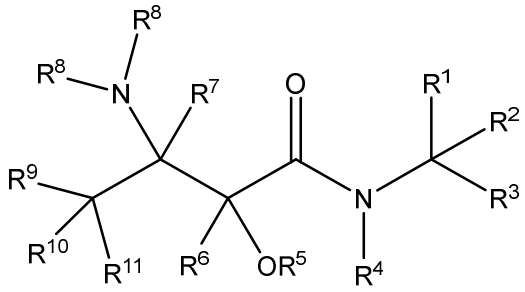
transpeptidase activity of CNDP2 enzyme in the formation of NLAA conjugates. Thus, the significant increase in circulating levels of NLAA observed in MELAS, PKU, sepsis, T2DM, and cancer might be due to a mitochondrial dysfunction mediated shift in cellular metabolism to generate excess lactate, a phenomenon similar to that elicited by metformin.

The modulation of the biochemical pathway involved in the formation of NLAAs and their release into the systemic circulation influences health and disease outcomes. This provides the scientific rationale for the development of therapeutic interventions directly targeting the enzymatic activity of CNDP2 to modulate the biosynthesis of NLAAs for the treatment of disease and maintenance of health.

Gait speed and grip strength are validated measures for reliable assessment of physical performance in aging adults and in other clinical conditions. In a population cohort of 1298 participants, N-lactoyl phenylalanine was one of seven metabolites associated with a decline in gait speed, suggesting the involvement of NLAAs in influencing physical performance (Nierenberg JL et al., 2020).

In another population study consisting of 3042 individuals (1290 men and 1752 women) over age 60, a comprehensive metabolomic profile found that an increase in NLAA levels is associated with decreased grip strength. (unpublished data).

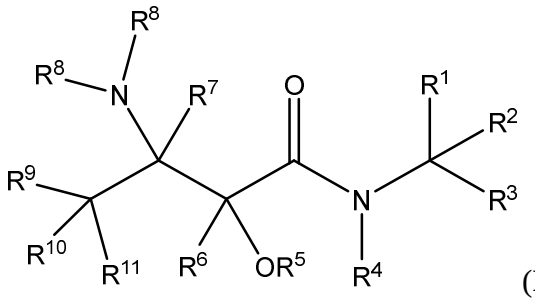
In one example, compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, are featured:



(**I**)

in which $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^a}$, $\mathbf{R^b}$, $\mathbf{R^c}$, $\mathbf{R^d}$, $\mathbf{R^e}$, $\mathbf{R^f}$, $\mathbf{R^g}$, **R'**, **R"**, $\mathbf{L^1}$, $\mathbf{L^2}$, $\mathbf{L^3}$, and $\mathbf{L^4}$ can be as defined anywhere herein.

In a first aspect of the present disclosure, there is provided a compound having formula **I**:



(**I**)

or a pharmaceutically acceptable thereof, wherein:

R^{1}, **R**^{2}, and **R**^{3} are defined according to **(A)** and **(B)** below:

(A)

R^{1} is selected from the group consisting of -CO_2H, -CO-N**R**^{12}**R**^{13}, and **R**^{1A}; wherein:

R^{1A} is a carboxylic acid isostere or bioisostere;

each occurrence of **R**^{12} and **R**^{13} is independently selected from the group consisting of H and C_{1-3} alkyl;

R^{2} and **R**^{3} are each independently selected from the group consisting of:

- H;
- halo;
- CN;
- C_{1-20} alkyl optionally substituted with 1-6 independently selected **R**^{a};
- **L**^{1}-C_{3-10} cycloalkyl or **L**^{1}-C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and **R**^{b}, wherein **L**^{1} is a bond or unsubstituted C_{1-6} alkylene;
- **L**^{2}-heterocyclyl or **L**^{2}-heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R**^{d}), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently

selected from the group consisting of oxo and $\mathbf{R^b}$, wherein $\mathbf{L^2}$ is a bond or unsubstituted C_{1-6} alkylene;

- $\mathbf{L^3}$-heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^3}$ is a bond or unsubstituted C_{1-6} alkylene; and
- $\mathbf{L^4}$-C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^4}$ is a bond or unsubstituted C_{1-6} alkylene; provided that one or both of $\mathbf{R^2}$ and $\mathbf{R^3}$ is other than H; or

$\mathbf{R^2}$ and $\mathbf{R^3}$, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;

(B)

$\mathbf{R^1}$, $\mathbf{R^2}$ and $\mathbf{R^3}$, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of

N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;

- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$;

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, and $\mathbf{R^{11}}$ are defined according to **(C)** and **(D)** below:

