyphenylpyruvate dioxygenase-like (HPDL)-related diseases or disorders. Some aspects of the present invention relate to methods of treating neurodegenerative, neurodevelopmental, or psychiatric disease, aging, obesity, diabetes, metabolic syndrome, insulin resistance, hyperlipidemia, cachexia, chronic fatigue syndrome, wound healing / non-healing wounds, cardiac disease, heart failure, hypertension, immune deficiency, cancer, vitamin deficiency, or infertility.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] This invention was made with government support under R35 GM147119 awarded by the National Institutes of Health. The government has certain rights in the invention.

SEQUENCE LISTING

[0004] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on July 09, 2024, is named 243735_000336_SL.xml and is 1,803 bytes in size.

BACKGROUND OF THE INVENTION

[0005] Gaseous oxygen (O₂) is essential for cellular respiration, the production of reactive oxygen species (ROS), and the activity of oxygen-dependent enzymes, such as dioxygenases. Oxygen-utilizing enzymes are essential for sensing, regulatory, and biosynthetic processes that are critical for cell growth and survival. Although the necessity of oxygen in sustaining life has been known since the late 1700s, the scope of oxygen-dependent processes in mammalian cells remains

unknown as there are no established methods for systematically identifying the targets of oxygen or any other labelled gas in mammalian cells. Identification of the targets and site-specific modifications of ROS and measuring the activity of oxygen-dependent enzymes in a systematic manner using direct mass spectrometric methods, would reveal these fundamental oxygen-dependent processes and novel biology.

[0006] Coenzyme Q (CoQ) is an essential component of eukaryotic cells. It plays an important role in mitochondrial ATP synthesis and functions as an antioxidant in mitochondrial membranes. It is also involved in the biosynthesis of pyrimidines and the modulation of apoptosis. CoQ10 requires more than ten genes for its biosynthesis. Mutations in these genes cause primary CoQ10 deficiency, a clinically and genetically heterogeneous disorder. Deficiency of CoQ10 is also associated with a number of human diseases and age-related chronic conditions such as, but not limited to, metabolic syndrome and diabetes, neurodegenerative disorders, cardiovascular diseases, and human fertility (Hernández-Camacho et al., “Coenzyme Q 10 Supplementation in Aging and Disease,” *Front Physiol.* 9:44 (2018); Doimo et al., “Genetics of Coenzyme q10 Deficiency,” *Mol Syndromol.* 5(3-4):156-62 (2014)). Because the pharmacokinetics of CoQ10 are not well understood and it is not clear how much orally ingested CoQ10 is actually absorbed, alternative therapies to CoQ10 supplementation are needed.

[0007] Cerebral palsy (CP) is a progressive and disabling neurodevelopmental disease of childhood, with an incidence as high as 4 in 1000 live births. Although CP was initially thought to be due to hypoxia at birth, it is now thought to be mostly due to pre-natal insults, and up to 50% of cases have no known cause. Recently, it has been found that inherited disorders can present with CP or CP-like symptoms such as spasticity and ataxia, which is consistent with consanguinity as a risk factor for CP.

[0008] Mutations in 4-hydroxyphenylpyruvate dioxygenase (HPDL) that segregate with a spastic neurodevelopmental disorder with similarities to cerebral palsy (Ghosh et al., “Biallelic Variants in HPDL, Encoding 4-Hydroxyphenylpyruvate Dioxygenase-Like Protein, Lead to an Infantile Neurodegenerative Condition,” *Genet. Med.* 23:524-533 (2021); Morgan et al., “Evidence that Autosomal Recessive Spastic Cerebral Palsy-1 (CPSQ1) is Caused by a Missense Variant in HPDL,” *Brain Commun.* 3(1):fcab002 (2021); Husain et al., “Bi-Allelic HPDL Variants Cause a Neurodegenerative Disease Ranging from Neonatal Encephalopathy to Adolescent-Onset Spastic Paraplegia,” *Am. J. Hum. Genet.* 107:364-373 (2020); Wiessner et al., “Biallelic Variants

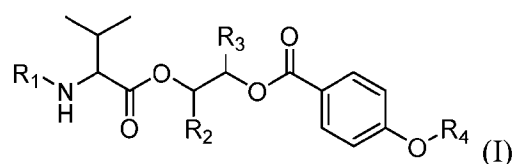
in HPDL Cause Pure and Complicated Hereditary Spastic Paraplegia,” *Brain* 144(5):1422–1434 (2021)). These mutations have not been functionally characterized but are thought to inactivate HPDL, as at least some of them are missense mutations that result in decreased expression of the protein. An HPDL knockout mouse (Ghosh et al., “Biallelic Variants in HPDL, Encoding 4-Hydroxyphenylpyruvate Dioxygenase-Like Protein, Lead to an Infantile Neurodegenerative Condition,” *Genet. Med.* 23:524-533 (2021)) recapitulates the phenotype of the disease.

[0009] Thus, there exists an unmet need for novel therapeutics for the treatment of pancreatic cancer, or for the treatment of diseases or disorders associated with CoQ10 deficiency and/or others that result from variations in the HPDL gene, including cerebral palsy. There is also a need for improved methods that allow isotopic labelling of oxygen or any other gas in cells.

SUMMARY OF THE INVENTION

[00010] Various non-limiting aspects and embodiments of the invention are described below.

[00011] In one aspect, provided herein is a compound having the structure according to Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

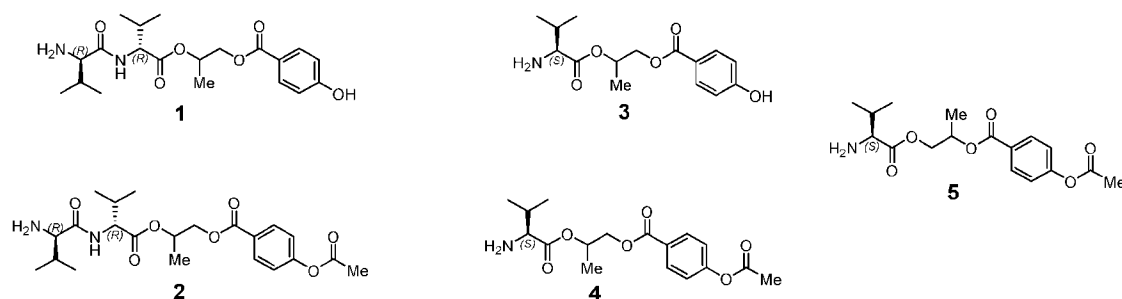
R₁ is selected from the group consisting of H and ;

R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

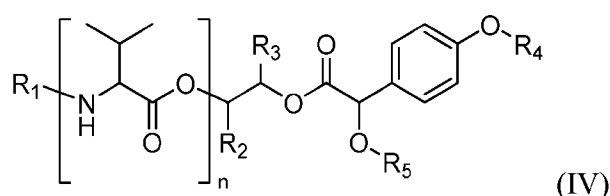
R₃ is selected from the group consisting of H and C₁-C₃ alkyl, and

R₄ is selected from the group consisting of H and .

[00012] In another aspect, provided herein is a compound of formula:



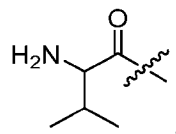
[00013] In one aspect, provided herein is a compound having the structure according to Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein:

n is 0 or 1;

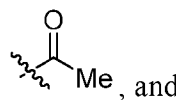
R₁ is selected from the group consisting of H and



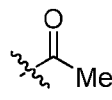
R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

R₄ is selected from the group consisting of H and



R₅ is selected from the group consisting of H and

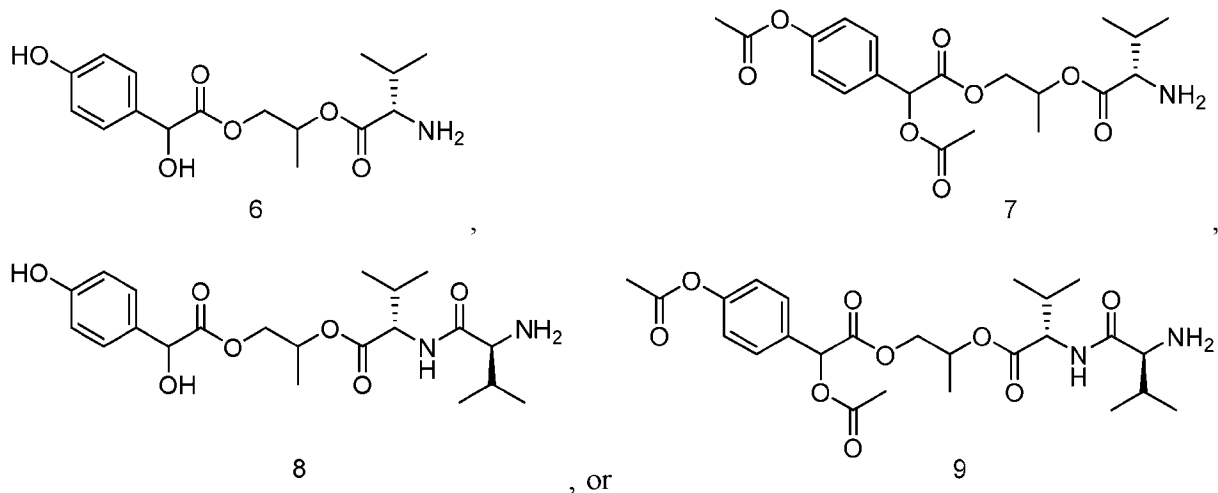


[00014] In another aspect, provided herein is a method of treating a 4-hydroxyphenylpyruvate dioxygenase-like (HPDL)-related disease or disorder in a subject in need thereof. This method comprises administering to the subject a therapeutically effective amount of the compound(s), the pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) described herein.

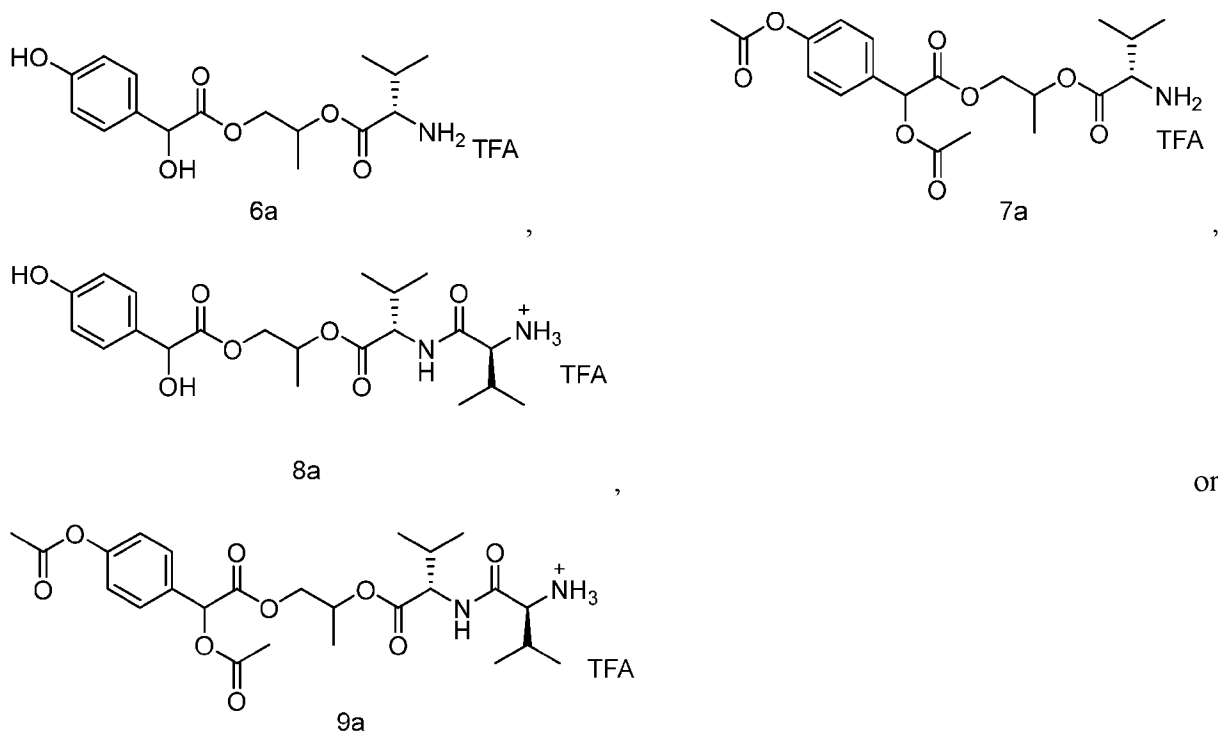
[00015] In another aspect, provided herein is a method of increasing CoQ10 biosynthesis in a subject in need thereof. This method comprises administering to the subject a therapeutically

effective amount of the compound(s), the pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) described herein.

[00016] In another aspect, provided herein is a compound of formula:

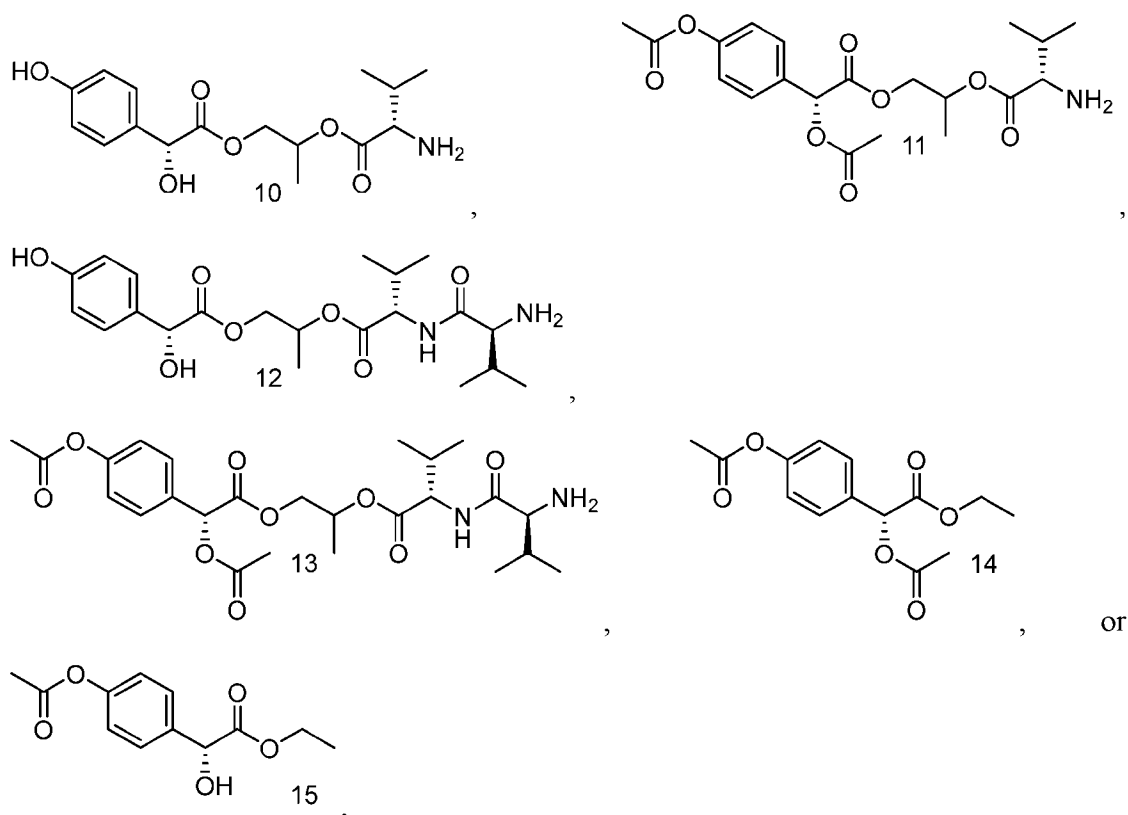


[00017] In another aspect, provided herein is a compound of formula:



or a pharmaceutically acceptable salt thereof.

[00018] In another aspect, provided herein is a compound of formula:



or a pharmaceutically acceptable salt thereof.

[00019] These and other aspects of the present invention will become apparent to those skilled in the art after a reading of the following detailed description of the invention, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[00020] **Figure 1** shows the structures of 4-HB esters.

