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(54) Title: THIOCARBAMATE AND SULFONAMIDE HYDROXAMATE INHIBITORS OF INSULIN-DEGRADING ENZYME

(57) Abstract: This disclosure relates to pharmaceutical compositions useful for inhibiting insulin-degrading enzyme (IDE) and methods of treating disorders involving the same or peptide substrates of the same. For example, provided herein are methods of treating diabetes, promotion of wound healing, and improvement of memory.



THIOCARBAMATE AND SULFONAMIDE HYDROXAMATE INHIBITORS OF INSULIN-DEGRADING ENZYME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/490,700, filed on May 27, 2011, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

This disclosure relates to pharmaceutical compositions useful for inhibiting insulin-degrading enzyme (IDE) and methods of treating disorders involving the same.

BACKGROUND

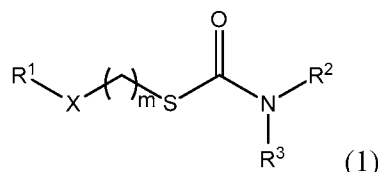
Insulin-degrading enzyme (IDE) is a Zn^{2+} -metalloprotease that catalyzes the proteolysis of insulin and several other peptide substrates, including glucagon, amylin, and amyloid- β protein (A β). Mice genetically engineered to lack IDE have increased fasting insulin levels in blood and improved insulin and glucose tolerance at 2 months of age, whereas enhanced IDE activity effectively reduces brain A β . See Abdul-Hay et al., *PLoS ONE*, 2011, 6(6) e20818. Thus, IDE is relevant to various diseases, including diabetes, insulin resistance, and Alzheimer's disease.

SUMMARY

The ability of insulin, related or unrelated peptides, or other molecules to exert a physiological function through binding to cognate receptors or other means, to gain entry into cells and/or to be transported across cell layers such as epithelial cells or the blood-brain-barrier is normally limited by the degradation of such molecules by enzymes. Methods that inhibit these enzymes and thereby prevent the degradation of therapeutic molecules would facilitate transport of the therapeutic molecules into organisms and/or into intraorganismal or intracellular compartments relevant to their therapeutic action. Provided herein are thiocarbamate and sulfonamide hydroxamate compounds that are useful for inhibiting the activity of IDE.

Provided herein are methods for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient. The methods include administering to the patient a therapeutically effective amount of a compound

of formula (1). Also provided herein are methods of inhibiting insulin-degrading enzyme in a cell. The methods include contacting the cell with an effective amount of the compound of formula (1). The compounds of formula (1) are compounds of the following formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl;

X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -NHNHC(O)-, -NH(C=NR^a)-, -S(O)₂NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R^a is selected from H, OH, (C₁-C₁₀)alkyl, substituted or unsubstituted (C₆-C₁₄)aryl, and S(O)₂R^b;

R^b is selected from (C₁-C₁₀)alkyl and substituted or unsubstituted (C₆-C₁₄)aryl; and

m is an integer selected from 1, 2 and 3.

Embodiments of the compounds of formula (1) include those wherein:

R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or

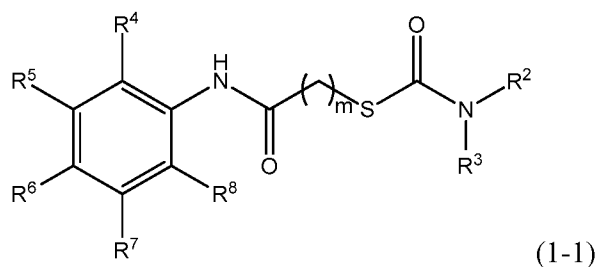
unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl;

X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and

m is an integer selected from 1, 2 and 3.

A compound of formula (1) can include a compound of formula (1-1):



or a pharmaceutically acceptable salt thereof, wherein:

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted

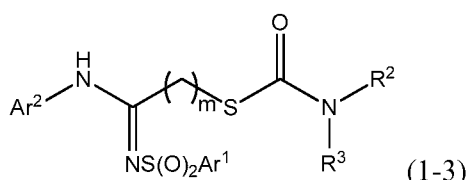
(C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R⁴, R⁵, R⁶, R⁷, and R⁸ are independently selected from H, halo, OH, O(C₁-C₁₀)alkyl, NR⁹R¹⁰, NO₂, (C₁-C₁₀)haloalkyl, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R⁹ and R¹⁰ are independently selected from H and (C₁-C₁₀)alkyl; and

m is an integer selected from 1, 2 and 3.

A compound of formula (1) can include a compound of formula (1-3):



or a pharmaceutically acceptable salt thereof, wherein:

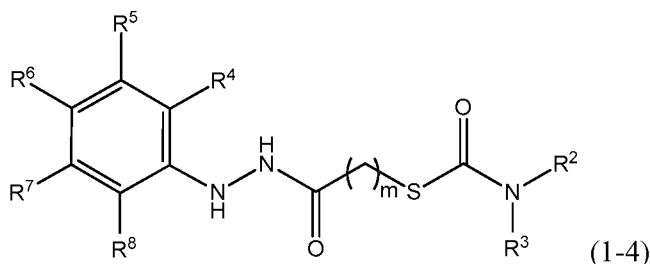
R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, and substituted or unsubstituted (C_4 - C_{12})heteroaryl;

Ar^1 is unsubstituted (C_6 - C_{14})aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, $O(C_1$ - $C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1 - C_{10})haloalkyl, substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, and substituted or unsubstituted (C_4 - C_{12})heteroaryl;

Ar^2 is unsubstituted (C_6 - C_{14})aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, $O(C_1$ - $C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1 - C_{10})haloalkyl, substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, and substituted or unsubstituted (C_4 - C_{12})heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1 - C_{10})alkyl; and m is an integer selected from 1, 2 and 3.