(C)

each occurrence of $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^8}$ is independently selected from the group consisting of: H and C_{1-3} alkyl;

each occurrence of $\mathbf{R^6}$ and $\mathbf{R^7}$ is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected $\mathbf{R^a}$; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;

each occurrence of $\mathbf{R^9}$ and $\mathbf{R^{10}}$ is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected $\mathbf{R^a}$; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; or

$\mathbf{R^9}$ and $\mathbf{R^{10}}$, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-6} cycloalkyl or C_{3-60} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and
- heterocyclyl or heterocycloalkenyl of 3-6 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or

heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and

$\mathbf{R^{11}}$ is selected from the group consisting of:

- $C_{3\text{-}10}$ cycloalkyl or $C_{3\text{-}10}$ cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;
- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- $C_{6\text{-}10}$ aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$;

(D)

one of $\mathbf{R^8}$ and $\mathbf{R^{11}}$, together with the atoms to which each is attached, form a ring selected from the group consisting of:

- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms (in addition to the ring N that is attached to $\mathbf{R^8}$) are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and
- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms (in addition to the ring N that is attached to $\mathbf{R^8}$) are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the

heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^{c}**;

the other of **R^{8}** is selected from the group consisting of: H and C_{1-3} alkyl; and

each occurrence of **R^{6}**, **R^{7}**, **R^{9}**, and **R^{10}** is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected **R^{a}**; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and **R^{b}**;

each occurrence of **R^{a}** is independently selected from the group consisting of: –OH; -halo; –N**R^{e}R^{f}**; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of **R^{b}** and **R^{c}** is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with 1-6 independently selected **R^{a}**; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -S(O)$_{1-2}$(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -N**R^{e}R^{f}**; N_3; –OH; -S(O)$_{1-2}$N**R'R''**; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N**R'R''**; -N**R'**C(=O)(C_{1-4} alkyl); Si(C_{1-4} aklyl)$_3$, –SF_5, and **R^{g}**;

each occurrence of **R^{d}** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-3 independently selected **R^{a}**; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; - S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of **R^{e}** and **R^{f}** is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of **R^{g}** is independently from the group consisting of:

- C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of C_{1-6} alkyl and **R^{a}**;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^{d}**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6} alkyl and **R^{a}**;
- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^{d}**), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-6} alkyl and **R^{a}**; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of C_{1-6} alkyl and **R^{a}**;

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl;

A) provided when:

- **R^{1}** is CO_2H,
- each of **R^{4}**, **R^{5}**, **R^{6}**, **R^{7}**, **R^{8}**, **R^{9}**, and **R^{10}** is H,
- **R^{11}** is phenyl that is optionally substituted with one or more of NO_2, F, Cl, $-OCH_3$, $-CH_3$, phenyl, 2-benzothiazolyloxy, benzyloxy, iodo, $-SCH_3$, $-SO_2CH_3$, *iso*-propyl, *iso*-propoxy, *iso*-butyl, -OH, N_3, and NH_2; and
- one of R^2 and R^3 is H,

then the other of R^2 and R^3 cannot be:

(i) the amino acid sidechain present in leucine, *iso*-leucine, threonine, tyrosine, O-benzyl-protected tyrosine, tryptophan, allothreonine, histidine, valine, alanine, arginine,

glutamine, glutamic acid, aspartic acid, serine, lysine, N-benzyloxy-protected lysine, or methionine; or

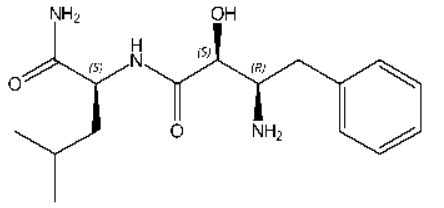
(ii) *n*-hexyl, *tert*-butyl, *n*-butyl, or *n*-propyl;

B) further provided when:

- $\mathbf{R^1}$ is CO_2H,
- each of $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, and $\mathbf{R^{10}}$ is H,
- $\mathbf{R^2}$ and $\mathbf{R^3}$ together with the carbon atom to which each is attached form a 3, 4, 5, or 6 member ring; and
- $\mathbf{R^1}$ is phenyl

then the phenyl ring cannot be substituted at the *para* position with $-SO_2CH_3$; and

C) further provided the compound is not



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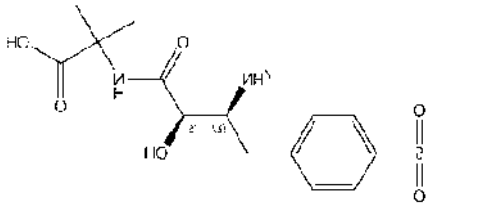
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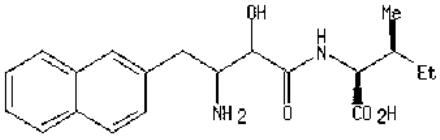