[00021] **Figure 2** shows the rescue data obtained for 4-HB esters tested in *Hpd1*^{-/-} mice (n=1 for each ester).

[00022] **Figure 3** shows mean concentrations of mouse PO data for 4-HB esters.

[00023] **Figures 4A-4B** show survival of *Hpd1*^{-/-} mice treated with R-4-HMA and S-4-HMA, the enantiomers of 4-HMA. n=5 (R-4-HMA), n=9 (S-4-HMA). All 5 pups treated with R-4-HMA survived. 2/9 pups treated with S-4-HMA survived.

DETAILED DESCRIPTION

[00024] Detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely illustrative of the invention that may be embodied in various forms. In addition, each of the examples given in connection with the various embodiments of the invention is intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

[00025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[00026] To facilitate an understanding of the principles and features of the various embodiments of the invention, various illustrative embodiments are explained below. Although exemplary embodiments of the invention are explained in detail, it is to be understood that other embodiments are contemplated. Accordingly, it is not intended that the invention is limited in its scope to the details of construction and arrangement of components set forth in the following description or examples. The invention is capable of other embodiments and of being practiced or carried out in various ways. Also, in describing the exemplary embodiments, specific terminology will be resorted to for the sake of clarity.

[00027] As used herein, the terms “about” or “approximately” for any numerical values or ranges indicate a suitable dimensional tolerance that allows the part or collection of components to function for its intended purpose as described herein. More specifically, “about” or “approximately” may refer to the range of values $\pm 20\%$ of the recited value, e.g. “about 90%” may refer to the range of values from 71% to 99%.

[00028] As used herein, the term “alkyl” is given its ordinary meaning in the art and can include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 1–20 carbon atoms in its backbone (e.g., C₁₋₂₀ for straight chain, C₂₋₂₀ for branched chain), and alternatively, about 1–10 carbon atoms, or about 1 to 6 carbon atoms. In some embodiments, a cycloalkyl ring has from about 3–10 carbon atoms in their ring structure where such rings are

monocyclic or bicyclic, and alternatively about 5, 6 or 7 carbons in the ring structure. In some embodiments, a cycloalkyl group is a cyclopropyl, a cyclobutyl, a cyclopentyl, or a cyclohexyl group. In some embodiments, an alkyl group can be a lower alkyl group, wherein a lower alkyl group comprises 1–4 carbon atoms (e.g., C₁₋₄ for straight chain lower alkyls). When used in the context of a divalent alkyl group, it is to be understood that “alkyl” refers to an alkylene group.

[00029] As used herein, a substituent, e.g., -B, can be represented as a , where  denotes a point of attachment.

[00030] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure.

[00031] The present application also includes pharmaceutically acceptable salts of the compounds described herein. The “pharmaceutically acceptable salts” include a subset of the “salts” described above which are conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Berge, SM *et al*, *Journal of Pharmaceutical Science*, 1977, 66, 1, 1-19. By way of an example, in an embodiment of the disclosure pharmaceutically acceptable salts can comprise a suitable anion selected from F⁻, Cl⁻, Br⁻, I⁻, OH⁻, ⁻BF₄, CF₃SO₃⁻, monobasic sulfate, dibasic sulfate, monobasic phosphate, dibasic phosphate, or tribasic phosphate, NO₃⁻, PF₆⁻, NO₂⁻, carboxylate, C_eF_fSO₃⁻, (where e=2-10 and f=2e+1), acetate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bitartrate, camsylate, carbonate, citrate, decanoate, edetate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollyalarsanilate, hexanoate, hydrabamine, hydroxynaphthoate, isothionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, mucate, napsylate, octanoate, oleate, oxalate, palmitate, pamoate, pantothenate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, tartrate, teoclate, tosylate, or triethiiiodide. By way of another example, in an embodiment of the disclosure pharmaceutically acceptable salts can comprise a suitable cation selected from

aluminum, arginine, benzathine, calcium, chlorprocaine, choline, diethanolamine, ethanolamine, ethylenediamine, lysine, magnesium, histidine, lithium, meglumine, potassium, procaine, sodium, triethylamine, or zinc. The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00032] The term “prodrug” as used herein includes a chemical which may be transformed *in vivo* to a pharmacologically active drug. The term “metabolite” as used herein includes a chemical that a given agent is transformed into *in vivo*.

[00033] The enantiomeric excess, or “ee,” for a given pair of enantiomers is the percentage of the major enantiomer less the percentage of the minor enantiomer. A “racemate” or “racemic mixture” is an equal mixture of two enantiomers and therefore has 0% ee.

[00034] The term “enantiomerically enriched” or “enantioenriched” as used herein includes compounds that are mixtures with one enantiomer's being present in excess over the other (ee >0% and <100%). For example, a sample of 40% ee consists of 70% of the major enantiomer and 30% of the minor enantiomer.

[00035] The term “enantiomerically pure” or “enantiopure” as used herein includes compounds where the quantification of the minor enantiomer becomes difficult, e.g., with an ee of 99% or greater. Ideally, enantiopure compounds consist of a single enantiomer only.

[00036] The term “sample” as used herein includes any biological specimen obtained from a subject or patient. Samples that can be used in the methods of the present disclosure include, without limitation, tumor sample, whole blood, plasma, serum, red blood cells, white blood cells (e.g., peripheral blood mononuclear cells (PBMC), polymorphonuclear (PMN) cells), ductal lavage fluid, nipple aspirate, lymph (e.g., disseminated tumor cells of the lymph node), bone marrow aspirate, saliva, urine, stool (i.e., feces), sputum, bronchial lavage fluid, tears, fine needle aspirate (e.g., harvested by random periareolar fine needle aspiration), any other bodily fluid, a tissue sample such as a biopsy (e.g., needle biopsy), and cellular extracts thereof. In some embodiments, when the subject is a pregnant female, the sample may be a fetal DNA sample (e.g., cell-free fetal DNA (cffDNA)).

[00037] As used herein, the term “subject” or “patient” refers to mammals and includes, without limitation, human and veterinary animals. In a preferred embodiment, the subject is human.

[00038] The terms “treat” or “treatment” of a state, disorder or condition include: (1) preventing or delaying the appearance of at least one clinical or sub-clinical symptom of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; or (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or sub-clinical symptom thereof; or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or sub-clinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[00039] An “effective amount” of a compound described herein refers to an amount sufficient to elicit the desired biological response, i.e., treating the state, disorder or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[00040] A “therapeutically effective amount” of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a state, disorder or condition or to delay or minimize one or more symptoms associated with the state, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent.

[00041] It must also be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. For example, reference to a component is intended also to include composition of a

plurality of components. References to a composition containing “a” constituent is intended to include other constituents in addition to the one named. In other words, the terms “a,” “an,” and “the” do not denote a limitation of quantity, but rather denote the presence of “at least one” of the referenced item.

[00042] Also, in describing the exemplary embodiments, terminology will be resorted to for the sake of clarity. It is intended that each term contemplates its broadest meaning as understood by those skilled in the art and includes all technical equivalents which operate in a similar manner to accomplish a similar purpose.

[00043] It is also to be understood that the mention of one or more method steps does not preclude the presence of additional method steps or intervening method steps between those steps expressly identified. Similarly, it is also to be understood that the mention of one or more components in a composition does not preclude the presence of additional components than those expressly identified.

[00044] The materials described hereinafter as making up the various elements of the present invention are intended to be illustrative and not restrictive. Many suitable materials that would perform the same or a similar function as the materials described herein are intended to be embraced within the scope of the invention. Such other materials not described herein can include, but are not limited to, materials that are developed after the time of the development of the invention, for example. Any dimensions listed in the various drawings are for illustrative purposes only and are not intended to be limiting. Other dimensions and proportions are contemplated and intended to be included within the scope of the invention.

Compounds of the Disclosure

[00045] The 4-hydroxyphenylpyruvate dioxygenase (HPDL) catalyzes the production of 4-hydroxymandelic acid (4-HMA). 4-HMA is the first committed step in the CoQ10 headgroup synthesis pathway, which ends with the production of 4-hydroxybenzoate (4-HB), the immediate precursor of the CoQ10 headgroup. *Hpd1*^{-/-} mice phenocopy patients with HPDL variants develop runting, spastic paresis, neurodevelopmental delay, and seizures. In addition, *Hpd1*^{-/-} mice die by postpartum day 15. Treatment of *Hpd1*^{-/-} mice with 4-HMA or 4-HB enables survival of ~1 year and substantially improves their neurological symptoms. In principle, treatment with 4-HB could

rescue variants in any of the CoQ headgroup synthesis enzymes. However, 4-HMA has a chiral center and 4-HB is not very soluble.

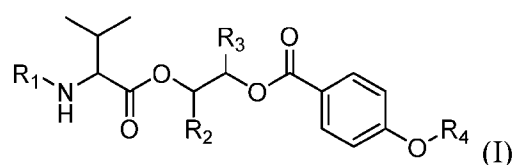
[00046] The present disclosure is based on the discovery of 4-HB esters with improved solubility in water, which will assist in their formulation and oral delivery. Four exemplary esters of 4-HB according to the present invention are shown in **Figure 1**. All four of these compounds improved the development and survival of Hpd1-/- mice. These compounds will be useful in ameliorating the symptoms of patients with HPDL variants, particularly if these compounds are administered early in extrauterine growth and development.

[00047] The esters of 4-HB described in the present disclosure will enable delivery of higher doses of 4-HB as they are more soluble and, thus, improve the formulation of this relatively insoluble molecule. The use of these compounds will also eliminate the need for the chiral center of 4-HMA. Finally, these 4-HB esters could treat any patient with variants in the known and unknown enzymes of CoQ headgroup synthesis, or with decreased CoQ headgroup synthesis due to medical conditions, such as premature delivery. Rescue of Hpd1-/- pups with 4-HMA is incomplete neurologically and this technology will enable treatment with higher concentrations of 4-HB, which may improve neurodevelopmental outcomes in the patients.

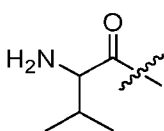
[00048] Esterification has shown to increase bioavailability of a pharmaceutical (Majumdar et al., "Bioreversion and Oral Bioavailability of the L-Valine Dipeptide Ester Prodrug of Acyclovir, Val-Valacyclovir, in Sprague-Dawley Rats," *Clinical Research and Regulatory Affairs* 21(1):67–79 (2004); Purifoy et al., "Review of Research Leading to New Anti-Herpesvirus Agents in Clinical Development: Valaciclovir Hydrochloride (256U, the L-Valyl Ester of Acyclovir) and 882C, a Specific Agent for Varicella Zoster Virus," *J. Med. Virol. Suppl* 1(S1):139–45 (1993); Tanino et al., "Enhancement of Oral Bioavailability of Phenytoin by Esterification, and in Vitro Hydrolytic Characteristics of Prodrugs," *Int. J. Pharm.* 163:91–102 (1998), which are hereby incorporated by reference in their entirety). For example, valine esters have increased bioavailability of a pharmaceutical (Majumdar et al., "Bioreversion and Oral Bioavailability of the L-Valine Dipeptide Ester Prodrug of Acyclovir, Val-Valacyclovir, in Sprague-Dawley Rats," *Clinical Research and Regulatory Affairs* 21(1):67–79 (2004); Purifoy et al., "Review of Research Leading to New Anti-Herpesvirus Agents in Clinical Development: Valaciclovir Hydrochloride (256U, the L-Valyl Ester of Acyclovir) and 882C, a Specific Agent for Varicella Zoster Virus," *J. Med. Virol. Suppl* 1(S1):139–45 (1993), which are hereby incorporated by reference in their

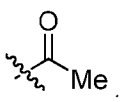
entirety). Bulky esterified compounds were shown to enter the brains of mice better and have a longer half-life (Genka et al., "Development of Lipophilic Anticancer Agents for the Treatment of Brain Tumors by the Esterification of Water-Soluble Chlorambucil," *Clin. Exp. Metastasis*. 11(2):131–40 (1993), which is hereby incorporated by reference in its entirety).

[00049] In one aspect, provided herein is a compound having the structure according to Formula (I):

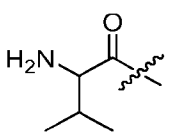


or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;
 R₂ is selected from the group consisting of H and C₁-C₃ alkyl;
 R₃ is selected from the group consisting of H and C₁-C₃ alkyl, and

R₄ is selected from the group consisting of H and .

[00050] In one embodiment, R₁ is H.

[00051] In one embodiment, R₁ is .

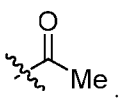
[00052] In one embodiment, R₂ is methyl.

[00053] In one embodiment, R₂ is H.

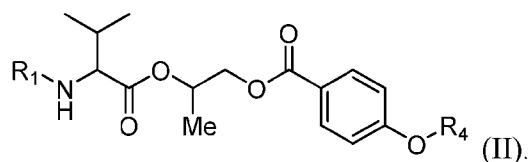
[00054] In one embodiment, R₃ is H.

[00055] In one embodiment, R₃ is methyl.

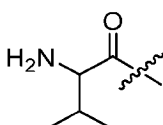
[00056] In one embodiment, R₄ is H.

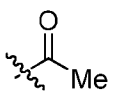
[00057] In one embodiment, R₄ is .

[00058] In one embodiment, the compound has a structure according to Formula (II):

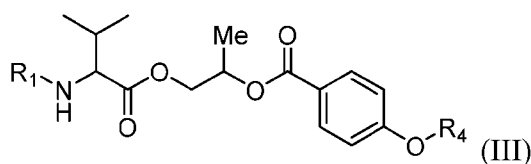


or a pharmaceutically acceptable salt thereof, wherein:

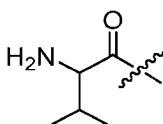
R₁ is selected from the group consisting of H and , and

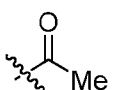
R₄ is selected from the group consisting of H and .

[00059] In one embodiment, the compound has a structure according to Formula (III):

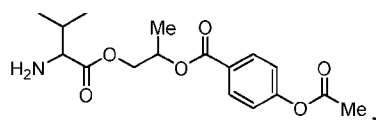
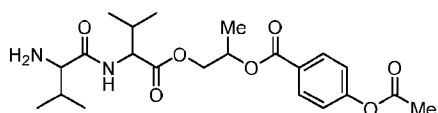
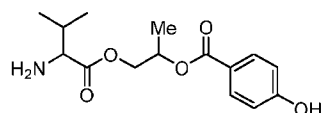
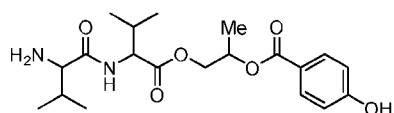
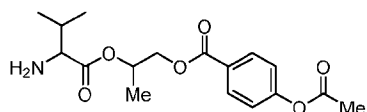
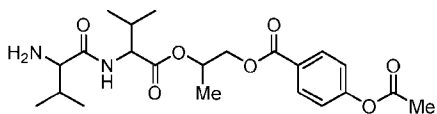
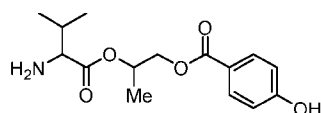
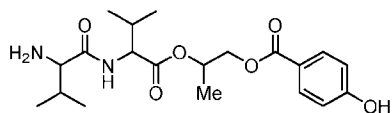


or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and , and

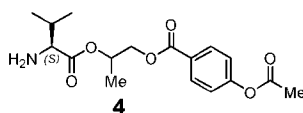
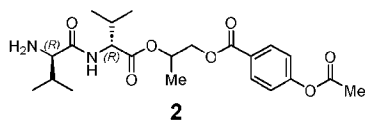
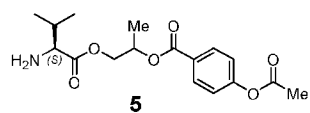
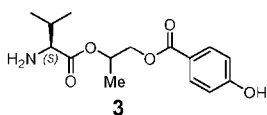
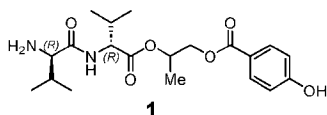
R₄ is selected from the group consisting of H and .