A compound of formula (1) can include a compound of formula (1-4):



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted

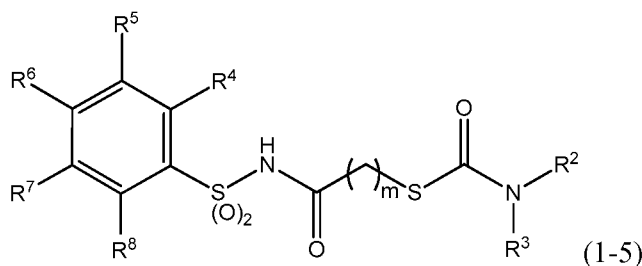
5 (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl,

10 substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and m is an integer selected from 1, 2 and 3.

A compound of formula (1) can include a compound of formula (1-5):



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or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl,

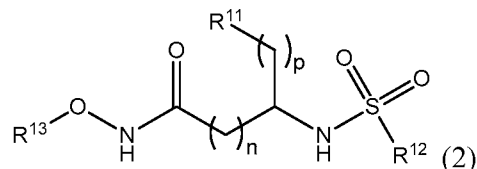
20 substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl,

25 substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and m is an integer selected from 1, 2 and 3.

Provided herein are methods for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient. The methods include administering to the patient a therapeutically effective amount of a compound of formula (2). Also provided herein are methods of inhibiting insulin-degrading enzyme in a cell. The methods include contacting the cell with an effective amount of the compound of formula (2). The compounds of formula (2) are compounds of the following formula (2):



or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, substituted or unsubstituted (C_4 - C_{12})heteroaryl, and an amino acid side chain;

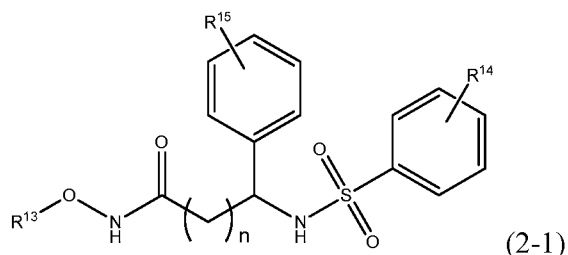
R^{12} is selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, substituted or unsubstituted (C_4 - C_{12})heteroaryl, and an amino acid side chain;

R^{13} is H or substituted or unsubstituted (C_1 - C_{10})alkyl;

n is an integer from 0 to 3; and

p is an integer from 0 to 3.

A compound of formula (2) can include a compound of formula (2-1):



or a pharmaceutically acceptable salt thereof, wherein:

R^{13} is H or substituted or unsubstituted (C_1 - C_{10})alkyl;

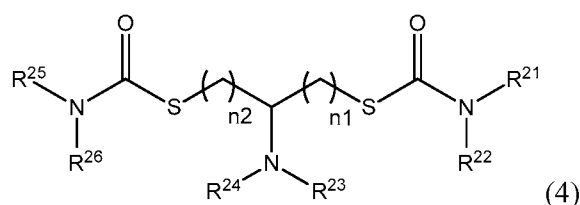
R^{14} is selected from H, halo, OH, $O(C_1-C_{10})alkyl$, $NR^{16}R^{17}$, NO_2 , $(C_1-C_{10})haloalkyl$, substituted or unsubstituted $(C_1-C_{10})alkyl$, substituted or unsubstituted $(C_2-C_{10})alkenyl$, substituted or unsubstituted $(C_2-C_{10})alkynyl$, substituted or unsubstituted $(C_3-C_{12})cycloalkyl$, substituted or unsubstituted $(C_6-C_{14})aryl$, substituted or unsubstituted $(C_3-C_{12})heterocycloalkyl$, and substituted or unsubstituted $(C_4-C_{12})heteroaryl$;

R^{15} is selected from H, halo, OH, $O(C_1-C_{10})alkyl$, $NR^{16}R^{17}$, NO_2 , $(C_1-C_{10})haloalkyl$, substituted or unsubstituted $(C_1-C_{10})alkyl$, substituted or unsubstituted $(C_2-C_{10})alkenyl$, substituted or unsubstituted $(C_2-C_{10})alkynyl$, substituted or unsubstituted $(C_3-C_{12})cycloalkyl$, substituted or unsubstituted $(C_6-C_{14})aryl$, substituted or unsubstituted $(C_3-C_{12})heterocycloalkyl$, and substituted or unsubstituted $(C_4-C_{12})heteroaryl$;

R^{16} and R^{17} are independently selected from H and substituted or unsubstituted $(C_1-C_{10})alkyl$; and

n is an integer from 1 to 10.

Provided herein are methods for inhibiting insulin degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient. The methods include administering to the patient a therapeutically effective amount of a compound of formula (4). Also provided herein are methods of inhibiting insulin degrading enzyme in a cell. The methods include contacting the cell with an effective amount of the compound of formula (4). The compounds of formula (4) are compounds of the following formula (4):



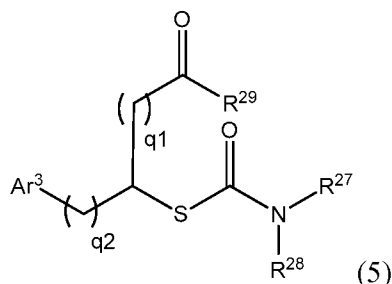
or a pharmaceutically acceptable salt thereof, wherein:

R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are independently selected from H and substituted or unsubstituted $(C_1-C_{10})alkyl$; and

n_1 and n_2 are integers each independently selected from 1, 2 and 3.

Also provided herein are methods for inhibiting insulin degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient. The methods include administering to the patient a therapeutically effective amount of a

compound of formula (5). Also provided herein are methods of inhibiting insulin degrading enzyme in a cell. The methods include contacting the cell with an effective amount of the compound of formula (5). The compounds of formula (5) are compounds of the following formula (5):



or a pharmaceutically acceptable salt thereof, wherein:

R²⁷ is selected from H, OH, NH₂, and (C₁-C₁₀)alkyl;

R²⁸ is selected from H and (C₁-C₁₀)alkyl;

R²⁹ is selected from OR³⁰ and NR³¹R³²;

R³⁰ is selected from H and (C₁-C₁₀)alkyl;

R³¹ is selected from H, OH, NH₂, and (C₁-C₁₀)alkyl;

R³² is selected from H and (C₁-C₁₀)alkyl;

q1 is selected from 0, 1 and 2;

q2 is selected from 0, 1 and 2; and

Ar³ is selected from substituted or unsubstituted (C₆-C₁₄)aryl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 illustrates the inhibition of IDE by various thiocarbamate compounds.