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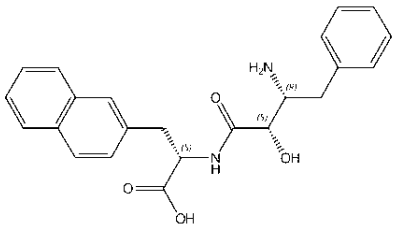

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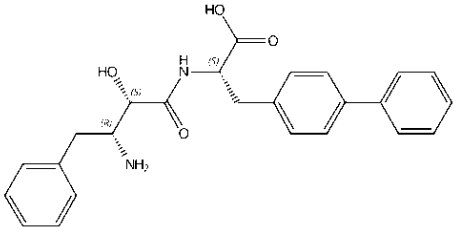

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In another example, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a

pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and one or more pharmaceutically acceptable excipients.

In a further example, this disclosure features methods of inhibiting Carnosine Dipeptidase 2 (CNDP2) in a subject, which include administering to the subject an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

In one example, methods of treating a condition, disease or disorder ameliorated by modulating (e.g., inhibiting) CNDP2 are featured, e.g., treating a condition, disease or disorder in which altered (e.g., increased) CNDP2 expression or activity contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of treating cancer are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further example, methods of treating frailty or one or more frailty conditions are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

As used herein, “frailty” refers to a syndrome characterized by reduced physical endurance and increased susceptibility to endogenous and exogenous stressors (see, e.g., Song X, et al., (2010) J Am Geriatr Soc. 58(4):681-7). Phenotypic frailty typically includes one or more of the following criteria: unintentional weight loss predominantly due to loss of muscle tissue, slow walking pace, exhaustion, weak grip strength, and physical inactivity (see, e.g., Fried, L., et al., (2001) J. Gerontology: Medical Sciences, 56A:3, M146-M156).

In some examples, the frailty condition includes one or more (e.g., 2, 3, or 4) of: weight loss, exhaustion, weakness, and physical inactivity.

In certain examples, the frailty condition is an age-related frailty condition (e.g., the subject is 60 years old or older; e.g., 60-69 years old, 70-79 years old, or 80-89 years old, 90-99 years old, or 100 years old or older).

In other examples, the frailty condition is not age-related.

In some examples, the subject has one or more (e.g., 2, 3, 4, or 5) symptoms of: decreased grip strength, muscle wasting, cachexia, physical injury, impaired locomotion, and decreased physical stability. In certain examples, the subject has decreased grip strength.

In some examples, the subject is male.

In some examples, the subject is female.

In some examples, the subject exhibits a BMI that is less than 18.5. In some examples, the subject exhibits a BMI that is 18.5 to <25. In some examples, the subject exhibits a BMI that is 25.0 to <30. In some examples, the subject exhibits a BMI that is 30.0 or higher.

In some examples, the subject the subject has an HbA1c level that is equal to or greater than 6.5% of whole blood. In some examples, the subject has an HbA1c level ranging from 6.5% to 20% of whole blood. In some examples, the subject has an HbA1c level that is equal to or greater than 7.0% of whole blood. In some examples, the subject has an HbA1c level ranging from 7.0% to 20% of whole blood. In some examples, the subject has an HbA1c level that is equal to or greater than 7.5% of whole blood. In some examples, the subject has an HbA1c level ranging from 7.5% to 20% of whole blood.

In another example, methods of treating mitochondrial dysfunction that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In some examples, the disease or symptom caused by mitochondrial dysfunction is selected from the group consisting of a mitochondrial disease, e.g., Leigh

syndrome, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), sepsis, or Leber's disease; diabetes and cancer.

In another example, methods of treating muscle loss (e.g., loss of muscle mass) that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of treating metabolic disorder (e.g., Type-2 diabetes, increased hemoglobin A1c, PKU, metabolic syndrome, or increased serum glucose) that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of treating obesity that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of treating insulin resistance or insulin sensitivity that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof for use in therapy.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of a condition, disease or disorder associated with increased (e.g., excessive) CNDP2 expression.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, described herein for use in the treatment of cancer.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of cancer selected from the group consisting of: ovarian cancer, colorectal cancer, and esophageal cancer. melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal

carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, glioblastoma multiforme, endometrial cancers, and hepatocellular carcinoma.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of frailty or one or more frailty conditions. Examples can include any one of the features delineated herein.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of mitochondrial dysfunction.

In some examples, the disease or symptom caused by mitochondrial dysfunction is selected from the group consisting of a mitochondrial disease, e.g., Leigh syndrome, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), sepsis, or Leber's disease; diabetes and cancer.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of muscle loss (e.g., loss of muscle mass).