[00060] In one embodiment, the compound has a structure selected from the group consisting of:



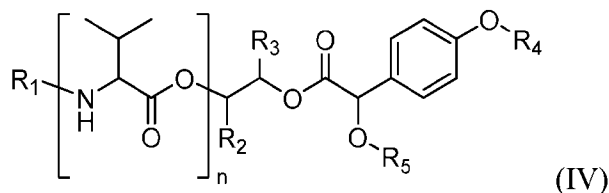
or a pharmaceutically acceptable salt thereof.

[00061] In one embodiment, the compound has a structure selected from the group consisting of:



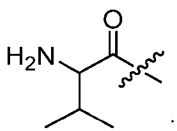
, or a pharmaceutically acceptable salt thereof.

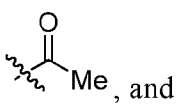
[00062] In another aspect, provided herein is a compound having the structure according to Formula (IV):

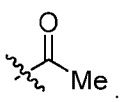


or a pharmaceutically acceptable salt thereof, wherein:

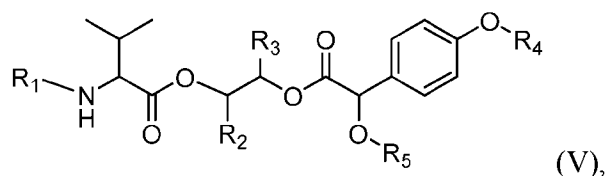
n is 0 or 1;

R₁ is selected from the group consisting of H and  ;
 R₂ is selected from the group consisting of H and C₁-C₃ alkyl;
 R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

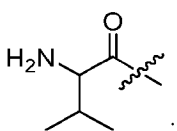
R₄ is selected from the group consisting of H and  , and

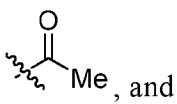
R₅ is selected from the group consisting of H and .

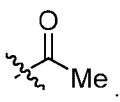
[00063] In one embodiment, the compound has a structure according to Formula (V):



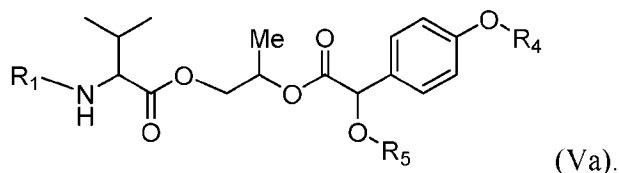
or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;
 R₂ is selected from the group consisting of H and C₁-C₃ alkyl;
 R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

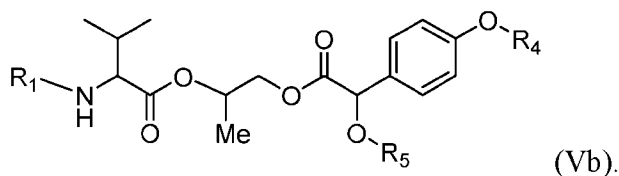
R₄ is selected from the group consisting of H and  , and

R₅ is selected from the group consisting of H and .

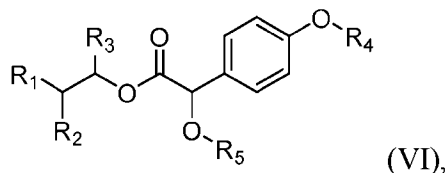
[00064] In one embodiment, the compound has a structure according to Formula (Va):



[00065] In one embodiment, the compound has a structure according to Formula (Vb):



[00066] In another embodiment, the compound has a structure according to Formula (VI):



or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and ;

R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

R₄ is selected from the group consisting of H and , and

R₅ is selected from the group consisting of H and .

[00067] In one embodiment, R₁ is H.

[00068] In one embodiment, R₁ is .

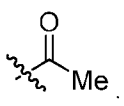
[00069] In one embodiment, R₂ is methyl.

[00070] In one embodiment, R₂ is H.

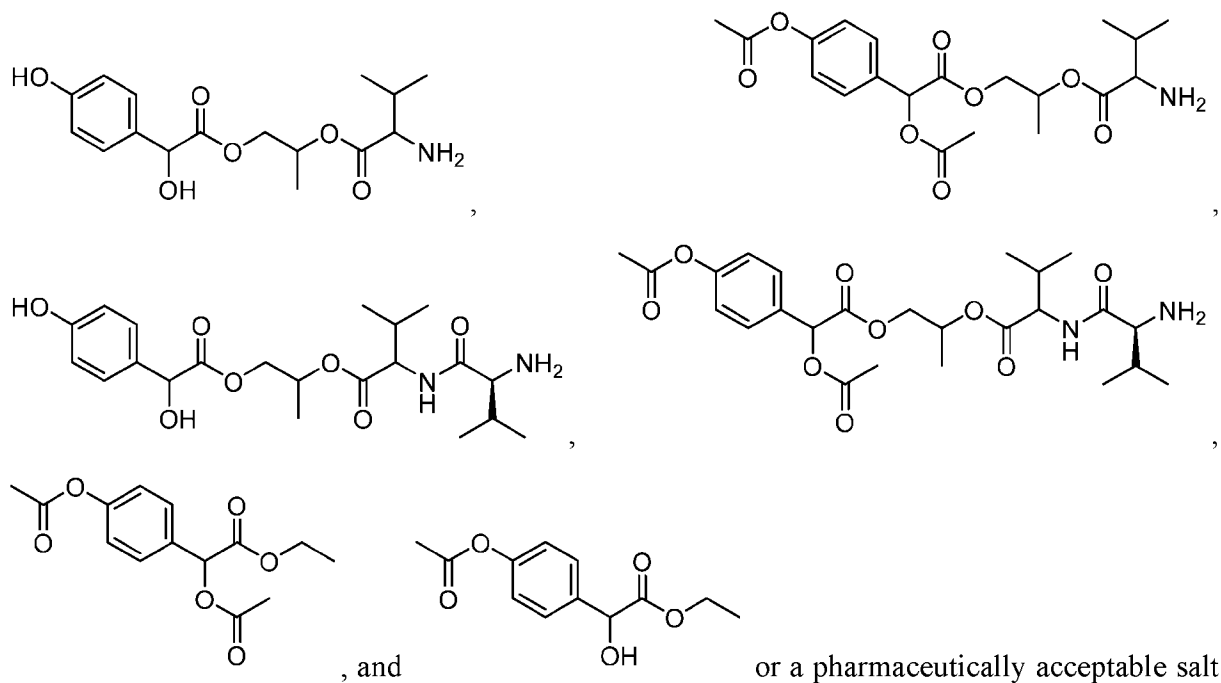
[00071] In one embodiment, R₃ is H.

[00072] In one embodiment, R₃ is methyl.

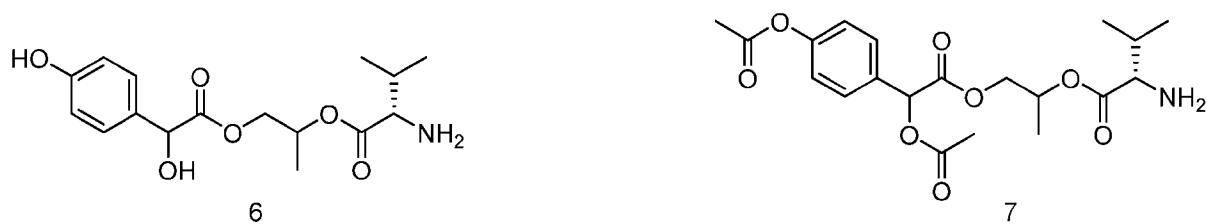
[00073] In one embodiment, R₄ is H.

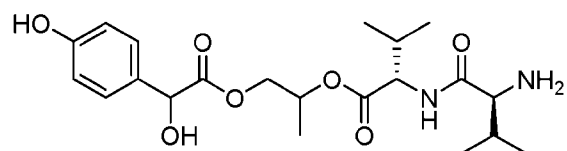
[00074] In one embodiment, R₄ is .

[00075] In one embodiment, the compound has a structure selected from the group consisting of:



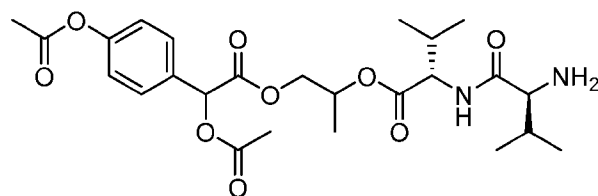
[00076] In another aspect, provided herein is a compound of formula:





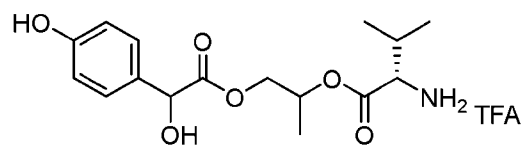
8

, or



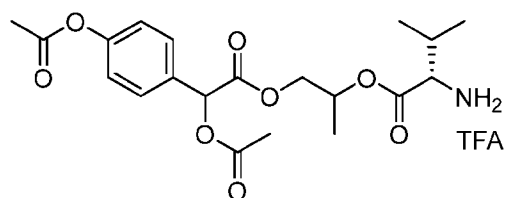
9

[00077] In another aspect, provided herein is a compound of formula:



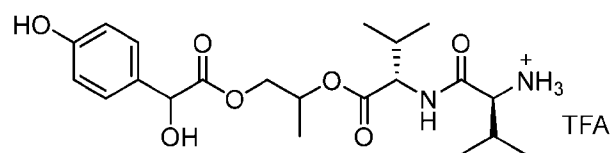
6a

,



7a

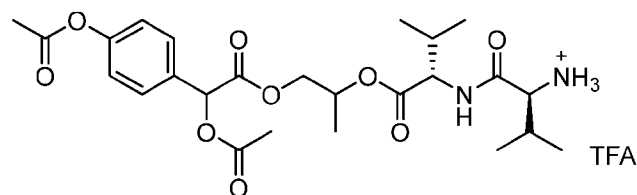
,



8a

,

or

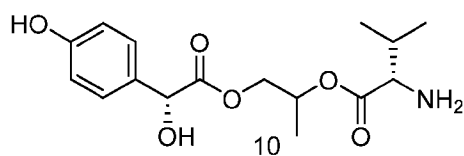


9a

,

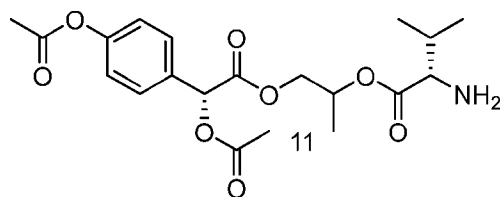
or a pharmaceutically acceptable salt thereof.

[00078] In another aspect, provided herein is a compound of formula:



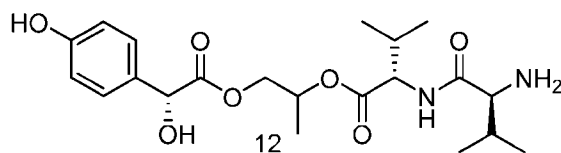
10

,



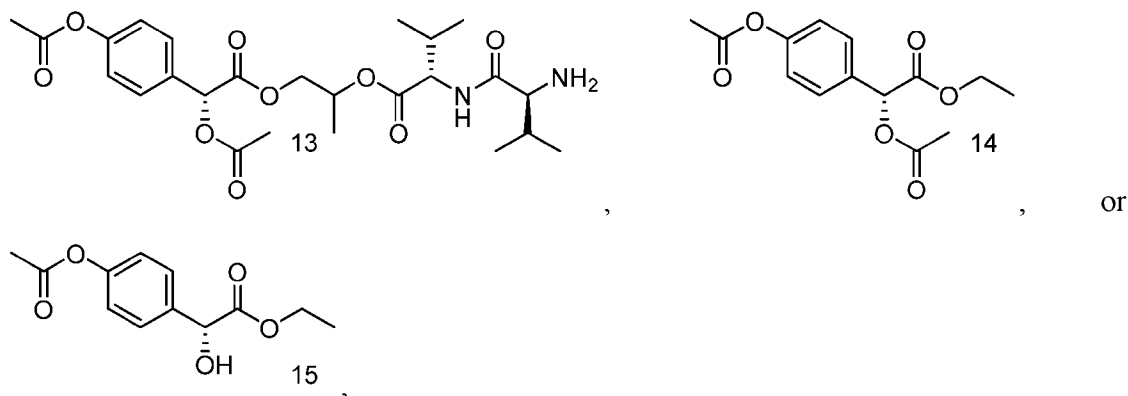
11

,



12

,



or a pharmaceutically acceptable salt thereof.

[00079] In one embodiment, a compound described herein (e.g., a compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above) is provided as an enantioenriched mixture of the R-enantiomer. In one embodiment, the compound described herein is present with an enantiomeric excess (ee) of the R-enantiomer of about 20% or greater, or about 30% or greater, or about 40% or greater, or about 50% or greater, or about 60% or greater, or about 70% or greater, or about 80% or greater, or about 85% or greater, or about 90% or greater, or about 95% or greater, or about 96% or greater, or about 97% or greater, or about 98% or greater, or about 99% or greater, or about 99.5% or greater, or about 99.9% or greater.

[00080] In some embodiments the compound described herein (e.g., a compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above) is present with an enantiomeric excess (ee) of the R-enantiomer of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 98%, or at least about 99%.

[00081] In some embodiments, the compound described herein (e.g., the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above) is provided as the enantiopure R-enantiomer.

[00082] In another embodiment, a compound described herein (e.g., a compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above) is provided as an enantioenriched mixture of the S-enantiomer. In one embodiment, the compound described herein is present with an enantiomeric excess (ee) of the S-

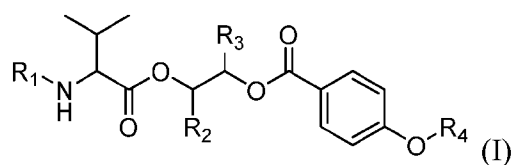
enantiomer of about 20% or greater, or about 30% or greater, or about 40% or greater, or about 50% or greater, or about 60% or greater, or about 70% or greater, or about 80% or greater, or about 85% or greater, or about 90% or greater, or about 95% or greater, or about 96% or greater, or about 97% or greater, or about 98% or greater, or about 99% or greater, or about 99.5% or greater, or about 99.9% or greater.

[00083] In one embodiment, the a compound described herein (e.g., a compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above) is present with an enantiomeric excess (ee) of the S-enantiomer of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 98%, or at least about 99%.

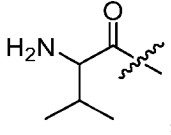
Pharmaceutical Compositions and Administration

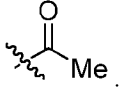
[00084] The present invention also provides pharmaceutical compositions comprising a compound described herein (e.g., a compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), and/or Formula (Formula (VI) as described above), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystals, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R₁, R₂, R₃, and R₄ are as defined above.

[00085] In one embodiment, a compound has the structure according to Formula (I):

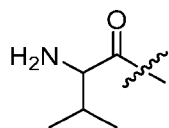


or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;
 R₂ is selected from the group consisting of H and C₁-C₃ alkyl;
 R₃ is selected from the group consisting of H and C₁-C₃ alkyl, and

R₄ is selected from the group consisting of H and .

[00086] In one embodiment, R₁ is H.



[00087] In one embodiment, R₁ is

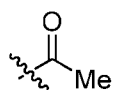
[00088] In one embodiment, R₂ is methyl.

[00089] In one embodiment, R₂ is H.

[00090] In one embodiment, R₃ is H.

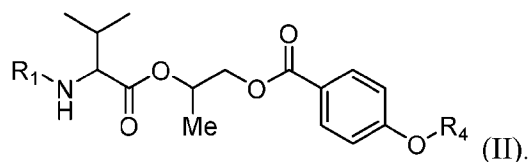
[00091] In one embodiment, R₃ is methyl.

[00092] In one embodiment, R₄ is H.