FIG. 2 Illustrates the percentage inhibition at 1μM observed for various thiocarbamate compounds.

FIG. 3 shows a dose-response curve for inhibition of IDE by compound 5A.

FIGs. 4A and 4B provide evidence that thiocarbamates do not inhibit IDE by interaction with cysteines.

FIG. 5 illustrates the inhibition of IDE by various sulfonamide hydroxamate compounds.

FIG. 6 illustrates the inhibition of IDE by pioglitazone and various pioglitazone analogs.

5

DETAILED DESCRIPTION

The ability of insulin, related or unrelated peptides, or other molecules to exert a physiological function through binding to cognate receptors or other means, to gain entry into cells and/or to be transported across cell layers such as epithelial cells or the blood-brain-barrier is normally limited by the degradation of such molecules by enzymes. Methods that inhibit these enzymes and thereby prevent the degradation of therapeutic molecules would enhance the physiological function or facilitate transport of the therapeutic molecules into organisms and/or into intraorganismal or intracellular compartments relevant to their therapeutic action. Provided herein are thiocarbamate and sulfonamide hydroxamate compounds that are useful for inhibiting the activity of IDE.

In the present description, it is appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features described herein which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications cited herein are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms cited herein, those in this section prevail unless otherwise stated.

For the terms “e.g.” and “such as,” and grammatical equivalents thereof, the phrase “and without limitation” is understood to follow unless explicitly stated otherwise. As used herein, the term “about” is meant to account for variations due to experimental error. All measurements reported herein are understood to be modified by the term “about,” whether or not the term is explicitly used, unless explicitly stated

otherwise. As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

The term “salt” includes any ionic form of a compound and one or more counter-ionic species (cations and/or anions). Salts also include zwitterionic compounds (*i.e.*, a molecule containing one more cationic and anionic species, *e.g.*, zwitterionic amino acids). Counter ions present in a salt can include any cationic, anionic, or zwitterionic species. Exemplary anions include, but are not limited to, chloride, bromide, iodide, nitrate, sulfate, bisulfate, sulfite, bisulfite, phosphate, acid phosphate, perchlorate, chlorate, chlorite, hypochlorite, periodate, iodate, iodite, hypiodite, carbonate, bicarbonate, isonicotinate, acetate, trichloroacetate, trifluoroacetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, trifluormethanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, *p*-trifluoromethylbenzenesulfonate, hydroxide, aluminates and borates. Exemplary cations include, but are not limited, to monovalent alkali metal cations, such as lithium, sodium, potassium, and cesium, and divalent alkaline earth metals, such as beryllium, magnesium, calcium, strontium, and barium. Also included are transition metal cations, such as gold, silver, copper, and zinc, as well as non-metal cations, such as ammonium salts. The term “pharmaceutically-acceptable salt” refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Preparation and selection of suitable salt forms is described in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* By P. H. Stahl and C. G. Wermuth (Wiley-VCH 2002).

When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. In general, the useful properties of the compounds described herein do not depend on whether the compound or salt thereof is or is in a particular solid state form, such as a polymorph or solvate, so, unless clearly indicated otherwise, reference in the specification to compounds and salts should be understood as encompassing any solid state form of the compound, whether or not this is explicitly stated.

Compounds provided herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the

same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds
5 herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The term "alkyl" corresponds to an alkane chain wherein one C-H bond is replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "(C_x-C_y)alkyl" (wherein x and y are integers) by itself or as part
10 of another substituent means, unless otherwise stated, an alkyl group containing from x to y carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. An alkyl group may be straight-chained or branched. Examples of straight-chained alkyl groups include methyl, ethyl, n-propyl, n-butyl, and n-octyl.
15 Examples of branched alkyl groups include *i*-propyl, *t*-butyl, and 2,2-dimethylethyl.

The term "(C_x-C_y)alkylene" (wherein x and y are integers) refers to an alkylene group containing from x to y carbon atoms. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the
20 alkylene group to the remainder of the compound. Examples are divalent straight hydrocarbon groups consisting of methylene groups, such as, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-. The (C_x-C_y)alkylene groups include (C₁-C₆)alkylene and (C₁-C₃)alkylene.

The term "alkenyl" denotes a radical wherein at least one carbon-carbon double bond is present. The term "(C_x-C_y) alkenyl" (wherein x and y are integers)
25 denotes a radical containing x to y carbons, wherein at least one carbon-carbon double bond is present (therefore x must be at least 2). Some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "alkenyl." Furthermore, the term "alkenyl" includes di- and tri-alkenyls. Accordingly, if more than one double bond is present
30 then the bonds may be all *E* or *Z* or a mixtures of *E* and *Z*. Examples of an alkenyl group include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, and 2,4-hexadienyl.

The term "alkynyl" denotes a radical containing at least one carbon-carbon triple bond. The term "(C_x-C_y) alkynyl" (wherein x and y are integers) denotes a radical containing x to y carbons, *e.g.*, 2 to 6 carbons, and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments are 2 carbons. Examples of an alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl. The term "alkynyl" includes di- and tri-ynes.

The term "cycloalkyl" as used herein describes a non-aromatic fully saturated or unsaturated, monocyclic or bicyclic alkyl ring system containing 3 to 12 carbons in the ring, such as cyclopentyl, cyclohexyl, cyclohexylmethyl, 4-methylcyclohexyl, bicyclo[2.2.1]heptanyl, norbornyl, and adamantyl. The term "(C_x-C_y) cycloalkyl" (wherein x and y are integers) denotes a cycloalkyl group containing from x to y carbon atoms in the ring. Cycloalkyl groups having 7 or more carbon atoms may contain more than one ring and be polycyclic. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (*i.e.* having $(4n + 2)$ delocalized π (pi) electrons where n is an integer).

The term "aryl" as used herein, employed alone or in combination with other terms, denotes an aromatic ring system composed of monocyclic or bicyclic rings and containing from 6 to 14 carbons in the ring, such as phenyl, biphenyl, and naphthyl.