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of a metabolic disorder (e.g., Type-2 diabetes, increased hemoglobin A1c, PKU, metabolic syndrome, or increased serum glucose).

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of obesity.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of insulin resistance or insulin sensitivity.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating a condition, disease or disorder ameliorated by modulating (e.g., inhibiting) CNDP2 (e.g., a condition, disease or disorder in which altered (e.g., increased) CNDP2 expression or activity contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder in a subject.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament

for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) CNDP2 expression.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of cancer.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in he manufacture of a medicament for treating cancer in a subject.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, glioblastoma multiforme, endometrial cancers, or hepatocellular carcinoma.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of frailty or one or more frailty conditions. Examples can include any one of the features delineated herein.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of mitochondrial dysfunction.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of mitochondrial disease, e.g., Leigh syndrome, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), sepsis, or Leber's disease; diabetes and cancer.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of muscle loss (e.g., loss of muscle mass).

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of a metabolic disorder (e.g., Type-2 diabetes, increased hemoglobin A1c, PKU, metabolic syndrome, or increased serum glucose).

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of obesity.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of insulin resistance or insulin sensitivity.

In another example, this disclosure features methods for modulating CNDP2 in a mammalian cell, the methods include contacting the mammalian cell with an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

In some examples, the contacting occurs *in vivo*.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating CNDP2 in a mammalian cell *in vivo*.

In some examples, the contacting occurs *in vitro*.

In yet another aspect of the present disclosure, there is provided a method for modulating CNDP2 in a mammalian cell, the method comprising contacting the mammalian cell *in vitro* with an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof.

In some examples, the cell includes altered (e.g., elevated) levels of lactate.

In some of the foregoing examples, the mammalian cell is a mammalian cancer cell.

In some examples, the subject is a subject identified or diagnosed as having one or more cancer cells, which have altered (e.g., elevated) levels of lactate.

In some examples, the subject is a subject identified or diagnosed as having one or more cancer cells, which have altered (e.g., excessive) levels of CNDP2 expression or activity.

In some examples, the subject is a subject identified or diagnosed as having one or more cancer cells, which have altered (e.g., elevated) levels of lactate and altered (e.g., excessive) levels of CNDP2 expression or activity.

In certain examples, the altered (e.g., elevated) levels of lactate are 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 250, 500, or 1000 time greater than normal or baseline levels of lactate.

In certain examples, the altered (e.g., excessive) levels of CNDP2 expression or activity are 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 250, 500, or 1000 time greater than normal or baseline levels of CNDP2 expression or activity.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens. For examples, methods can further include administering one or more (e.g., two, three, four, five, six, or more) additional agents.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens that are useful for treating other CNDP2-associated conditions, e.g., cancer.

The subject can have cancer; e.g., the subject has undergone and/or is undergoing and/or will undergo one or more cancer therapies.

The methods can further include identifying the subject.

Other examples include those described in the Detailed Description and/or in the claims.

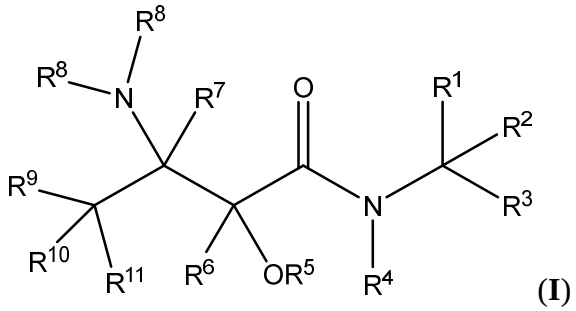
Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term “CNDP2” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, antibodies, homologous and/or orthologous CNDP2 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

WHAT IS CLAIMED IS:

1. A compound having formula **I**:



(**I**)

or a pharmaceutically acceptable thereof, wherein:

$\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$ are defined according to **(A)** and **(B)** below:

(A)

$\mathbf{R^1}$ is selected from the group consisting of -CO_2H, -CO-N$\mathbf{R^{12}R^{13}}$, and $\mathbf{R^{1A}}$;

wherein:

$\mathbf{R^{1A}}$ is a carboxylic acid isostere or bioisostere;

each occurrence of $\mathbf{R^{12}}$ and $\mathbf{R^{13}}$ is independently selected from the group consisting of H and C_{1-3} alkyl;

$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently selected from the group consisting of:

- H;
- halo;
- CN;
- C_{1-20} alkyl optionally substituted with 1-6 independently selected $\mathbf{R^a}$;
- $\mathbf{L^1}$-C_{3-10} cycloalkyl or $\mathbf{L^1}$-C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$, wherein $\mathbf{L^1}$ is a bond or unsubstituted C_{1-6} alkylene;