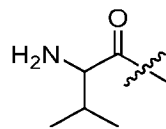


[00093] In one embodiment, R₄ is

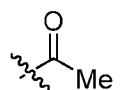
[00094] In one embodiment, the compound has a structure according to Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

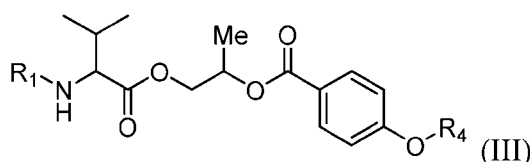


R₁ is selected from the group consisting of H and

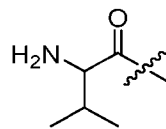


R₄ is selected from the group consisting of H and

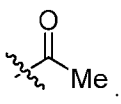
[00095] In one embodiment, the compound has a structure according to Formula (III):



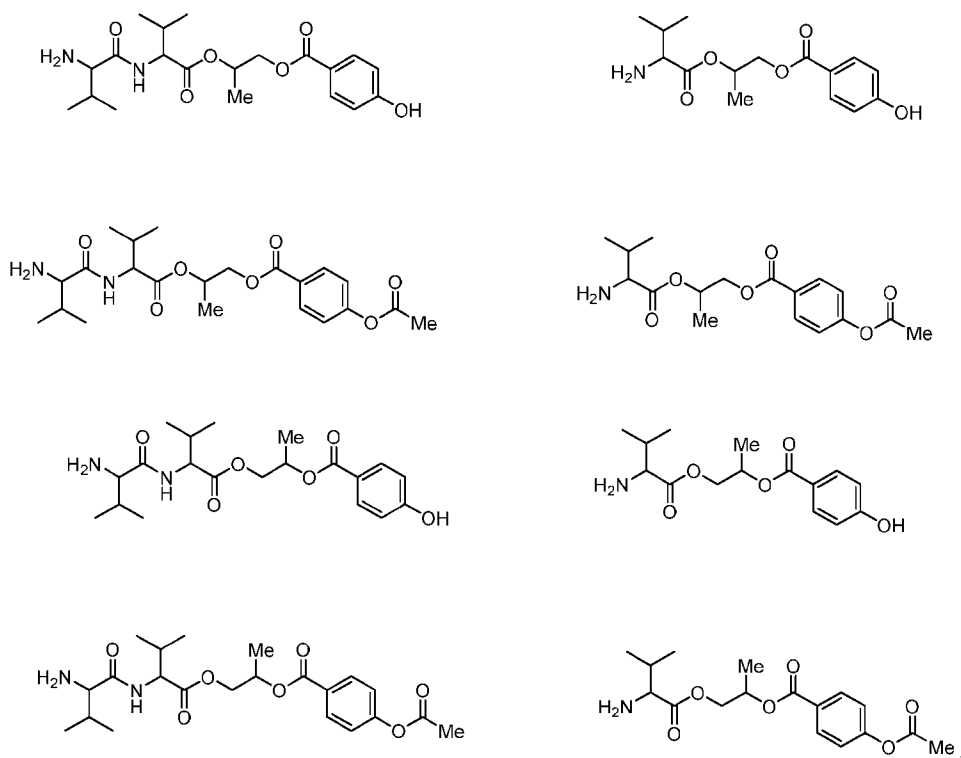
or a pharmaceutically acceptable salt thereof, wherein:



R₁ is selected from the group consisting of H and

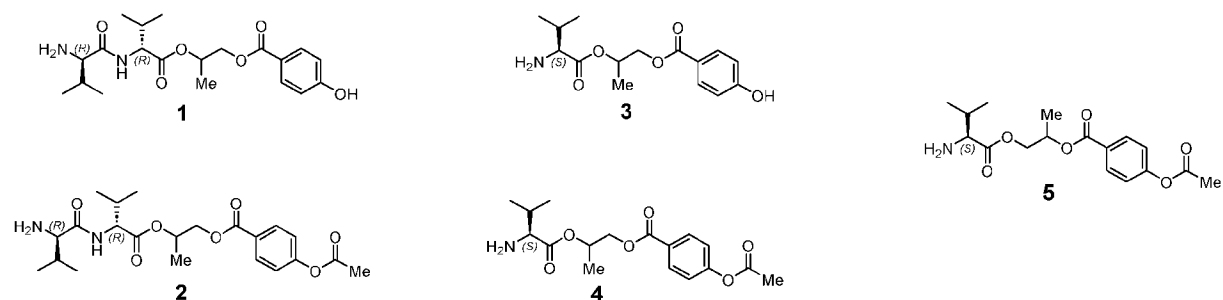
R₄ is selected from the group consisting of H and .

[00096] In one embodiment, the compound has a structure selected from the group consisting of:



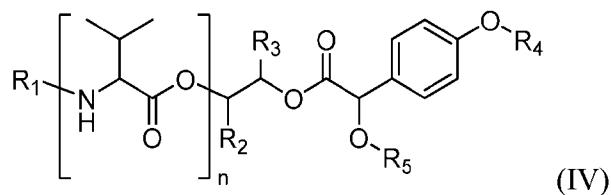
or a pharmaceutically acceptable salt thereof.

[00097] In one embodiment, the compound has a structure selected from the group consisting of:



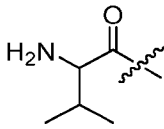
, or a pharmaceutically acceptable salt thereof.

[00098] In another aspect, provided herein is a compound having the structure according to Formula (IV):



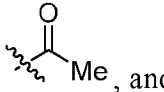
or a pharmaceutically acceptable salt thereof, wherein:

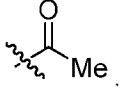
n is 0 or 1;

R₁ is selected from the group consisting of H and  ;

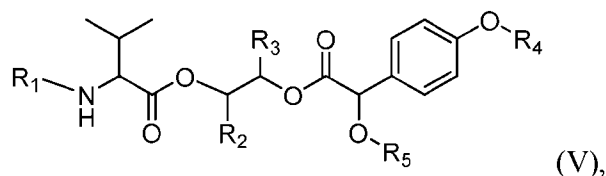
R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

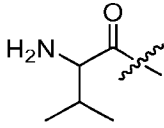
R₄ is selected from the group consisting of H and  , and

R₅ is selected from the group consisting of H and  .

[00099] In one embodiment, the compound has a structure according to Formula (V):

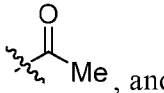


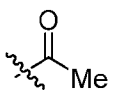
or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;

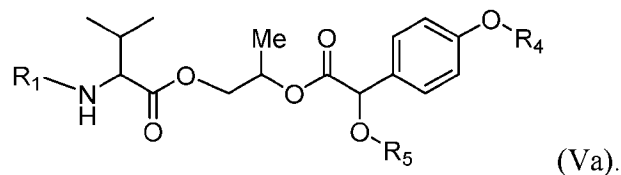
R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

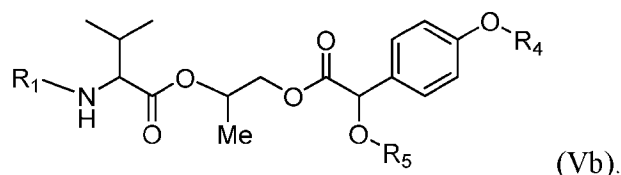
R₄ is selected from the group consisting of H and  , and

R₅ is selected from the group consisting of H and .

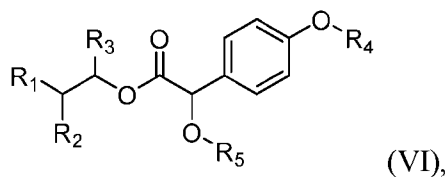
[000100] In one embodiment, the compound has a structure according to Formula (Va):



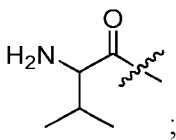
[000101] In one embodiment, the compound has a structure according to Formula (Vb):



[000102] In another embodiment, the compound has a structure according to Formula (VI):

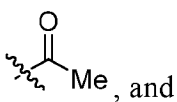


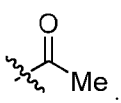
or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;

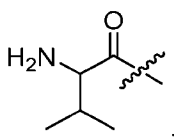
R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

R₄ is selected from the group consisting of H and  , and

R₅ is selected from the group consisting of H and .

[000103] In one embodiment, R₁ is H.

[000104] In one embodiment, R₁ is .

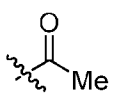
[000105] In one embodiment, R₂ is methyl.

[000106] In one embodiment, R₂ is H.

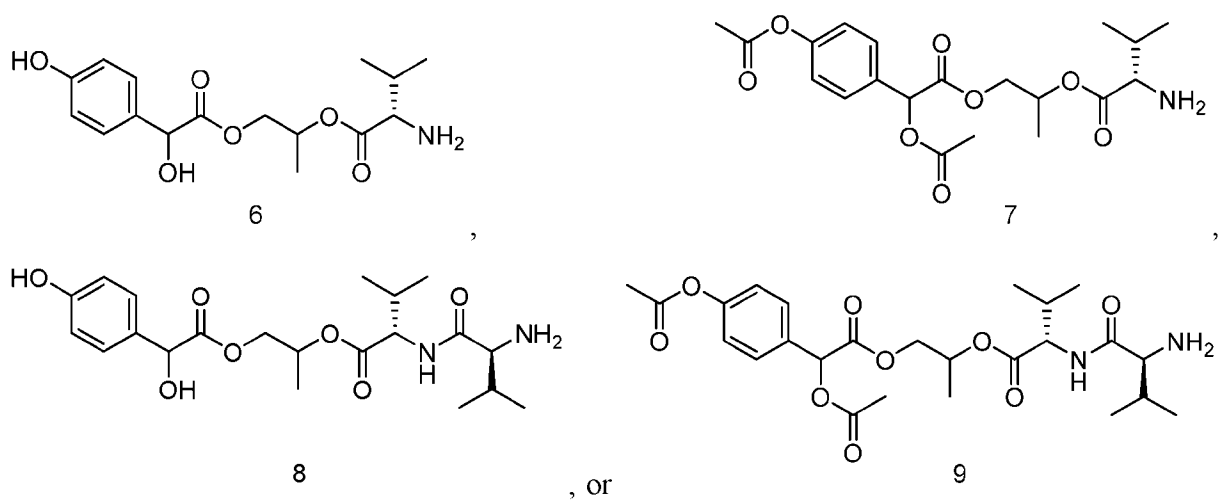
[000107] In one embodiment, R₃ is H.

[000108] In one embodiment, R₃ is methyl.

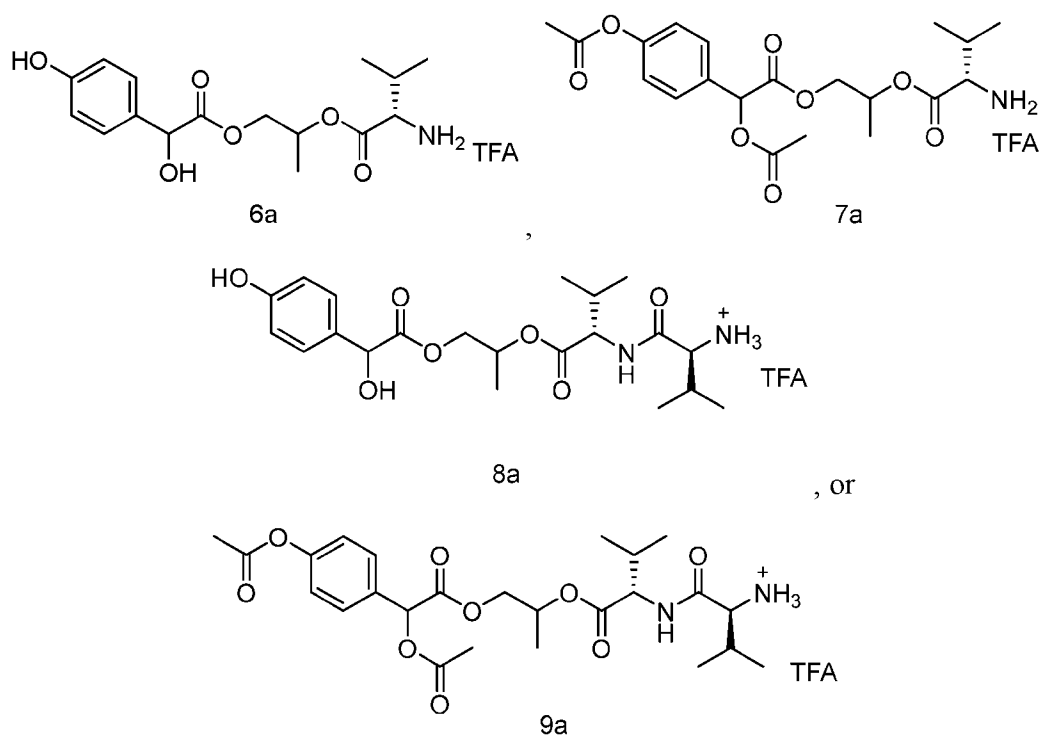
[000109] In one embodiment, R₄ is H.

[000110] In one embodiment, R₄ is .

[000111] In another aspect, provided herein is a compound of formula:

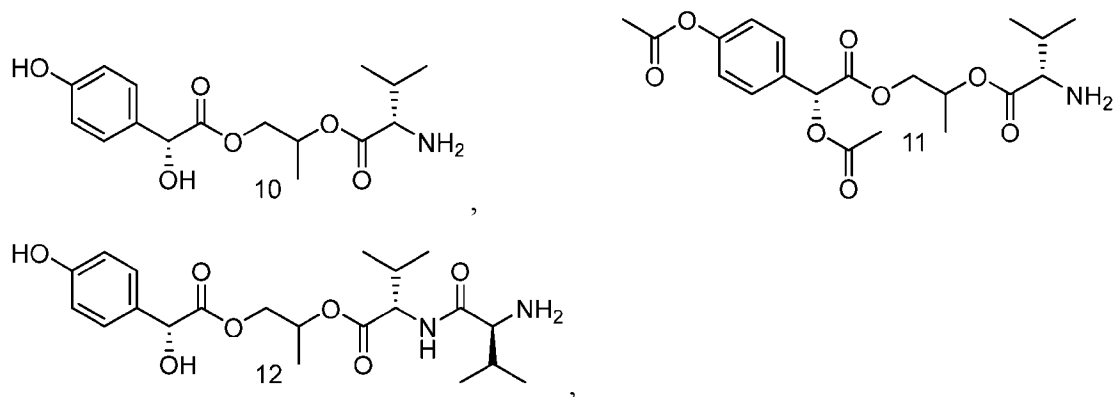


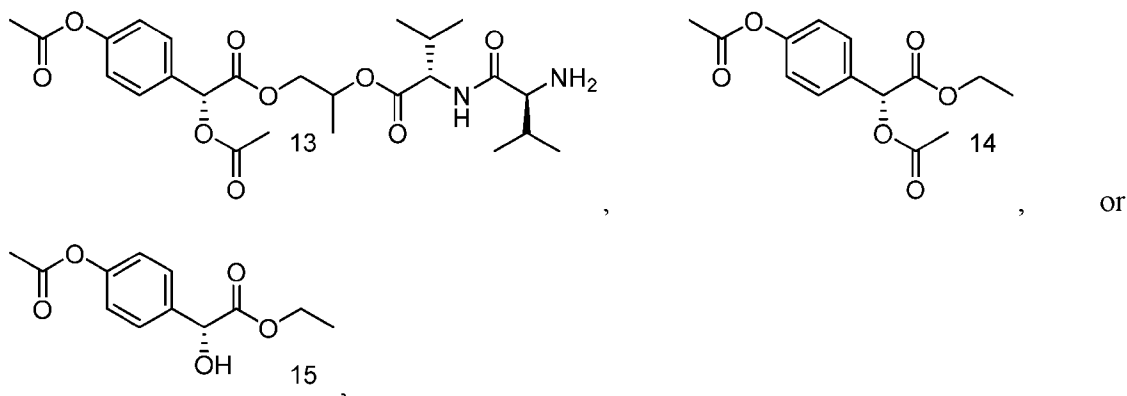
[000112] In another aspect, provided herein is a compound of formula:



or a pharmaceutically acceptable salt thereof.

[000113] In another aspect, provided herein is a compound of formula:





or a pharmaceutically acceptable salt thereof.

[000114] In some embodiments, the esters of 4-HB described in the present disclosure may increase bioavailability and/or half-life ($t_{1/2}$) of 4-HB. In one embodiment, the esters of 4-HB described in the present disclosure have higher bioavailability than 4-HB. In one embodiment, the esters of 4-HB described in the present disclosure have a longer half-life than 4-HB.