The term "heteroaryl" as used herein refers to an aromatic ring system having at least one heteroatom in at least one ring, and from 2 to 9 carbon atoms in the ring system. The heteroaryl group has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaryls include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, and isoquinolinyl.

The term “heterocycloalkyl” as used herein refers non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles.

5 Example heterocycloalkyl groups include pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropuran, oxetanyl, azetidiny, morpholino, thiomorpholino, piperaziny, tetrahydrofuranyl, tetrahydrothienyl, piperidiny, pyrrolidiny, isoxazolidiny, isothiazolidiny, pyrazolidiny, oxazolidiny, thiazolidiny, imidazolidiny, azepanyl, benzazapene, and the like. Ring-forming carbon atoms and
10 heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O), S(O), C(S), or S(O)₂, etc.). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for
15 example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl has 4-10, 4-7 or 4-6 ring atoms with 1 or 2 heteroatoms independently selected from nitrogen, oxygen or sulfur and having one or
20 more oxidized ring members.

The terms “halogen” or “halo” as used herein refer to chlorine, bromine, fluorine, and iodine.

As used herein, the term "haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having one or more hydrogen atoms replaced by
25 halogen atoms. The term “(C_x-C_y)haloalkyl”, refers to an alkyl group having from x to y carbon atoms. In some embodiments, the haloalkyl group is fluorinated only (a fluoroalkyl group). In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “amino acid side chain” refers to the side chain on
30 one of the twenty most commonly occurring amino acids.

The term “substituted” means that an atom or group of atoms formally replaces hydrogen as a “substituent” attached to another group. The term “substituted”, unless otherwise indicated, refers to any level of substitution, namely

mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. When groups are described herein as being substituted, the substituents can include, but are not limited to, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, halogen, (C₁-C₆)haloalkyl, -CN, -NO₂, -C(=O)R, -OC(=O)Ar, -C(=O)OR, -C(=O)NR₂, -C(=NR)NR₂, -OR, -Ar, -OAr, -((C₁-C₆)alkylene)Ar, -((C₁-C₆)alkylene)OAr, -O((C₁-C₆)alkylene)Ar, -((C₁-C₃)alkylene)-O((C₁-C₃)alkylene)Ar, -OC(=O)(C₁-C₆)alkyl, -OC(=O)O(C₁-C₆)alkyl, -OC(=O)NR₂, -NR₂, -NRAr, -NR((C₁-C₆)alkylene)Ar, -NRC(=O)R, -NRC(=O)Ar, -NRC(=O)O(C₁-C₆)alkyl, -NRC(=O)NR₂, -NRSO₂R, -SR, -S(O)R, -SO₂R, -OSO₂(C₁-C₆)alkyl, -SO₂NR₂, (C₁-C₈)perfluoroalkyl, -(C₂-C₆)alkylene-OR, -O(C₂-C₆)alkylene-N((C₁-C₆)alkyl)₂, -P(=O)(OR)₂, -OP(=O)(OR)₂, wherein each R group is hydrogen or (C₁-C₆ alkyl), *e.g.*, methyl and wherein each Ar is independently unsubstituted aryl or heteroaryl or aryl or heteroaryl substituted with one or more of (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, halogen, (C₁-C₆)haloalkyl, -CN, -NO₂, -C(=O)R, -C(=O)OR, -C(=O)NR₂, -C(=NR)NR₂, -OR, -OC(=O)(C₁-C₆)alkyl, -OC(=O)O(C₁-C₆)alkyl, -OC(=O)NR₂, -NR₂, -NRC(=O)R, -NRC(=O)O(C₁-C₆)alkyl, -NRC(=O)NR₂, -NRSO₂R, -SR, -S(O)R, -SO₂R, -OSO₂(C₁-C₆)alkyl, -SO₂NR₂, (C₁-C₈)perfluoroalkyl, -(C₂-C₆)alkylene-OR, -O(C₂-C₆)alkylene-N((C₁-C₆)alkyl)₂, -P(=O)(OR)₂, -OP(=O)(OR)₂ wherein each R group is hydrogen or (C₁-C₆ alkyl).

Divalent groups that are unsymmetrical may be attached at either of the possible attachment points (when chemically possible to form a stable molecule), but preferably are attached in the same orientation as depicted relative to the molecule. For example, when a group C-D- is Z in a molecule A-Z-B, the molecule can be A-C-D-B or A-D-C-B, but is preferably A-C-D-B. Both orientations are separately contemplated.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.* hydrates and solvates).

In some embodiments, the compounds provided herein, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the

compounds described herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

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.

The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the compounds described herein include the conventional non-toxic salts of the parent compound formed, *e.g.*, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the compounds described herein can be synthesized from a parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety. Conventional methods for preparing salt forms are described, *e.g.*, in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, Wiley-VCH, 2002.

The term “contacting” means bringing at least two moieties together, whether in an *in vitro* system or an *in vivo* system.

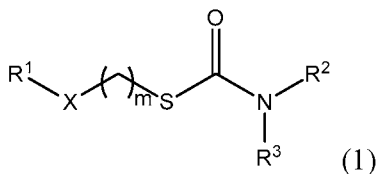
The expression “therapeutically effective amount,” when used to describe an amount of compound administered in a method, refers to the amount of a compound that achieves the desired pharmacological effect or other effect, *e.g.*, an amount that inhibits the activity of IDE, resulting in a useful effect.

The terms “treating” and “treatment” mean causing a therapeutically beneficial effect, such as ameliorating existing symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, postponing or preventing the further development of a disorder, and/or reducing the severity of symptoms that will or are expected to develop.

As used herein, “patient” (as in the subject of the treatment) includes both mammals and non-mammals. Mammals include, *e.g.*, humans; non-human primates, *e.g.*, apes and monkeys; cattle; horses; sheep; rats; mice; dogs; cats; pigs; and goats. Non-mammals include, *e.g.*, fish and birds.