- **L²**-heterocyclyl or **L²**-heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^b**, wherein **L²** is a bond or unsubstituted C_{1-6} alkylene;
- **L³**-heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^c**, wherein **L³** is a bond or unsubstituted C_{1-6} alkylene; and
- **L⁴**-C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and **R^c**, wherein **L⁴** is a bond or unsubstituted C_{1-6} alkylene; provided that one or both of **R²** and **R³** is other than H; or

R² and **R³**, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and **R^b**; and
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^b**;

(B)

R¹, **R²** and **R³**, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;
- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$;

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, and $\mathbf{R^{11}}$ are defined according to **(C)** and **(D)** below:

(C)

each occurrence of $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^8}$ is independently selected from the group consisting of: H and C_{1-3} alkyl;

each occurrence of $\mathbf{R^6}$ and $\mathbf{R^7}$ is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected $\mathbf{R^a}$; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;

each occurrence of $\mathbf{R^9}$ and $\mathbf{R^{10}}$ is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected $\mathbf{R^a}$; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; or

R^{9} and **R^{10}**, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- C_{3-6} cycloalkyl or C_{3-60} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and **R^{b}**; and
- heterocyclyl or heterocycloalkenyl of 3-6 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^{d}**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^{b}**; and

R^{11} is selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and **R^{b}**;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^{d}**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^{b}**;
- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^{d}**), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and **R^{c}**; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and **R^{c}**;

(D)

one of **R^{8}** and **R^{11}**, together with the atoms to which each is attached, form a ring selected from the group consisting of:

- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms (in addition to the ring N that is attached to $\mathbf{R^8}$) are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and
- heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms (in addition to the ring N that is attached to $\mathbf{R^8}$) are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;

the other of $\mathbf{R^8}$ is selected from the group consisting of: H and C_{1-3} alkyl; and

each occurrence of $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^9}$, and $\mathbf{R^{10}}$ is independently selected from the group consisting of: H; F; C_{1-6} alkyl optionally substituted with 1-4 independently selected $\mathbf{R^a}$; and C_{3-6} cycloalkyl or C_{3-6} cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: –OH; -halo; –N$\mathbf{R^eR^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON$\mathbf{R'R''}$; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -$S(O)_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ and $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -$S(O)_{1-2}$(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -N$\mathbf{R^eR^f}$; N_3; –OH; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N$\mathbf{R'R''}$; -N$\mathbf{R'}$C(=O)(C_{1-4} alkyl); Si(C_{1-4} aklyl)$_3$, –SF_5, and $\mathbf{R^g}$;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: $C_{1\text{-}6}$ alkyl optionally substituted with 1-3 independently selected $\mathbf{R^a}$; -C(O)($C_{1\text{-}4}$ alkyl); -C(O)O($C_{1\text{-}4}$ alkyl); -CON**R'R''**; -$S(O)_{1\text{-}2}$N**R'R''**; - $S(O)_{1\text{-}2}$($C_{1\text{-}4}$ alkyl); -OH; and $C_{1\text{-}4}$ alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; $C_{1\text{-}6}$ alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, halo, $C_{1\text{-}4}$ alkoxy, and $C_{1\text{-}4}$ haloalkoxy; -C(O)($C_{1\text{-}4}$ alkyl); -C(O)O($C_{1\text{-}4}$ alkyl); -CON**R'R''**; -$S(O)_{1\text{-}2}$N**R'R''**; -$S(O)_{1\text{-}2}$($C_{1\text{-}4}$ alkyl); -OH; and $C_{1\text{-}4}$ alkoxy;

each occurrence of $\mathbf{R^g}$ is independently from the group consisting of:

- $C_{3\text{-}8}$ cycloalkyl or $C_{3\text{-}8}$ cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of $C_{1\text{-}6}$ alkyl and $\mathbf{R^a}$;
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1\text{-}6}$ alkyl and $\mathbf{R^a}$;
- heteroaryl of 5-6 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of $C_{1\text{-}6}$ alkyl and $\mathbf{R^a}$; and
- $C_{6\text{-}10}$ aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of $C_{1\text{-}6}$ alkyl and $\mathbf{R^a}$;

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and $C_{1\text{-}4}$ alkyl;

A) provided when:

- **R[1]** is CO_2H,
- each of **R[4]**, **R[5]**, **R[6]**, **R[7]**, **R[8]**, **R[9]**, and **R[10]** is H,
- **R[11]** is phenyl that is optionally substituted with one or more of NO_2, F, Cl, $-OCH_3$, $-CH_3$, phenyl, 2-benzothiazolyloxy, benzyloxy, iodo, $-SCH_3$, $-SO_2CH_3$, *iso*-propyl, *iso*-propoxy, *iso*-butyl, -OH, N_3, and NH_2; and
- one of R^2 and R^3 is H,

then the other of R^2 and R^3 cannot be:

(i) the amino acid sidechain present in leucine, *iso*-leucine, threonine, tyrosine, O-benzyl-protected tyrosine, tryptophan, allothreonine, histidine, valine, alanine, arginine, glutamine, glutamic acid, aspartic acid, serine, lysine, N-benzyloxy-protected lysine, or methionine; or

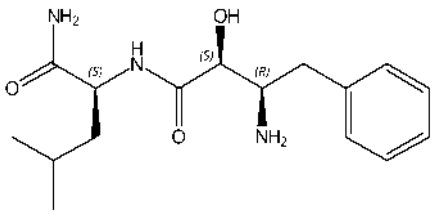
(ii) *n*-hexyl, *tert*-butyl, *n*-butyl, or *n*-propyl;

B) further provided when:

- **R[1]** is CO_2H,
- each of **R[4]**, **R[5]**, **R[6]**, **R[7]**, **R[8]**, **R[9]**, and **R[10]** is H,
- **R[2]** and **R[3]** together with the carbon atom to which each is attached form a 3, 4, 5, or 6 member ring; and
- **R[1]** is phenyl

then the phenyl ring cannot be substituted at the *para* position with $-SO_2CH_3$; and

C) further provided the compound is not



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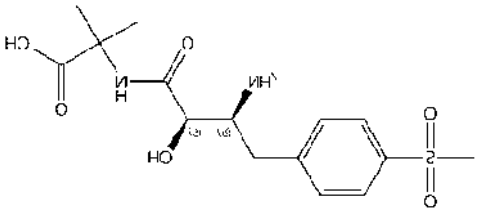

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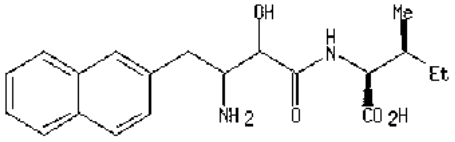

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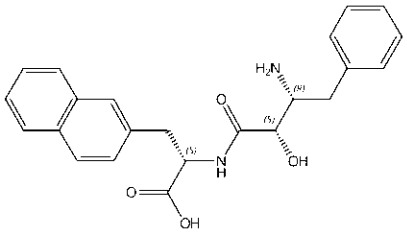

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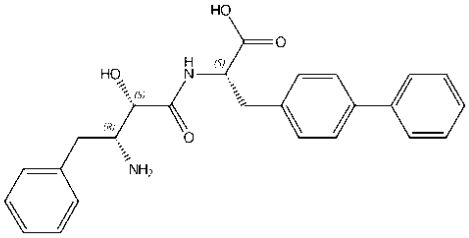

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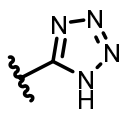
2. The compound of claim 1, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$ are defined according to **(A)**.

3. The compound of claim 1, wherein $\mathbf{R^1}$ is selected from the group consisting of $-CO_2H$, $-C\mathbf{R^{12a}}\mathbf{R^{13a}}CO_2H$, $-CO(N\mathbf{R^{12}})-OH$, $-CO-N\mathbf{R^{12}}\mathbf{R^{13}}$, $-CO-N\mathbf{R^{12}}-SO_2\mathbf{R^{14}}$, $-CO-N\mathbf{R^{12}}-CN$, and $-CO-N\mathbf{R^{12}}-CH_2-CF_3$.

4. The compound of claim 1, wherein $\mathbf{R^1}$ is $-CO_2H$.

5. The compound of claim 1, wherein $\mathbf{R^1}$ is selected from the group consisting of: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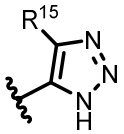

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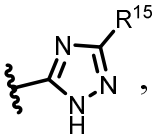

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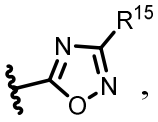

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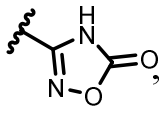
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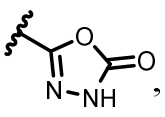
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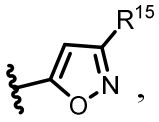

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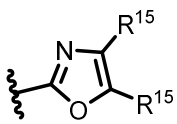

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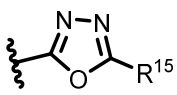

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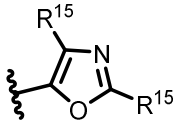

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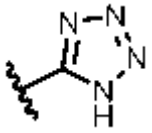
6. The compound of claim 1, wherein $\mathbf{R^1}$ is  .