[000115] In some embodiments, the esters of 4-HB according to the present disclosure have a pK_a that is higher than pK_a of 4-HB.

[000116] In some embodiments, the esters of 4-HB according to the present disclosure (or 4-HB released from the esters according to the present disclosure) have a half-life ($t_{1/2}$) that is longer than about 0.2 hr, about 0.25 hr, about 0.30 hr, about 0.35 hr, about 0.40 hr, about 0.45 hr, about 0.50 hr, about 0.55 hr, about 0.60 hr, or about 0.65 hr. In some embodiments, $t_{1/2}$ of the esters of 4-HB according to the present disclosure is longer than the $t_{1/2}$ of 4-HB. In some embodiments, the esters of 4-HB according to the present disclosure (or 4-HB released from the esters according to the present disclosure) have a $t_{1/2}$ that is about 0.05 hr, about 0.10 hr, about 0.15 hr, about 0.20 hr, about 0.25 hr, or about 0.30 hr longer than the $t_{1/2}$ of 4-HB. In some embodiments, the esters of 4-HB according to the present disclosure (or 4-HB released from the esters according to the present disclosure) have a $t_{1/2}$ that is at least 0.05 hr, at least 0.10 hr, at least 0.15 hr, at least 0.20 hr, at least 0.25 hr, or at least 0.30 hr longer than the $t_{1/2}$ of 4-HB.

[000117] In some embodiments, the esters of 4-HB according to the present disclosure have a low but steady concentration in the plasma.

[000118] The effective amount of the compound in the composition may be useful for treating or preventing (or both) a disease or disorder associated with aberrant activity (e.g., reduced or abolished activity) of HPDL, treating or preventing (or both) a disease associated with abnormal

production of CoQ10 (e.g., insufficient CoQ10 production), modulating HPDL expression and/or activity, and/or modulating (e.g., increasing) CoQ10 production as a single agent, a mixture, or in combination with one or more additional pharmaceutical agents.

[000119] The effective amount of the compound in the composition may be useful for treating or preventing (or both) a disease or disorder associated with upregulated activity of HPDL, and/or inhibiting HPDL expression and/or activity as a single agent, a mixture, or in combination with one or more additional pharmaceutical agents.

[000120] An effective amount of a compound may vary from about 0.001 mg/kg to about 1000 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration). In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, and from about 10.0 mg/kg to about 150 mg/kg.

[000121] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound(s) described herein (i.e., the “active ingredient”) into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[000122] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000123] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) of the active ingredient.

[000124] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface

active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[000125] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[000126] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[000127] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g., acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g., bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g., stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, propylene glycol monostearate, and polyvinyl alcohol), carbomers (e.g., carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g., carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g., polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (e.g., polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate,

and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g., Cremophor™), polyoxyethylene ethers (e.g., polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[000128] Exemplary binding agents include starch (e.g., cornstarch and starch paste), gelatin, sugars (e.g., sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g., acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[000129] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[000130] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[000131] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof.

[000132] Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin,

hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[000133] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[000134] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[000135] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[000136] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl.

[000137] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[000138] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[000139] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor,

cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mint, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils.

[000140] Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[000141] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[000142] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland

fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[000143] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000144] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

[000145] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[000146] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[000147] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents. They can also be in a form of a composition that releases the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000148] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be a part of a composition that can release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes.

[000149] Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can

be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[000150] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[000151] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000152] Low boiling propellants generally include liquid propellants having a boiling point of below 65° F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[000153] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such

formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[000154] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation can be administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[000155] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[000156] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein.

Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[000157] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[000158] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[000159] The compounds and compositions provided herein can be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, intradermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (e.g., systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration).

[000160] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[000161] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[000162] In certain embodiments, the compounds described herein may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect.

[000163] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[000164] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (e.g., therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (e.g., activity in treating or preventing (or both) a disease or disorder associated with aberrant activity (e.g., reduced or abolished activity) of HPDL, treating or preventing (or both) a disease associated with abnormal production of CoQ10 (e.g., insufficient CoQ10 production), modulating

HPDL expression and/or activity, and/or modulating (e.g., increasing) CoQ10 production), bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body of a subject. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[000165] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, e.g., combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Methods of the Treatment and Uses

[000166] The present invention also provides methods of using the compound(s), or pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) described herein for treating or preventing a disease or disorder.

[000167] In various embodiments, the disease or disorder is related to or caused by one or more mutations in the *HPDL* gene. Such mutations may be present in one or both alleles in the *HPDL* gene. In one embodiment, the one or more mutations in the *HPDL* gene is bi-allelic.

[000168] In some embodiments, the one or more mutations in the *HPDL* gene result in reduced or abolished activity and/or expression of the HPDL protein.

[000169] Mutations in the *HPDL* gene that may be associated with a childhood neurodegenerative disease have been described (Ghosh et al., “Biallelic Variants in HPDL, Encoding 4-Hydroxyphenylpyruvate Dioxygenase-Like Protein, Lead to an Infantile Neurodegenerative Condition,” *Genet. Med.* 23:524-533 (2021); Morgan et al., “Evidence that

Autosomal Recessive Spastic Cerebral Palsy-1 (CPSQ1) is Caused by a Missense Variant in HPDL,” *Brain Commun.* 3(1):fcab002 (2021); Husain et al., “Bi-Allelic HPDL Variants Cause a Neurodegenerative Disease Ranging from Neonatal Encephalopathy to Adolescent-Onset Spastic Paraplegia,” *Am. J. Hum. Genet.* 107:364-373 (2020); Wiessner et al., “Biallelic Variants in HPDL Cause Pure and Complicated Hereditary Spastic Paraplegia,” *Brain* 144(5):1422–1434 (2021), which are hereby incorporated by reference in their entirety). Such mutations include, but are not limited to, p. Leu176Pro (c.527 T > C; rs773333490), p. Ala78Thr, p. Gly126Ser, p. Leu164Pro, p. Gly301Val, p. Gly50Asp (c.149G>A), p. Trp157Arg (c.469T>C), p. Cys168Tyr (c.503G>A), p. Trp179Cys (c.537G>C), p. Leu217Pro (c.650T>C), p. Leu234Pro (c.701T>C), p. Leu248Pro (c.743T>C), p. His251Gln (c.753C>A), p. Gly260Glu (c.779G>A), p. Ile266Thr (c.797T>C), p. Tyr287His (c.859T>C), p. His163Ala, p. His258Ala, p. Gly319Argfs*15, p. Gln32*, p. Glu94Serfs*37 (c.280del), p. Ala115Cysfs*82 (c.342_343insTGCC), p. Leu234Glyfs*94 (c.698_699insTGGGCCAGCATTGTCCCCACTCTTGTCTGGCTGAGTC (SEQ ID NO: 1)), p. Gln241* (c.721C>T), and p. Gln342* (c.1024C>T).

[000170] In some embodiments, the disease or disorder is related to or caused by one or more mutations in additional gene(s) involved in CoQ10 headgroup synthesis. Such mutations may be present in one or both alleles in the target gene.

[000171] In some embodiments, the one or more mutations in additional gene(s) involved in CoQ10 headgroup synthesis result in reduced or abolished activity and/or expression of the protein(s) produced by said gene(s).

[000172] The additional gene(s) involved in CoQ10 headgroup synthesis may include, but are not limited to, Tyrosine Aminotransferase (TAT), Lactate Dehydrogenase D (LDHD), D-2-Hydroxyglutarate Dehydrogenase (D2HGDH), Aldehyde Dehydrogenase 3 Family Member A1 (ALDH3A1), 4-hydroxybenzoate polyprenyltransferase, mitochondrial, (COQ2), Ubiquinone biosynthesis monooxygenase COQ6, mitochondrial (COQ6), Ubiquinone biosynthesis O-methyltransferase, mitochondrial (COQ3), 2-methoxy-6-polyprenyl-1,4-benzoquinol methylase, mitochondrial (COQ5), 5-demethoxyubiquinone hydroxylase, mitochondrial (COQ7), Hydroxylamine oxidoreductase (HAO), Malic Enzyme 3 (ME3), mitochondrial-targeted aldehyde dehydrogenase, and/or Ubiquinone biosynthesis O-methyltransferase, mitochondrial (COQ3). Non-limiting examples of mutations in such genes include, but are not limited to, LDHD mutations Arg370Trp, Thr463Met, Trp376Cys; D2HGDH mutations Val444Ala, Ile147Ser, c.293-23A>G

(IVS1AS, A-G, -23), c.685-2A>G (IVS4AS, A-G, -2), Asn439Asp, 326dupTC, Asp375Tyr; COQ2 mutations Tyr297Cys, Arg197His, Asn228Ser, Ser146Asn, Met128Val, Val393Ala, Arg387Ter, Arg387Gln, 1198delT; COQ5 mutation 9.6-kb Dup; and COQ7 mutation Val141Glu.

[000173] In one aspect, provided herein is a method of treating a 4-hydroxyphenylpyruvate dioxygenase-like (HPDL)-related disease or disorder in a subject in need thereof. This method comprises administering to the subject a therapeutically effective amount of the compound(s), or pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) described herein.

[000174] In another aspect, provided herein is a method of increasing CoQ10 biosynthesis in a subject in need thereof. This method comprises administering to the subject a therapeutically effective amount of the compound(s), pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) described herein.

[000175] In some embodiments, the compound(s), pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) of the present disclosure may be useful in treating a neurodegenerative, neurodevelopmental, or psychiatric disease, aging, obesity, diabetes, metabolic syndrome, insulin resistance, hyperlipidemia, cachexia, chronic fatigue syndrome, wound healing / non-healing wounds, cardiac disease, heart failure, hypertension, immune deficiency, cancer, vitamin deficiency, or infertility.

[000176] In some embodiments, the compound(s), pharmaceutical composition comprising the compound(s), or the dosage form comprising the compound(s) of the present disclosure may be useful in treating a childhood neurodegenerative or neurodevelopmental disease. Non-limiting examples of childhood neurodegenerative diseases include cerebral palsy including autosomal recessive spastic cerebral palsy, mitochondrial diseases, neonatal encephalopathy, adolescent-onset spastic paraplegia, pure and complicated hereditary spastic paraplegia.

[000177] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating cerebral palsy.

[000178] In some embodiments, when the subject being treated is a child, the child may be treated with the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure, in utero, immediately after birth, or in postpartum days.

[000179] In some embodiments, the method may involve treating a newborn or infant by administering the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure, to the newborn or infant.

[000180] In some embodiments, the method may involve treating an unborn fetus by administering the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure, to the pregnant female.

[000181] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating an adult neurodegenerative disease. Non-limiting examples of adult neurodegenerative diseases include Alzheimer's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, chronic traumatic encephalopathy, and Parkinson's disease. For Alzheimer's disease, genome-wide association study (GWAS) data are available showing an association between Alzheimer's disease and HPDL (see, e.g., ebi.ac.uk/gwas/genes/HPDL).

[000182] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating a psychiatric diseases. Non-limiting examples of psychiatric diseases include schizophrenia, major depressive disorder, and bipolar disorders.

[000183] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating aging, obesity, metabolic syndrome, diabetes, insulin resistance, or hyperlipidemia, in which mitochondrial function declines.

[000184] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating cachexia or chronic fatigue syndrome.

[000185] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating a cardiac disease. Non-limiting examples of cardiac diseases include myocardial infarction, heart failure, and hypertension.

[000186] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating an immune deficiency or vitamin deficiencies (e.g. scurvy, which has low vitamin C).

[000187] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating an autosomal recessive spastic paraplegia-83 (SPG83). SPG83 is a neurologic disorder characterized by progressive lower limb spasticity resulting in gait instability.

[000188] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in treating a neurodevelopmental disorder with progressive spasticity and brain white matter abnormalities (NEDSWMA). NEDSWMA is an autosomal recessive disorder characterized by impaired psychomotor development apparent in infancy. Affected individuals show poor overall growth, progressive microcephaly, and axial hypotonia, with later onset of spasticity. The disorder is progressive. Some patients show normal early development, but later have regression of motor, cognitive, and language skills.

[000189] In some embodiments, the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure may be useful in wound healing and/or treating non-healing wounds.

[000190] Additional diseases that may be treated with the compound(s), the pharmaceutical composition(s), or the dosage form(s) of the present disclosure include but, are not limited to, a kidney disease, inflammation, and/or those described in, for example, Hernández-Camacho et al., “Coenzyme Q 10 Supplementation in Aging and Disease,” *Front. Physiol.* 9:44 (2018); Doimo et al., “Genetics of Coenzyme q10 Deficiency,” *Mol. Syndromol.* 5(3-4):156-62 (2014), which are hereby incorporated by reference in their entirety.

[000191] In some embodiments, the methods of the present disclosure may include administering to the subject a therapeutically effective amount of an activator of HPDL. In one embodiment, activator of HPDL is the vitamin C, or a pharmaceutically acceptable salt, prodrug, solvate, or hydrate thereof. Vitamin C may activate dioxygenases including HPDL. Treatment with vitamin C may activate HPDL and stimulate it to generate enough 4-HMA to compensate low 4-HMA levels due to inactive HPDL.

[000192] In various embodiments of the methods described above, the subject is a mammal. In some embodiments, the subject is a human. In some embodiments, the subject is a child, including an unborn fetus, a newborn, an infant, or a toddler. In some embodiments, the subject is an adult. In some embodiments, treating an unborn fetus using methods described herein may involve treating a pregnant female carrying the unborn fetus. Accordingly, the subject can be a

pregnant female and the one or more mutations in the *HPDL* gene and/or additional gene(s) involved in CoQ10 headgroup synthesis can be present in the fetal DNA derived from the pregnant female.

EXAMPLES

[000193] The following examples illustrate specific aspects of the instant description. The examples should not be construed as limiting, as the examples merely provide specific understanding and practice of the embodiments and their various aspects.