II. Compounds

Provided herein is a compound of formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from H, OH, SH, NH_2 , substituted or unsubstituted $(\text{C}_1\text{-C}_{10})$ alkyl, substituted or unsubstituted $(\text{C}_2\text{-C}_{10})$ alkenyl, substituted or unsubstituted $(\text{C}_2\text{-C}_{10})$ alkynyl, substituted or unsubstituted $(\text{C}_3\text{-C}_{12})$ cycloalkyl, substituted or unsubstituted $(\text{C}_6\text{-C}_{14})$ aryl, substituted or unsubstituted $(\text{C}_3\text{-C}_{12})$ heterocycloalkyl, substituted or unsubstituted $(\text{C}_4\text{-C}_{12})$ heteroaryl;

X is a chemical moiety linking R^1 to the remainder of the molecule selected from -NHC(O)- , -NHNHC(O)- , $\text{-NH(C=NR}^a\text{)-}$, $\text{-S(O)}_2\text{NHC(O)-}$, -O- , -S- , $\text{-S(O)}_2\text{-}$, -C(O)- , -C(S)- , -NH- , $\text{-NHS(O)}_2\text{-}$, $\text{-(1,2,3-triazolyl)-}$, $\text{-(1,2,4-triazolyl)-}$, or a pharmaceutically acceptable bioisostere of any of the preceding;

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted $(\text{C}_1\text{-C}_{10})$ alkyl, substituted or unsubstituted $(\text{C}_2\text{-C}_{10})$ alkenyl, substituted or unsubstituted $(\text{C}_2\text{-C}_{10})$ alkynyl, substituted or unsubstituted $(\text{C}_3\text{-C}_{12})$ cycloalkyl,

substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R^a is selected from H, OH, (C₁-C₁₀)alkyl, substituted or unsubstituted (C₆-C₁₄)aryl, and S(O)₂R^b;

5 R^b is selected from (C₁-C₁₀)alkyl and substituted or unsubstituted (C₆-C₁₄)aryl; and

m is an integer selected from 1, 2 and 3.

In some embodiments of the compounds of formula (1):

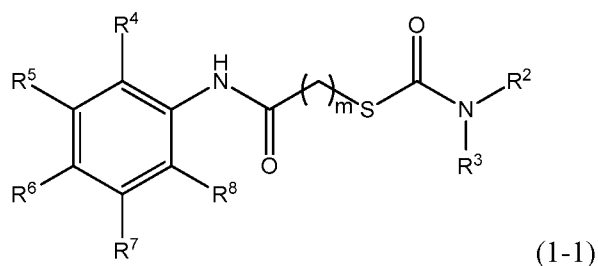
R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

15 X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and m is an integer selected from 1, 2 and 3.

25 In some embodiments, R¹ is a substituted or unsubstituted (C₆-C₁₄)aryl, *e.g.*, phenyl. For example, R¹ may be a substituted C₆ aryl. In some embodiments, X is -NH₂C(O)-. In some embodiments, R² and R³ are H. In some embodiments, m is 1.

A compound of formula (1) can include a compound of formula (1-1):



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted

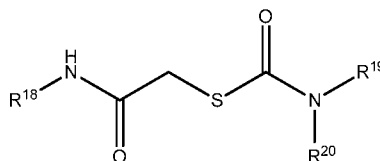
5 (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

10 R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and m is an integer selected from 1, 2 and 3.

In some embodiments, one or more of R^2 , R^3 , R^7 , and R^8 are H. In some
15 embodiments R^2 and R^3 . In some embodiments, R^7 and R^8 are H. In some
embodiments, m can be 1. In some embodiments, R^4 is H or substituted or
unsubstituted (C_1-C_{10}) alkyl, *e.g.*, methyl or ethyl. In some embodiments, R^4 is H or
substituted or unsubstituted $O(C_1-C_{10})$ alkyl, *e.g.*, methoxy or ethoxy. In some
embodiments, R^5 can be H, halo, $-O(C_1-C_{10})$ alkyl, *e.g.*, methoxy or ethoxy, or
20 substituted or unsubstituted (C_1-C_{10}) alkyl, *e.g.*, methyl or ethyl. For example, R^5 can
be selected from H, halo, $-OCH_3$, and CH_3 . In some embodiments, R^6 can be H,
 $-O(C_1-C_{10})$ alkyl, *e.g.*, methoxy or ethoxy, or substituted or unsubstituted
 (C_1-C_{10}) alkyl, *e.g.*, methyl or ethyl. For example, R^6 can be selected from H,
 $-OCH_2CH_3$, and CH_3 .

25 A compound of formula (1) can include a compound of formula (1-2):



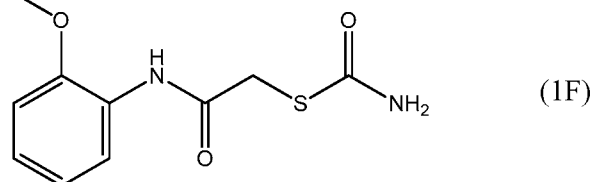
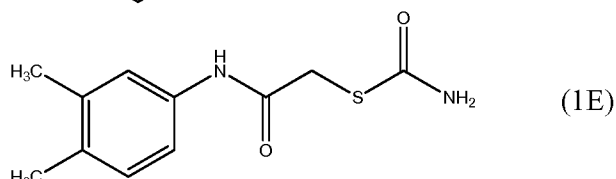
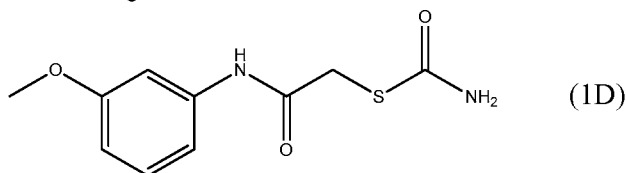
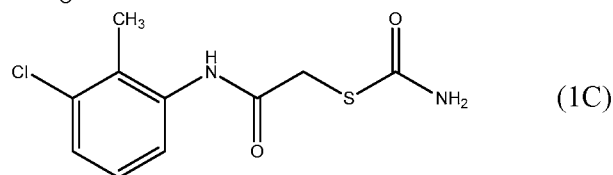
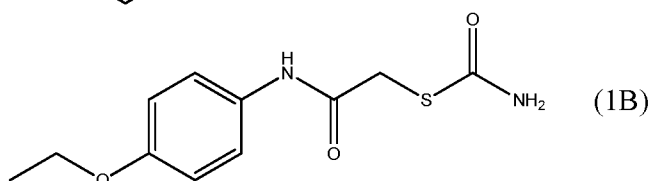
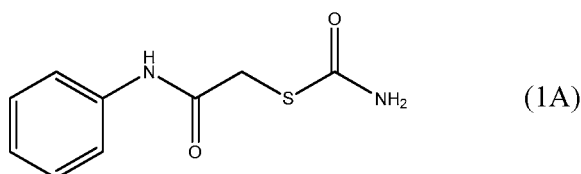
or a pharmaceutically acceptable salt thereof, wherein:

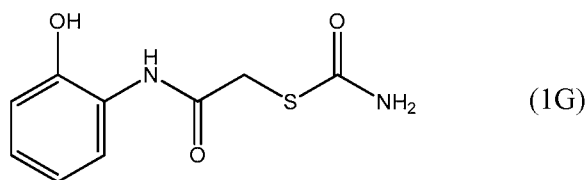
R^{18} is selected from H, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted
or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl,
30 substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted

(C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and

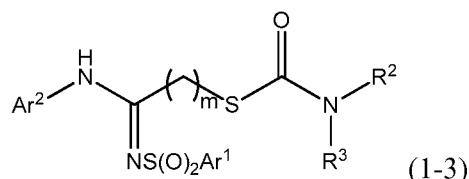
R¹⁹ and R²⁰ are independently selected from H, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or
 5 unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and
 m is an integer from 1 to 10.

Non-limiting examples of a compound of formula (1), formula (1-1), and/or
 10 formula (1-2) include compounds of the following formulae, and pharmaceutically acceptable salts thereof.





In some embodiments of the compounds of formula (1), X is -NH(C=NR^a)-. In some embodiments, the compounds are according to formula (1-3):



or a pharmaceutically acceptable salt thereof, wherein:

5 R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted
10 (C₄-C₁₂)heteroaryl;

Ar¹ is unsubstituted (C₆-C₁₄)aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, O(C₁-C₁₀)alkyl, NR⁹R¹⁰, NO₂, (C₁-C₁₀)haloalkyl, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl,
15 substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

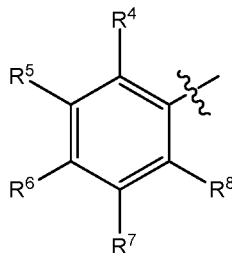
Ar² is unsubstituted (C₆-C₁₄)aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, O(C₁-C₁₀)alkyl, NR⁹R¹⁰, NO₂, (C₁-C₁₀)haloalkyl, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl,
20 substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

25 R⁹ and R¹⁰ are independently selected from H and (C₁-C₁₀)alkyl; and
m is an integer selected from 1, 2 and 3.

In some embodiments of such compounds, one or both of R² and R³ may be H.

In some embodiments Ar^1 may be phenyl. Ar^1 may be, *e.g.*, unsubstituted phenyl. Ar^1 may be, *e.g.*, mono-, di- or tri-substituted phenyl. Ar^1 may be, *e.g.*, para-substituted phenyl, *e.g.*, para-mono-substituted phenyl. Ar^1 may be substituted, *e.g.*, at the para-position with (C1-C10)alkyl, *e.g.*, methyl or ethyl, or halogen. Ar^1 may be, *e.g.*, 4-tolyl or 4-halosubstituted phenyl.

In some embodiments, Ar^2 may be a group of the following formula:



R^4 , R^5 , R^6 , R^7 , and R^8 may be independently selected from H, halo, OH, $\text{O}(\text{C}_1\text{-C}_{10})\text{alkyl}$, NR^9R^{10} , NO_2 , $(\text{C}_1\text{-C}_{10})\text{haloalkyl}$, substituted or unsubstituted (C1-C10)alkyl, substituted or unsubstituted (C2-C10)alkenyl, substituted or unsubstituted (C2-C10)alkynyl, substituted or unsubstituted (C3-C12)cycloalkyl, substituted or unsubstituted (C6-C14)aryl, substituted or unsubstituted (C3-C12)heterocycloalkyl, and substituted or unsubstituted (C4-C12)heteroaryl, and R^9 and R^{10} may be independently selected from H and (C1-C10)alkyl.

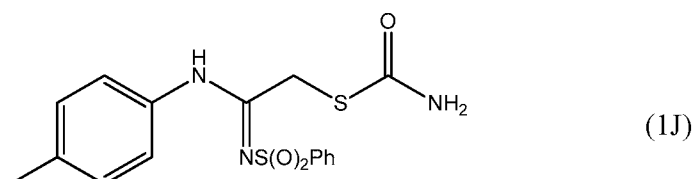
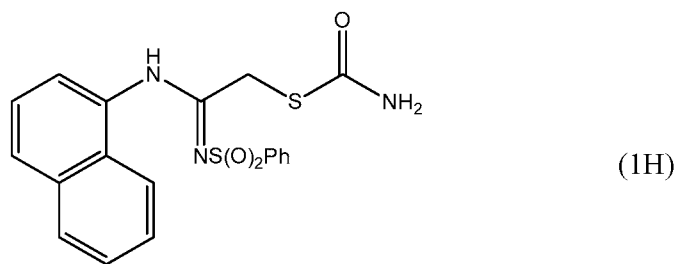
In some such embodiments, R^7 or R^8 or both may be H. In some such embodiments, R^4 may be H, substituted or unsubstituted (C1-C10)alkyl, *e.g.*, methyl or ethyl, or $-\text{O}(\text{C}_1\text{-C}_{10})\text{alkyl}$, *e.g.*, methoxy or ethoxy. R^4 may be, *e.g.*, H or substituted or unsubstituted (C1-C10)alkyl, *e.g.*, methyl or ethyl. In some embodiments, R^4 may be CH_3 or OCH_3 .