7. The compound of claim 1, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently selected from the group consisting of:

- H;
- halo;
- CN;
- $C_{1\text{-}20}$ alkyl optionally substituted with 1-6 independently selected $\mathbf{R^a}$;
- $\mathbf{L^1}$-$C_{3\text{-}10}$ cycloalkyl or $\mathbf{L^1}$-$C_{3\text{-}10}$ cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$, wherein $\mathbf{L^1}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene;
- $\mathbf{L^2}$-heterocyclyl or $\mathbf{L^2}$-heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$, wherein $\mathbf{L^2}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene;
- $\mathbf{L^3}$-heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^3}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene; and
- $\mathbf{L^4}$-$C_{6\text{-}10}$ aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^4}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene; provided that one or both of $\mathbf{R^2}$ and $\mathbf{R^3}$ is other than H.

8. The compound of claim 1, wherein one of $\mathbf{R^2}$ and $\mathbf{R^3}$ is $\mathbf{L^4}$-$C_{6\text{-}10}$ aryl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^4}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene; and the other of $\mathbf{R^2}$ and $\mathbf{R^3}$ is H.

9. The compound of claim 8, wherein one of $\mathbf{R^2}$ and $\mathbf{R^3}$ is $\mathbf{L^4}$-phenyl optionally substituted with 1-4 substituents independently independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein $\mathbf{L^4}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene; and the other of $\mathbf{R^2}$ and $\mathbf{R^3}$ is H.

10. The compound of claim 8 or 9, wherein $\mathbf{L^4}$ is a bond.

11. The compound of claim 1, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$, together with the carbon atom to which each is attached, form a ring selected from the group consisting of:

- $C_{3\text{-}10}$ cycloalkyl or $C_{3\text{-}10}$ cycloalkenyl, each of which is optionally substituted with 1-6 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$; and
- heterocyclyl or heterocycloalkenyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^b}$.

12. The compound of claim 1, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^3}$ are defined according to **(B)**.

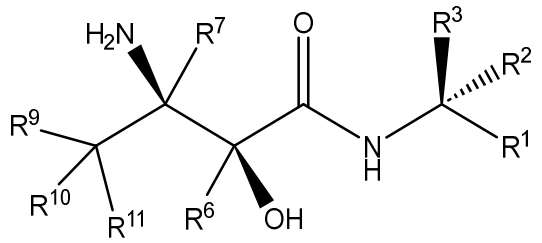
13. The compound of claim 1, wherein $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, and $\mathbf{R^{11}}$ are defined according to **(C)**.

14. The compound of claim 1, wherein $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, and $\mathbf{R^{10}}$ are H.

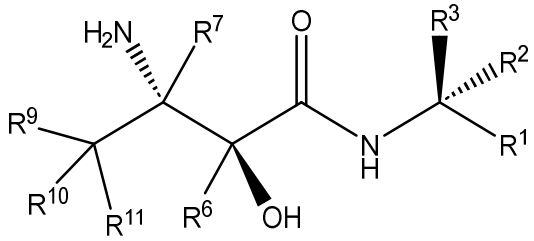
15. The compound of claim 1, wherein $\mathbf{R^{11}}$ is $C_{6\text{-}10}$ aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

16. The compound of claim 1, wherein $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, and $\mathbf{R^{11}}$ are defined according to **(D)**.

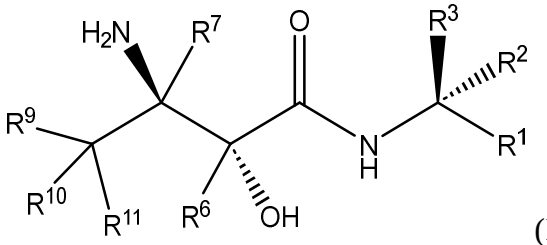
17. The compound of claim 1, wherein the compound is a compound of Formula (I-i), (I-j), (I-k), or (I-l):



(I-i),

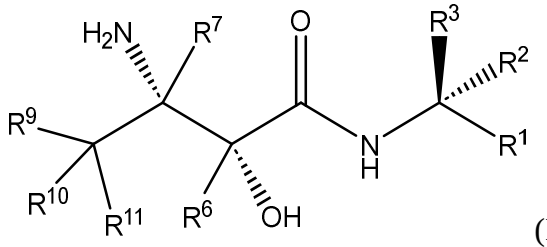


(I-j),



(I-k),

or



(I-l);

wherein:

R^1 is selected from the group consisting of CO_2H, -CO-N$\mathbf{R^{12}R^{13}}$, and $\mathbf{R^{1A}}$;

wherein:

$\mathbf{R^{1A}}$ is a carboxylic acid isostere or bioisostere optionally substituted with 1-3 independently selected $\mathbf{R^{15}}$;