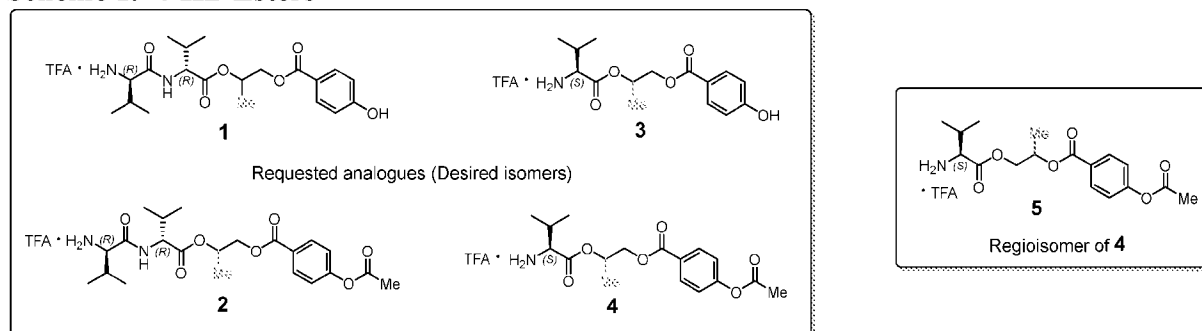
General Information

[000194] Abbreviations

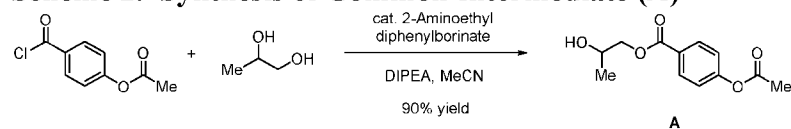
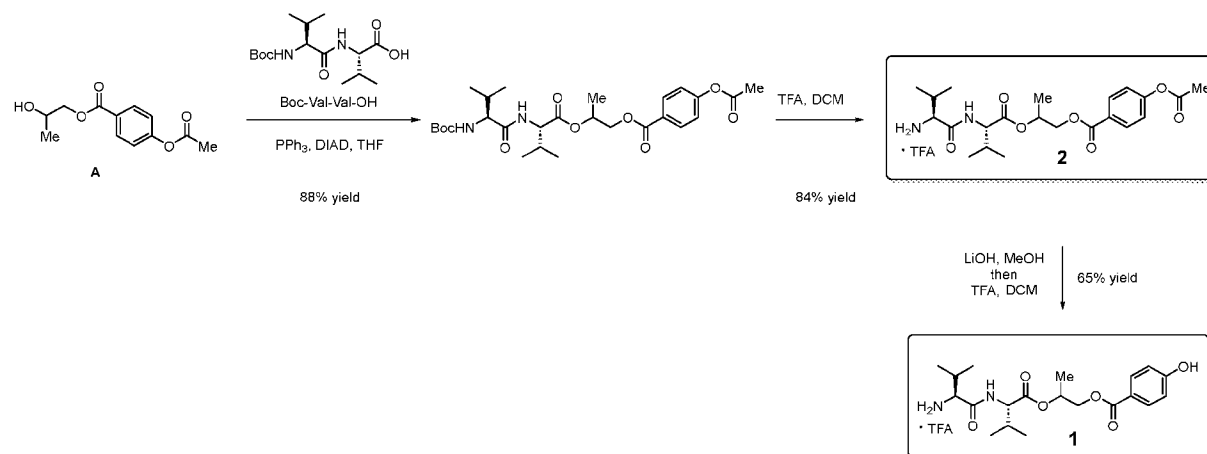
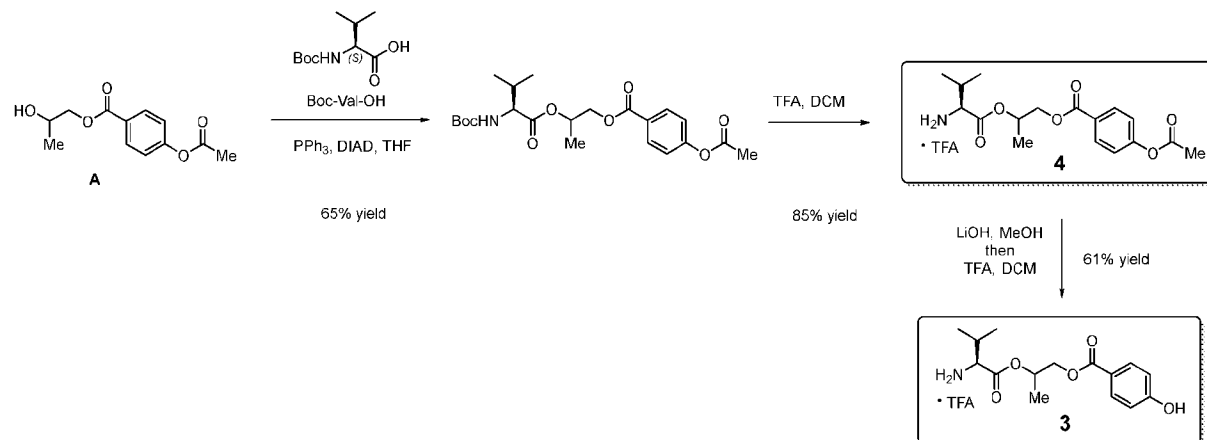
TFA	Trifluoroacetate
DIPEA	Diisopropylethylamine
MeCN	Acetonitrile
PPh ₃	Triphenylphosphine
DIAD	Diisopropyl azodicarboxylate
THF	Tetrahydrofuran
DCM	Dichloromethane
MeOH	Methanol
LiOH	Lithium hydroxide

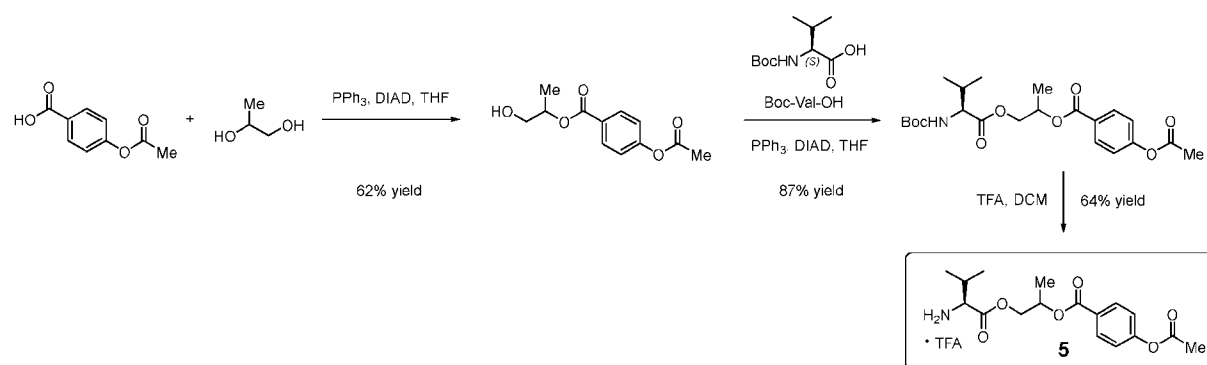
Example 1: Synthesis of 4-HB Esters

Scheme 1. 4-HB Esters



[000195] Compounds **1-5** were synthesized from a common intermediate (**A**), as described in Schemes 2-5 below.

Scheme 2. Synthesis of Common Intermediate (A)**Scheme 3. Synthesis of Compound (1) and Compound (2)****Scheme 4. Synthesis of Compound (3) and Compound (4)**

Scheme 5. Synthesis of Compound (5)**Example 2: Growth Rescue**

[000196] The 4-HB esters (compounds **1-5**, Scheme 1) have been tested in Hpd1^{-/-} mice (n=1 for each ester) and have shown to rescue the growth of these mice (**Figure 2**).

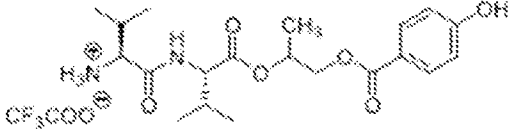
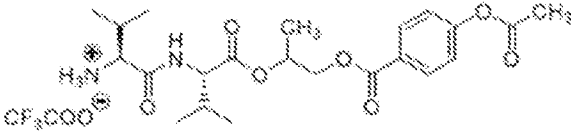
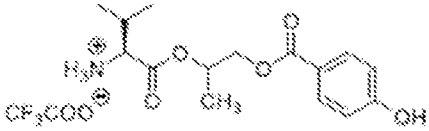
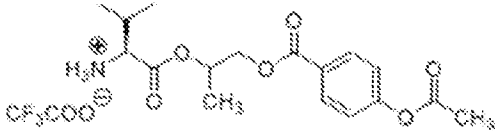
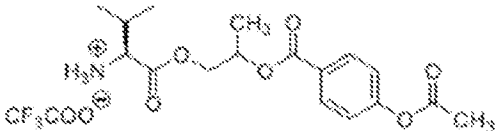
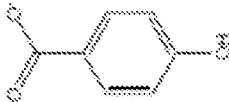
Example 3: Pharmacokinetic Studies

[000197] With the exception for compound **4**, 4-HB and 4-HB esters were not detected intact in plasma (**Figure 3**).

[000198] The half-life ($t_{1/2}$) and mean residence time (MRT) for 4-HB and 4-HB esters were measured. For 4-HB, $t_{1/2}$ = 0.348 hr and MRT = 0.661 hr. Compound **1** shown $t_{1/2}$ = 0.542 hr and MRT = 0.912 hr. Compound **4** shown $t_{1/2}$ = 0.318 hr and MRT = 0.575 hr.

[000199] The solubility of 4-HB esters (compounds **1-5**) was tested (**Table 1**). The solubility of all 4-HB esters was at least double the solubility of 4-HB.

Table 1. Solubility of 4-HB Esters

Compound	Solubility
	≥10 mg/mL in water
	≥10 mg/mL in water
	≥10 mg/mL in water
	≥10 mg/mL in water
	
	5 mg/mL in water (Human Metabolome Database)

[000200] The efficiency of 4-HB esters in mice was tested. 2 out of 4 breeding pairs of *Hpd1*^{-/-} mice rescued with the esters produced viable offspring. None of the breeding pairs of *Hpd1*^{-/-} mice rescued with 4-HB produced viable offspring.

Fertility of *Hpd1*^{+/+} ♂ x *Hpd1*^{+/+} ♀ treated with 4-HB: 0 / 4 breeding pairs

Fertility of *Hpd1*^{+/+} ♂ x *Hpd1*^{+/+} ♀ treated with 4-HB esters: 2 / 4 breeding pairs

Example 4: Differential Efficacy of 4-HMA Enantiomers

[000201] Enantiopure R- and S- 4-HMA were obtained from WuXi Apptec and purified using chiral chromatography. Compounds were dissolved in water and administered orally to *Hpdl*^{-/-} mouse pups at a dose of 10 mg/kg once daily. Compounds were administered for 30 days and subsequently stopped.

[000202] All *Hpdl*^{-/-} mice rescued to date with 4-HMA have been treated with a racemic mixture of equal quantities of R- HMA and S-4-HMA. Treatment of *Hpdl*^{-/-} mice with enantiopure 4-HMA revealed that only R-4-HMA rescues mice effectively (Figures 4A-4B).

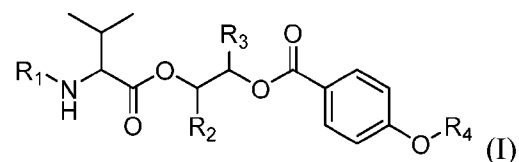
[000203] S-4-HMA could act as an inhibitor of HPDL. At a minimum this indicates that the rescue is actually twice as effective, because only half of the racemic mixture rescues the survival of the *Hpdl*^{-/-} mice.

[000204] As various changes can be made in the above-described subject matter without departing from the scope and spirit of the present invention, it is intended that all subject matter contained in the above description, or defined in the appended claims, be interpreted as descriptive and illustrative of the present invention. Many modifications and variations of the present invention are possible in light of the above teachings. Accordingly, the present description is intended to embrace all such alternatives, modifications, and variances which fall within the scope of the appended claims.

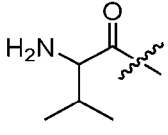
[000205] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference in their entirety as if physically present in this specification.

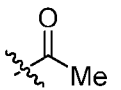
WHAT IS CLAIMED IS:

1. A compound having the structure according to Formula (I):

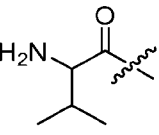


or a pharmaceutically acceptable salt thereof, wherein:

- R_1 is selected from the group consisting of H and  ;
- R_2 is selected from the group consisting of H and C₁-C₃ alkyl;
- R_3 is selected from the group consisting of H and C₁-C₃ alkyl, and

R_4 is selected from the group consisting of H and .

2. The compound of claim 1, wherein R_1 is H.

3. The compound of claim 1, wherein R_1 is .

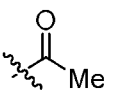
4. The compound of claim 1, wherein R_2 is methyl.

5. The compound of claim 1, wherein R_2 is H.

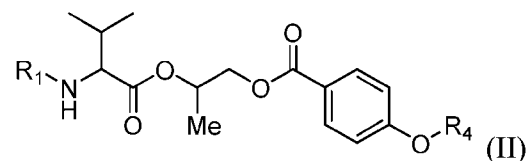
6. The compound of claim 1, wherein R_3 is H.

7. The compound of claim 1, wherein R_3 is methyl.

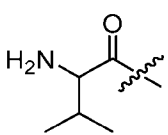
8. The compound of claim 1, wherein R_4 is H.

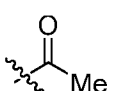
9. The compound of claim 1, wherein R₄ is .

10. The compound of claim 1 having the structure according to Formula (II):

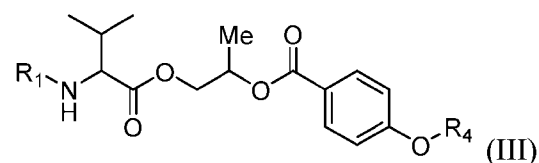


or a pharmaceutically acceptable salt thereof, wherein:

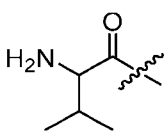
R₁ is selected from the group consisting of H and , and

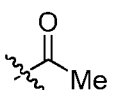
R₄ is selected from the group consisting of H and .

11. The compound of claim 1 having the structure according to Formula (III):

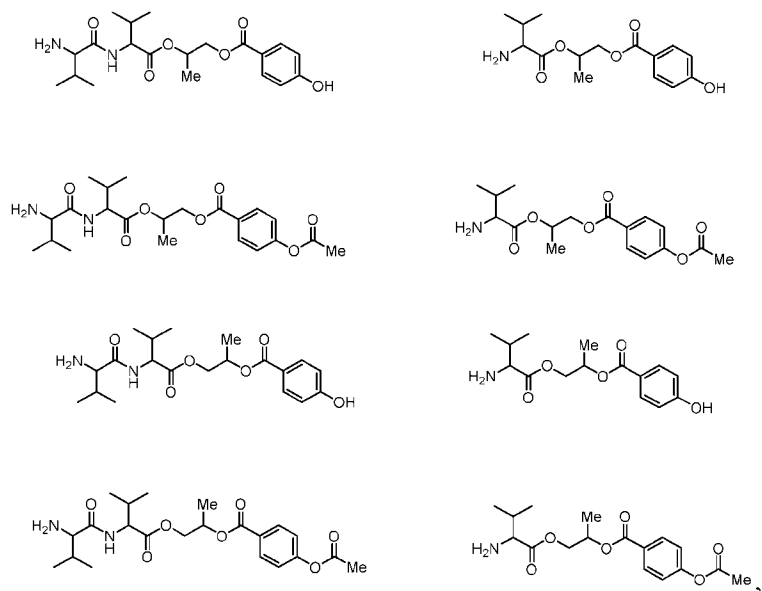


or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and , and

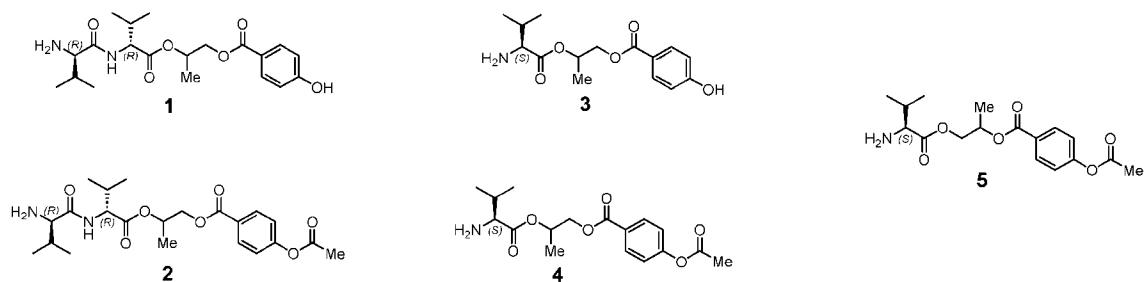
R₄ is selected from the group consisting of H and .

12. The compound of claim 1, wherein the compound has a structure selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

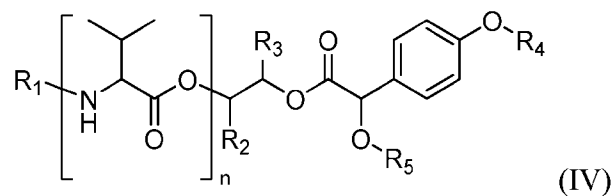
13. The compound of claim 1, wherein the compound has a structure selected from the group consisting of:



, or a

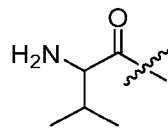
pharmaceutically acceptable salt thereof.

14. A compound having the structure according to Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein:

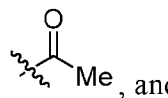
n is 0 or 1;



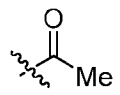
R₁ is selected from the group consisting of H and ;

R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

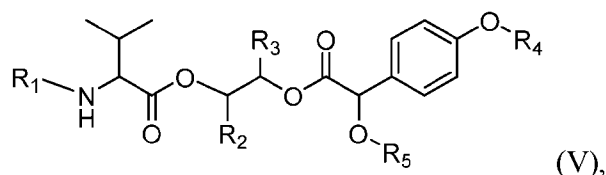


R₄ is selected from the group consisting of H and , and

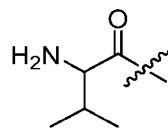


R₅ is selected from the group consisting of H and .