In some such embodiments, R^5 may be selected from H, halo, $-\text{O}(\text{C}_1\text{-C}_{10})\text{alkyl}$, *e.g.*, methoxy or ethoxy, and substituted or unsubstituted (C1-C10)alkyl, *e.g.*, methyl or ethyl. R^5 may be selected, *e.g.*, H, halo, $-\text{OCH}_3$, or CH_3 .

In some such embodiments, R^6 may be selected from H, $-\text{O}(\text{C}_1\text{-C}_{10})\text{alkyl}$, *e.g.*, methoxy or ethoxy, and substituted or unsubstituted (C1-C10)alkyl, *e.g.*, methyl or ethyl. R^6 may be, *e.g.*, H, $-\text{OCH}_2\text{CH}_3$, or CH_3 . In some embodiments, R^6 is H.

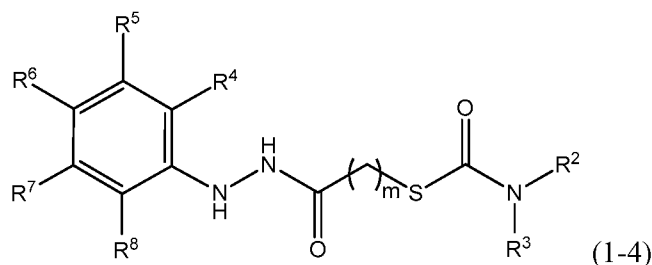
In some embodiments, Ar^2 may be 1-naphthyl, *e.g.*, unsubstituted 1-naphthyl. In some embodiments, Ar^2 may be 2-naphthyl, *e.g.*, unsubstituted 2-naphthyl.

Compounds of formula (1-3) include compounds of the following formulae, and pharmaceutically acceptable salts thereof:



In some embodiments of the compounds of formula (1), X is -NHNHC(O)-..

In some embodiments, the compounds are according to formula (1-4):



or a pharmaceutically acceptable salt thereof, wherein:

5 R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

10 R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

15 R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and

m is an integer selected from 1, 2 and 3.

In some such embodiments, R^2 or R^3 or both may be H.

In some such embodiments, m may be 1.

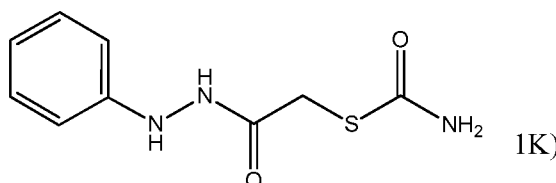
In some such embodiments, R^4 or R^5 or both may be H.

In some such embodiments, R^7 or R^8 or both may be H.

In some embodiments, R^6 is H, (C_1-C_{10}) alkyl, *e.g.*, methyl or ethyl, or halogen.

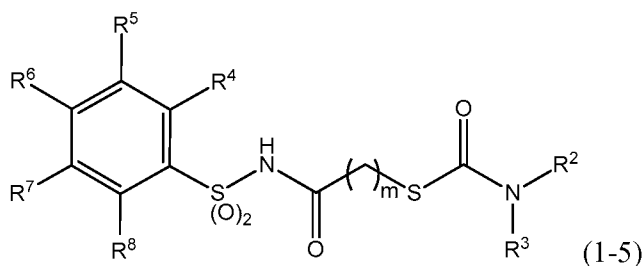
In some embodiments, R^6 is H.

- 5 Compounds of formula (1-4) include compounds of the following formula, and pharmaceutically acceptable salts thereof:



In some embodiments of the compounds of formula (1), X is $-S(O)_2NHC(O)-$.

In some embodiments, the compounds are according to formula (1-5):



- 10 or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted

- 15 (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl,

- 20 substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and

m is an integer selected from 1, 2 and 3.

In some such embodiments, R^2 or R^3 or both may be H.

In some such embodiments, m may be 1.

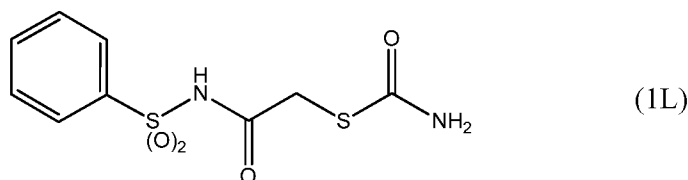
In some such embodiments, R⁴ or R⁵ or both may be H.

In some such embodiments, R⁷ or R⁸ or both may be H.

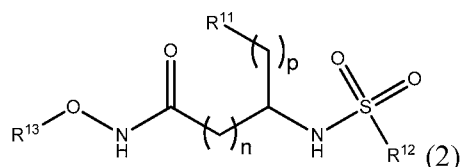
In some embodiments, R⁶ is H, (C₁-C₁₀)alkyl, *e.g.*, methyl or ethyl, or halogen.

5 In some embodiments, R⁶ is H.

Compounds of formula (1-5) include compounds of the following formula, and pharmaceutically acceptable salts thereof:



Further provided herein is a compound of formula (2):



10 or a pharmaceutically acceptable salt thereof, wherein:

R¹¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl, and an amino acid side chain;

R¹² is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl, and an amino acid side chain;

R¹³ is H or substituted or unsubstituted (C₁-C₁₀)alkyl;

n is an integer from 0 to 3; and

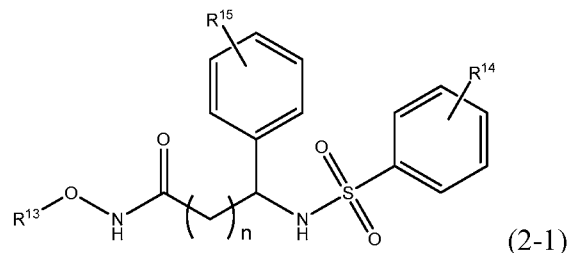
25 p is an integer from 0 to 3.

In some embodiments, R¹¹ is a substituted or unsubstituted (C₆-C₁₄)aryl. For example, R¹¹ can be a substituted phenyl. In some embodiments, R¹¹ is an amino acid

side chain. For example, R^{11} can be a tyrosine or arginine side chain. In some embodiments, R^{12} is a substituted or unsubstituted (C_6 - C_{14})aryl. For example, R^{12} is a substituted phenyl. In some embodiments, R^{12} is an amino acid side chain. For example, R^{12} can be an arginine side chain. In some embodiments, R^{13} is H. In some

5 embodiments, n is 1. In some embodiments, p is 0.