$\mathbf{R^2}$ is H or CH_3;

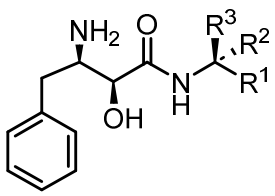
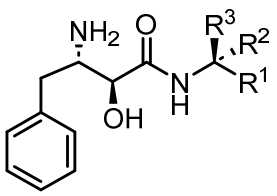
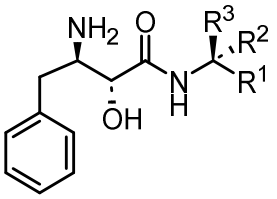
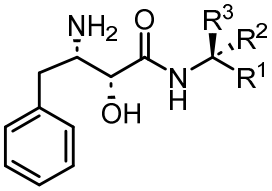
$\mathbf{R^3}$ is selected from the group consisting of:

- H
- $C_{1\text{-}6}$ alkyl optionally substituted with 1-6 independently selected $\mathbf{R^a}$;
- $\mathbf{L^1}$-$C_{3\text{-}10}$ cycloalkyl optionally substituted with 1-6 $\mathbf{R^b}$, wherein $\mathbf{L^1}$ is a bond or unsubstituted $C_{1\text{-}6}$ alkylene;
- $\mathbf{L^2}$-heterocyclyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and

$S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with 1-4 $\mathbf{R^b}$, wherein $\mathbf{L^2}$ is a bond or unsubstituted C_{1-6} alkylene;

- $\mathbf{L^3}$-heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 $\mathbf{R^c}$, wherein $\mathbf{L^3}$ is a bond or unsubstituted C_{1-6} alkylene; and
- $\mathbf{L^4}$-C_{6-10} aryl optionally substituted with 1-4 $\mathbf{R^c}$, wherein $\mathbf{L^4}$ is a bond or unsubstituted C_{1-6} alkylene; provided that one or both of $\mathbf{R^2}$ and $\mathbf{R^3}$ is other than H.

18. The compound of claim 1, wherein the compound is a compound of Formula (I-ia), (I-ja), (I-ka), or (I-la):


(I-ia),

(I-ja),

(I-ka),

or (I-la);

wherein:

R^1 is CO_2H, -CO-N$\mathbf{R^{12}R^{13}}$, and $\mathbf{R^{1A}}$;

wherein:

$\mathbf{R^{1A}}$ is a carboxylic acid isostere or bioisostere optionally substituted with 1-3 independently selected $\mathbf{R^{15}}$;

R^2 is H or CH_3;

R^3 is selected from the group consisting of:

- H
- C_{1-6} alkyl optionally substituted with 1-6 independently selected $\mathbf{R^a}$;

- **L^1**-C_{3-10} cycloalkyl optionally substituted with 1-6 **R^b**, wherein **L^1** is a bond or unsubstituted C_{1-6} alkylene;
- **L^2**-heterocyclyl of 3-10 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with 1-4 **R^b**, wherein **L^2** is a bond or unsubstituted C_{1-6} alkylene;
- **L^3**-heteroaryl of 5-10 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(**R^d**), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 **R^c**, wherein **L^3** is a bond or unsubstituted C_{1-6} alkylene; and
- **L^4**-C_{6-10} aryl optionally substituted with 1-4 **R^c**, wherein **L^4** is a bond or unsubstituted C_{1-6} alkylene; provided that one or both of **R^2** and **R^3** is other than H.

19. The compound of claim 1, wherein the compound is selected from the group of compounds delineated in Table C1.

20. A pharmaceutical composition comprising a compound of claim 1 and one or more pharmaceutically acceptable excipients.

21. A method for modulating CNDP2 in a mammalian cell, the method comprising contacting the mammalian cell *in vitro* with an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

22. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating CNDP2 in a mammalian cell *in vivo*.

23. Use of a compound of claim 1 in the manufacture of a medicament for treating a condition, disease or disorder ameliorated by modulating (e.g., inhibiting) CNDP2 (e.g., a condition, disease or disorder in which altered (e.g., increased) CNDP2 expression or activity contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder in a subject.

24. Use of a compound of claim 1 in the manufacture of a medicament for treating cancer in a subject.

25. The use of claim 23, wherein the condition, disease or disorder is frailty or one or more frailty conditions.

26. The use of claim 23, wherein the condition, disease or disorder is mitochondrial dysfunction.

27. The use of claim 23, wherein the condition, disease or disorder is muscle loss.

28. The use of claim 23, wherein the condition, disease or disorder is a metabolic disorder, obesity, insulin resistance, or insulin sensitivity.

29. A compound of claim 1, or a pharmaceutically acceptable salt thereof for use in therapy.