15. The compound of claim 14, the compound has a structure according to Formula (V):



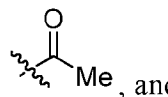
or a pharmaceutically acceptable salt thereof, wherein:



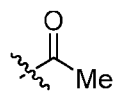
R₁ is selected from the group consisting of H and ;

R₂ is selected from the group consisting of H and C₁-C₃ alkyl;

R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

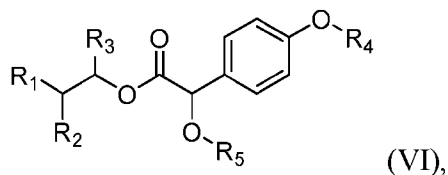


R₄ is selected from the group consisting of H and , and

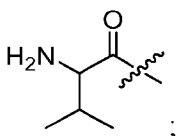


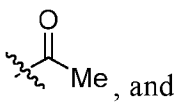
R₅ is selected from the group consisting of H and .

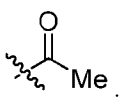
16. The compound of claim 14, the compound has a structure according to Formula (VI):



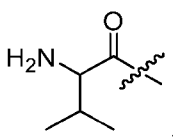
or a pharmaceutically acceptable salt thereof, wherein:

R₁ is selected from the group consisting of H and  ;
 R₂ is selected from the group consisting of H and C₁-C₃ alkyl;
 R₃ is selected from the group consisting of H and C₁-C₃ alkyl;

R₄ is selected from the group consisting of H and  , and

R₅ is selected from the group consisting of H and .

17. The compound of claim 14, wherein R₁ is H.

18. The compound of claim 14, wherein R₁ is .

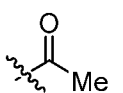
19. The compound of claim 14, wherein R₂ is methyl.

20. The compound of claim 14, wherein R₂ is H.

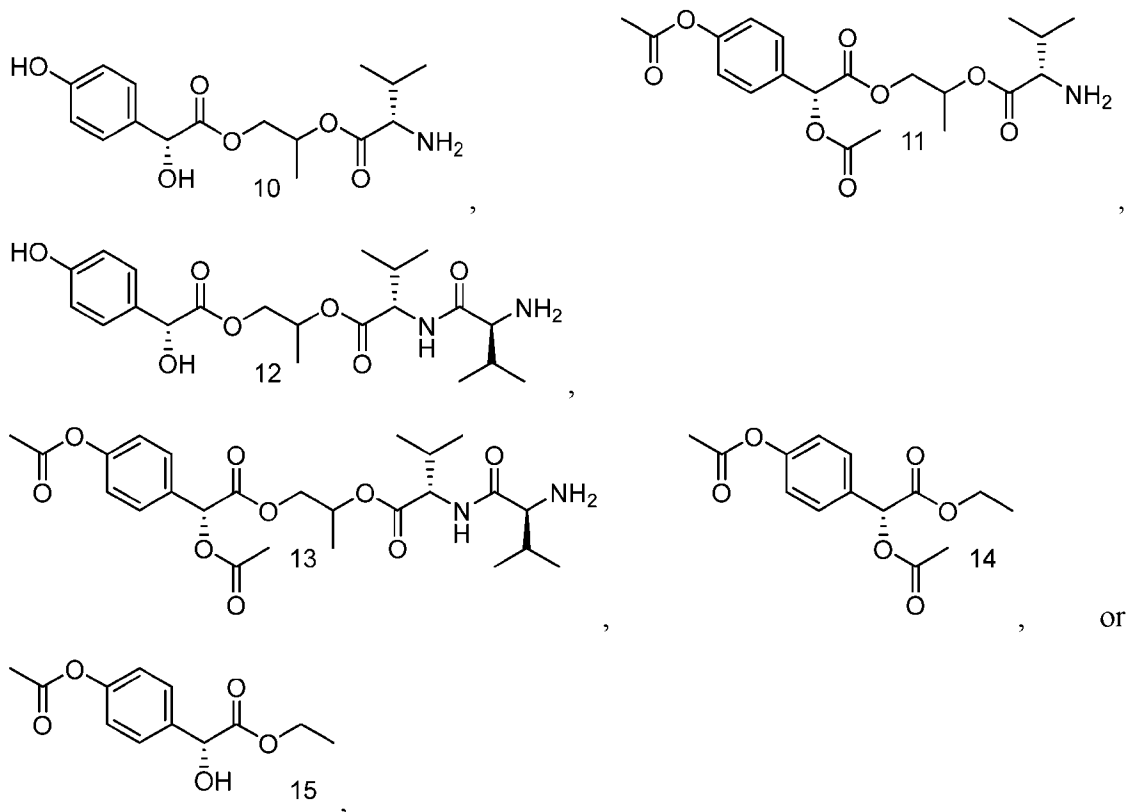
21. The compound of claim 14, wherein R₃ is H.

22. The compound of claim 14, wherein R₃ is methyl.

23. The compound of claim 14, wherein R₄ is H.

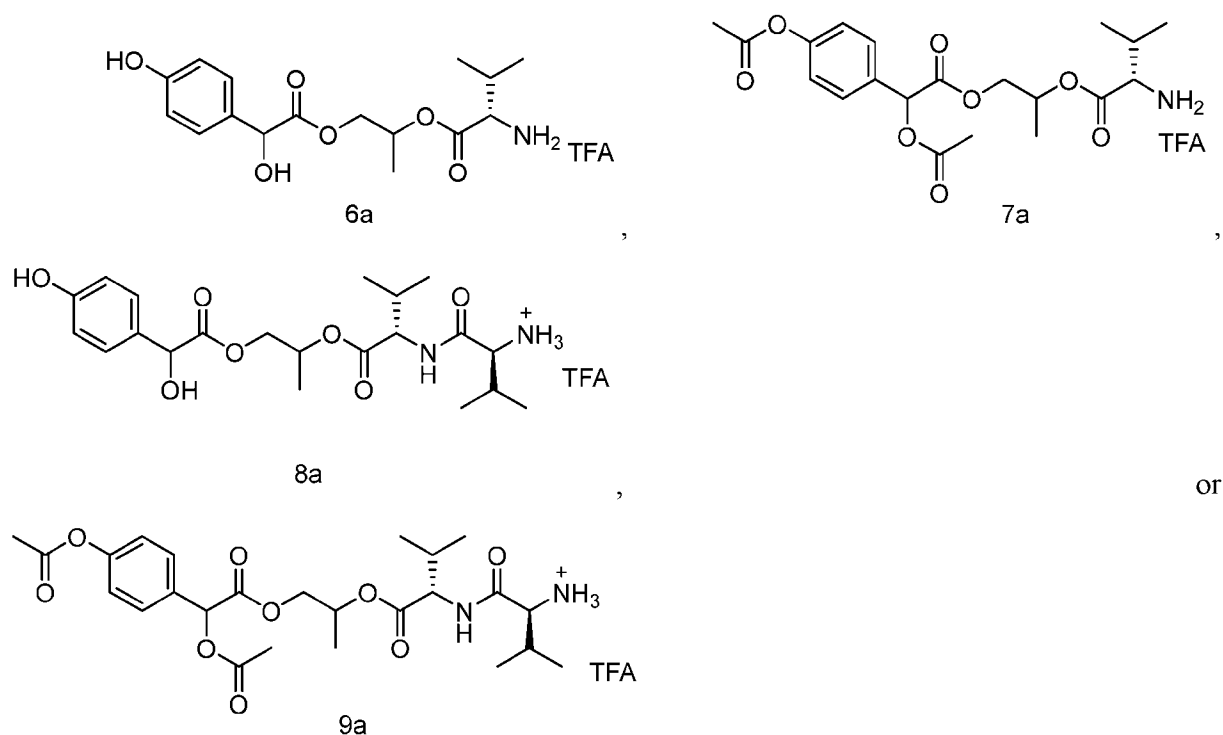
24. The compound of claim 14, wherein R₄ is .

25. The compound of claim 14, wherein the compound has a structure selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

26. A compound of formula:



or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising the compound of any one of claims 1-26 or a pharmaceutically acceptable salt, solvate, or hydrate thereof and a pharmaceutically acceptable carrier.
28. A pharmaceutical dosage form comprising the compound of any one of claims 1-26 or a pharmaceutically acceptable salt, solvate, or hydrate thereof or the pharmaceutical composition of claim 27.
29. A method of treating a 4-hydroxyphenylpyruvate dioxygenase-like (HPDL)-related disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-26, the pharmaceutical composition of claim 27, or the dosage form of claim 28.

30. A method of increasing CoQ10 biosynthesis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-26, the pharmaceutical composition of claim 27, or the dosage form of claim 28.
31. The method of any one of claims 29 or 30, further comprising administering to the subject a therapeutically effective amount of an activator of HPDL.
32. The method of claim 31, wherein the activator of HPDL is vitamin C, or a pharmaceutically acceptable salt, prodrug, solvate, or hydrate thereof.
33. The method of any one of claims 29-32, wherein the subject has one or more mutations in the *HPDL* gene.
34. The method of claim 33, wherein the one or more mutations in the *HPDL* gene result in reduced or abolished activity and/or expression of the HPDL protein.
35. The method of claim 33 or 34, wherein the one or more mutations in the *HPDL* gene is bi-allelic.
36. The method of any one of claims 33-35, wherein the one or more mutations in the *HPDL* gene is selected from p. Leu176Pro (c.527 T > C; rs773333490), p.Ala78Thr, p.Gly126Ser, p.Leu164Pro, p.Gly301Val, p.Gly50Asp (c.149G>A), p.Trp157Arg (c.469T>C), p.Cys168Tyr (c.503G>A), p.Trp179Cys (c.537G>C), p.Leu217Pro (c.650T>C), p.Leu234Pro (c.701T>C), p.Leu248Pro (c.743T>C), p.His251Gln (c.753C>A), p.Gly260Glu (c.779G>A), p.Ile266Thr (c.797T>C), p.Tyr287His (c.859T>C), p.His163Ala, p.His258Ala, p.Gly319Argfs*15, p.Gln32*, p.Glu94Serfs*37 (c.280del), p.Ala115Cysfs*82 (c.342_343insTGCC), p.Leu234Glyfs*94 (c.698_699insTGGGCCAGCATTGTCCCCACTCTTGTCTGGCTGAGTC (SEQ ID NO: 1)), p.Gln241* (c.721C>T), and p.Gln342* (c.1024C>T).

37. The method of any one of claims 29-36, wherein the subject has one or more mutations in additional gene(s) involved in CoQ10 headgroup synthesis.
38. The method of claim 37, wherein the one or more mutations in additional gene(s) involved in CoQ10 headgroup synthesis result in reduced or abolished activity and/or expression of the protein(s) produced by said gene(s).
39. The method of claim 37 or 38, wherein the additional gene(s) involved in CoQ10 headgroup synthesis is Tyrosine Aminotransferase (TAT), Lactate Dehydrogenase D (LDHD), D-2-Hydroxyglutarate Dehydrogenase (D2HGDH), Aldehyde Dehydrogenase 3 Family Member A1 (ALDH3A1), 4-hydroxybenzoate polyprenyltransferase, mitochondrial, (COQ2), Ubiquinone biosynthesis monooxygenase COQ6, mitochondrial (COQ6), Ubiquinone biosynthesis O-methyltransferase, mitochondrial (COQ3), 2-methoxy-6-polyprenyl-1,4-benzoquinol methylase, mitochondrial (COQ5), 5-demethoxyubiquinone hydroxylase, mitochondrial (COQ7), Hydroxylamine oxidoreductase (HAO), Malic Enzyme 3 (ME3), mitochondrial-targeted aldehyde dehydrogenase, and/or Ubiquinone biosynthesis O-methyltransferase, mitochondrial (COQ3).
40. The method of any one of claims 37-39, wherein the one or more mutations are selected from LDHD mutations Arg370Trp, Thr463Met, Trp376Cys; D2HGDH mutations Val444Ala, Ile147Ser, c.293-23A>G (IVS1AS, A-G, -23), c.685-2A>G (IVS4AS, A-G, -2), Asn439Asp, 326dupTC, Asp375Tyr; COQ2 mutations Tyr297Cys, Arg197His, Asn228Ser, Ser146Asn, Met128Val, Val393Ala, Arg387Ter, Arg387Gln, 1198delT; COQ5 mutation 9.6-kb Dup; and COQ7 mutation Val141Glu.
41. The method of claim 29, wherein the HPDL-related disease or disorder is a neurodegenerative, neurodevelopmental, or psychiatric disease, aging, obesity, diabetes, metabolic syndrome, insulin resistance, hyperlipidemia, cachexia, chronic fatigue syndrome, wound healing / non-healing wounds, cardiac disease, heart failure, hypertension, immune deficiency, cancer, vitamin deficiency, or infertility.

42. The method of claim 41, wherein the HPDL-related disease or disorder is a childhood neurodegenerative or neurodevelopmental disease.
43. The method of claim 42, wherein the childhood neurodegenerative disease is cerebral palsy, mitochondrial disease, neonatal encephalopathy, adolescent-onset spastic paraplegia, pure and complicated hereditary spastic paraplegia.
44. The method of any one of claims 41-43, wherein the HPDL-related disease or disorder is cerebral palsy.
45. The method of any one of claims 41-43, wherein the HPDL-related disease or disorder is SPG83.
46. The method of any one of claims 41-43, wherein the HPDL-related disease or disorder is NEDSWMA.
47. The method of claim 41, wherein the HPDL-related disease or disorder is an adult neurodegenerative disease.
48. The method of claim 47, wherein the adult neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, chronic traumatic encephalopathy, or Parkinson's disease.
49. The method of any one of claims 29-48, wherein the subject is a mammal.
50. The method of claim 49, wherein the subject is a human.
51. The method of claim 49 or 50, wherein the subject is a child.
52. The method of claim 49 or 50, wherein the subject is an adult.

53. The compound according to any one of claims 1-26, wherein the compound has a half-life ($t_{1/2}$) that is longer than about 0.5 hr.
54. The compound according to any one of claims 1-26, wherein the compound has a half-life ($t_{1/2}$) that is about 0.15 hr longer than the $t_{1/2}$ of 4-HB.
55. The compound according to any one of claims 1-26, wherein the compound has a bioavailability that is higher than the bioavailability of 4-HB.

1/6

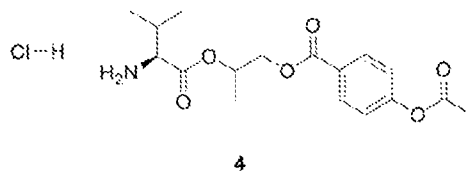
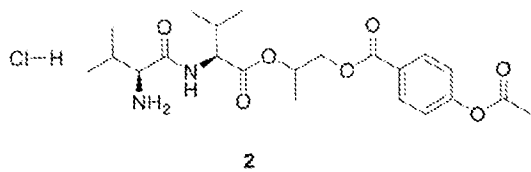
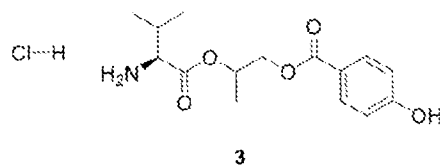
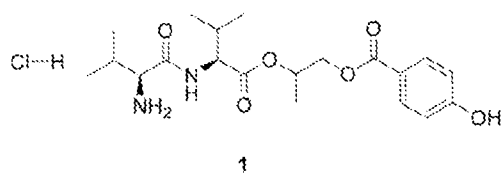
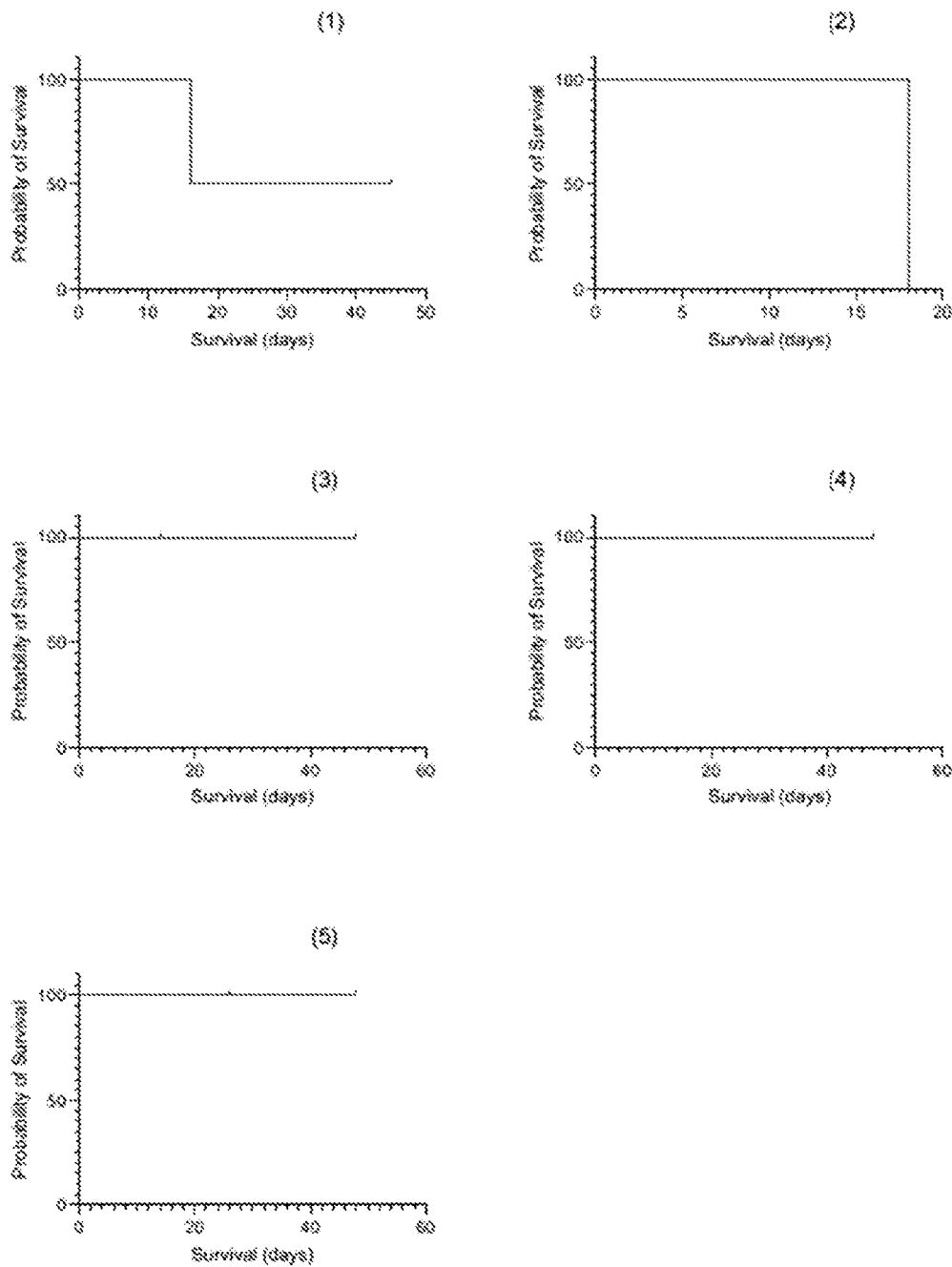
FIGURE 1

FIGURE 2



3/6

FIGURE 3

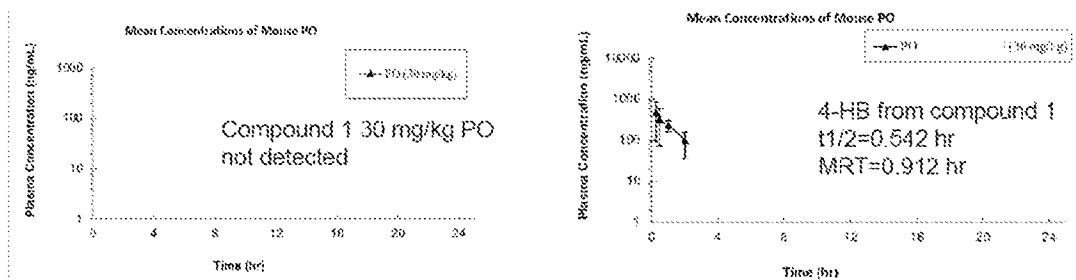
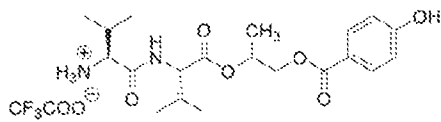
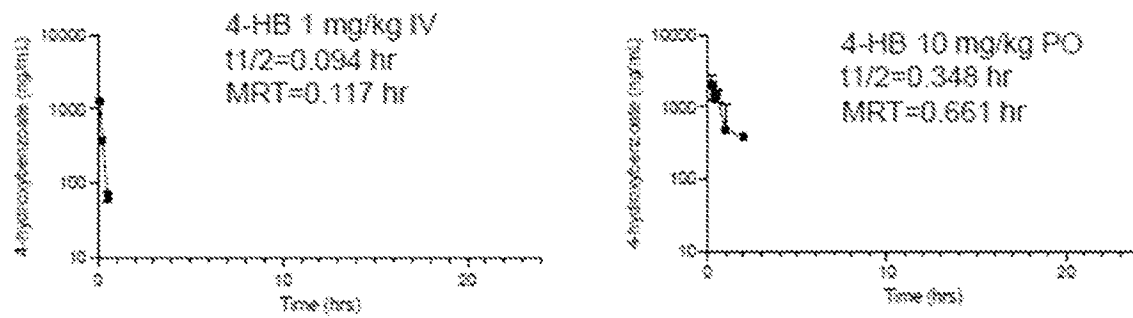
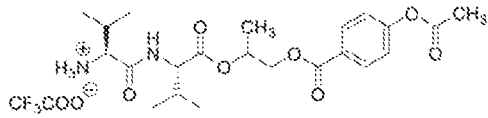
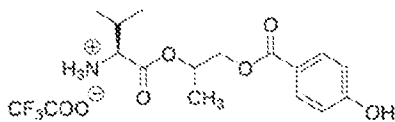
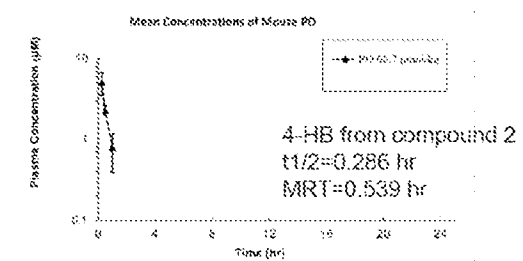
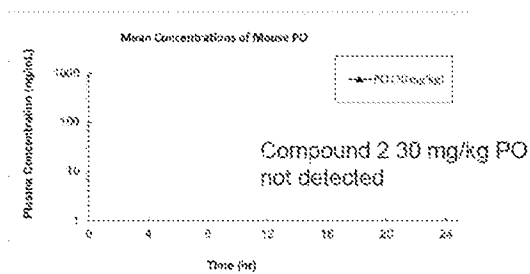


FIGURE 3 (cont.)

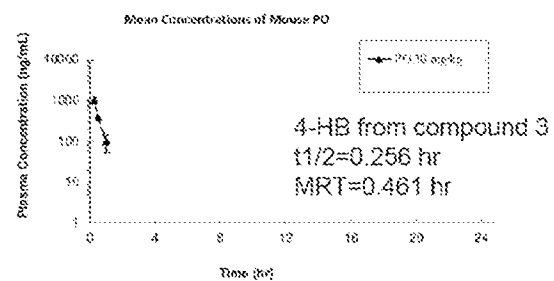
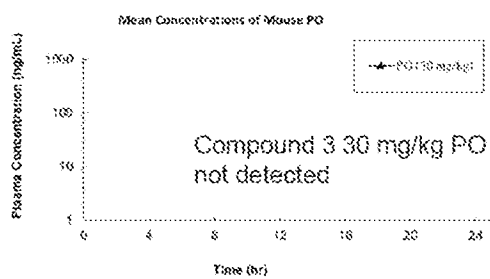


2

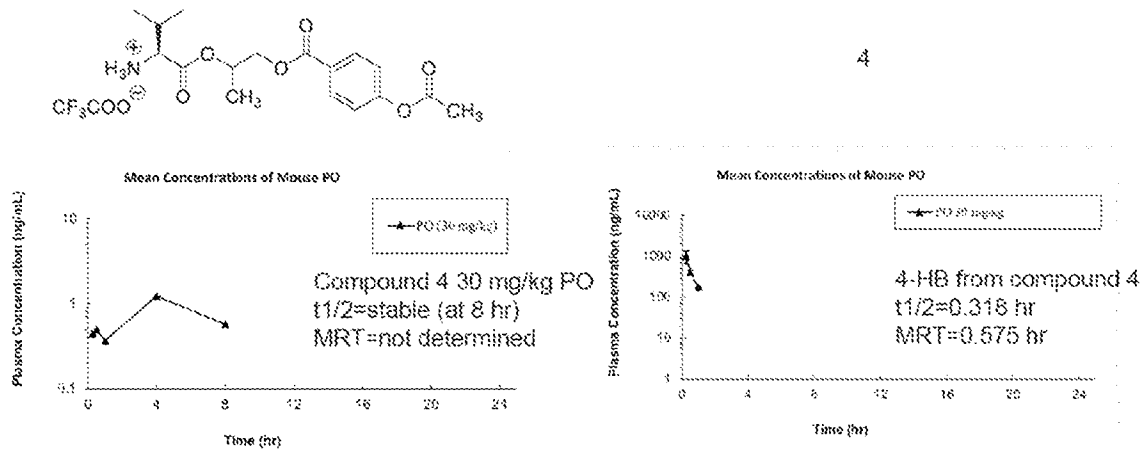
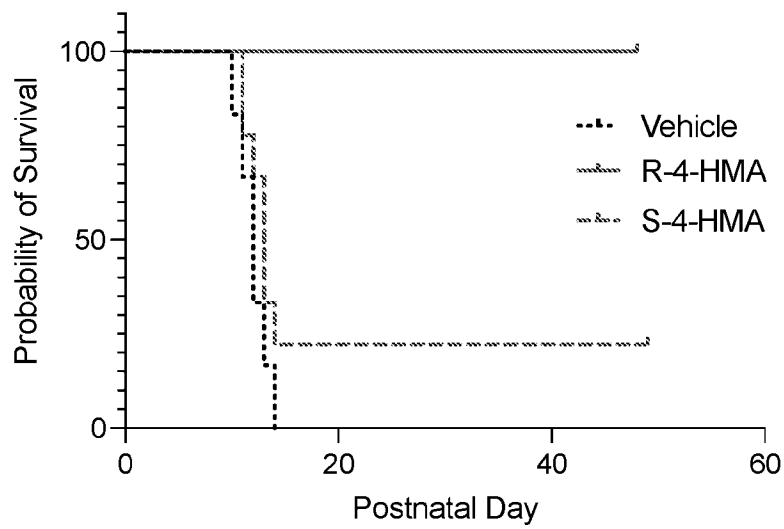


3

≥10 mg/mL in water



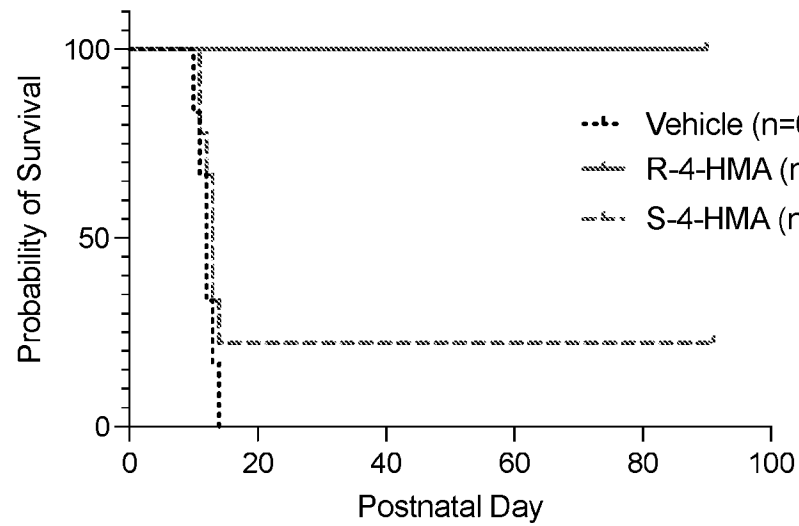
5/6

FIGURE 3 (cont.)**FIGURE 4A****Enantiomers**

6/6

FIGURE 4B

Enantiomers



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037534

A. CLASSIFICATION OF SUBJECT MATTERIPC: **C07C 63/06** (2023.01); **A61K 31/19** (2023.01); **A61P 25/28** (2023.01)CPC: **C07C 63/06**; **A61K 31/19**; **A61P 25/28**

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	WO 2010/047775 A2 (XENOPORT INC.) 29 April 2010 (29.04.2010) entire document	1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55
A	US 2022/0251295 A1 (DYNAMIC BIOLOGICS INC.) 11 August 2022 (11.08.2022) entire document	1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55
A	WO 2022/159473 A1 (NEW YORK UNIVERSITY) 28 July 2022 (28.07.2022) entire document	1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55
A	PUBCHEM, SID 43898548, Modify Date: 05 December 2007 [retrieved on 22 August 2024].,Retrieved from the Internet <url: https:="" pubchem.ncbi.nlm.nih.gov="" substance="" 43898548=""> entire document</url:>	1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55

☒ 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

05 September 2024 (05.09.2024)

Date of mailing of the international search report

23 October 2024 (23.10.2024)

Name and mailing address of the ISA/US

COMMISSIONER FOR PATENTS
MAIL STOP PCT, ATTN: ISA/US
P.O. Box 1450
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UNITED STATES OF AMERICA

Authorized officer

TAINA MATOS

Facsimile No. 571-273-8300

Telephone No. (571)272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/037534

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, SID 187564854, Modify Date: 04 October 2017 [retrieved on 19 August 2024]., Retrieved from the Internet <url: https:="" pubchem.ncbi.nlm.nih.gov="" substance="" 187564854=""> entire document</url:>	1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037534

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037534

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **28-52**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-27 and 53-55 are drawn to compounds having the structure according to Formula (I), or a pharmaceutically acceptable salt thereof, compounds having the structure according to Formula (IV), or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions.

The first invention of Group I+ is restricted to a compound having the structure according to Formula (I), or a pharmaceutically acceptable salt thereof, specifically the first shown compound in instant claim 12, compounds having the structure according to Formula (IV) comprising the same, and pharmaceutical compositions comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claim 12). It is believed that claims 1, 3, 4, 6, 8, 10, 12, 13, 27, and 53-55 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having the structure according to Formula (I), or a pharmaceutically acceptable salt thereof, specifically the second shown compound in instant claim 12, compounds having the structure according to Formula (IV) comprising the same, and pharmaceutical compositions comprising the same. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Group I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/037534

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the variables, R1, R2, R3, R4, R5, n, and accordingly these groups lack unity a priori.

Additionally, even if Group I+ were considered to share the technical features of a compound having the core structure of Formula (I), or a pharmaceutically acceptable salt thereof; a compound having the core structure of Formula (IV), or a pharmaceutically acceptable salt thereof; and a pharmaceutical composition comprising a compound and a pharmaceutically acceptable carrier, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2010/047775 A2 to Xenoport, Inc. (hereinafter, "Xenoport"), Substance Record for SID 187564854 to PubChem (hereinafter, "PubChem"), and US 2022/0251295 A1 to Dynamic Biologics Inc. (hereinafter, "DBI").

Xenoport teaches a compound having the core structure of Formula (I), or a pharmaceutically acceptable salt thereof (Para. [071], compound 6).

PubChem teaches a compound having the core structure of Formula (IV), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown);

DBI teaches a pharmaceutical composition comprising a compound and a pharmaceutically acceptable carrier (Para. [0017], the present invention provides a compound of formula I; Para. [0027], embodiments of the invention provide compositions comprising a pharmaceutically effective amount of the compound formula I and one or more pharmaceutically acceptable carriers).

The inventions listed in Group I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1, 3, 4, 6, 8, 10, 12, 13, 27, 53-55**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.