A compound of formula (2) can include a compound of formula (2-1):



or a pharmaceutically acceptable salt thereof, wherein:

R^{13} is H or substituted or unsubstituted (C_1 - C_{10})alkyl;

10 R^{14} is selected from H, halo, OH, $O(C_1$ - $C_{10})$ alkyl, $NR^{16}R^{17}$, NO_2 , (C_1 - C_{10})haloalkyl, substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, and substituted or

15 unsubstituted (C_4 - C_{12})heteroaryl;

R^{15} is selected from H, halo, OH, $O(C_1$ - $C_{10})$ alkyl, $NR^{16}R^{17}$, NO_2 , (C_1 - C_{10})haloalkyl, substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted (C_2 - C_{10})alkenyl, substituted or unsubstituted (C_2 - C_{10})alkynyl, substituted or unsubstituted (C_3 - C_{12})cycloalkyl, substituted or unsubstituted

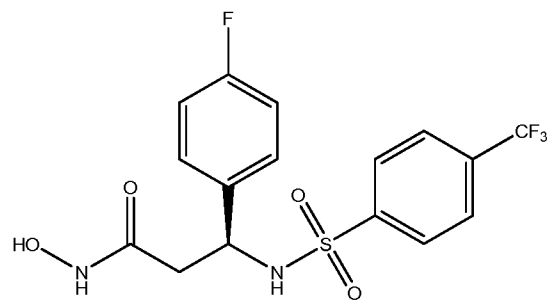
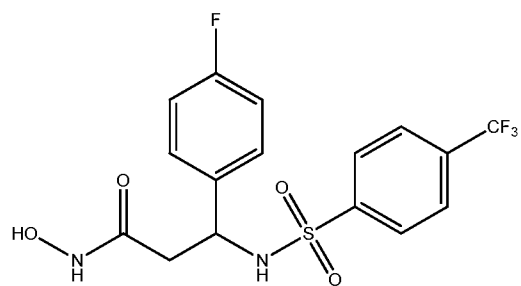
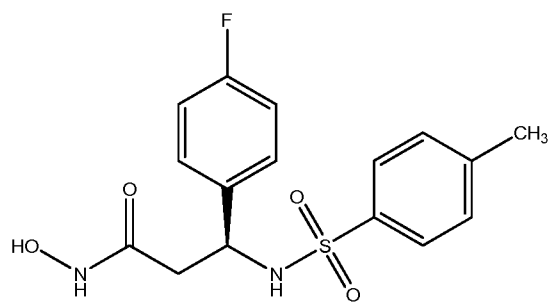
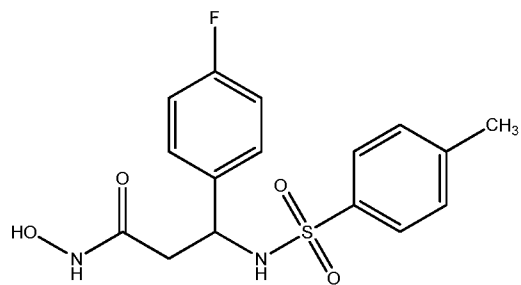
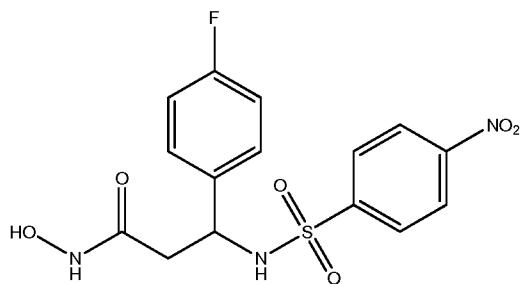
20 (C_6 - C_{14})aryl, substituted or unsubstituted (C_3 - C_{12})heterocycloalkyl, and substituted or unsubstituted (C_4 - C_{12})heteroaryl;

R^{16} and R^{17} are independently selected from H and substituted or unsubstituted (C_1 - C_{10})alkyl; and

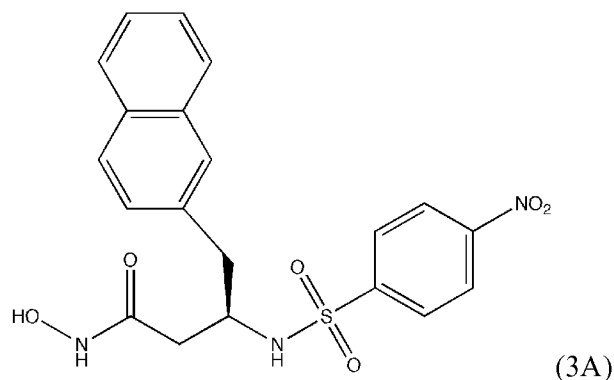
n is an integer from 1 to 10.

25 In some embodiments, R^{13} is H. In some embodiments, R^{14} is selected from NO_2 , (C_1 - C_{10})haloalkyl, and (C_1 - C_{10})alkyl. In some embodiments, R^{15} is halo. For example, R^{15} is F.

Non-limiting examples of a compound of formula (2) and/or formula (2-1) include compounds of the following formulae, and pharmaceutically acceptable salts thereof:

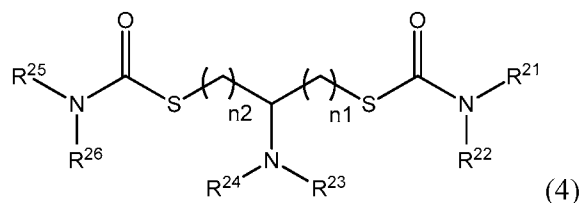


Also provided herein is a compound of formula (3A)



or a pharmaceutically acceptable salt thereof.

The present disclosure also provides a compound of formula (4):



or a pharmaceutically acceptable salt thereof, wherein:

R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are independently selected from H and substituted or unsubstituted (C₁-C₁₀)alkyl; and

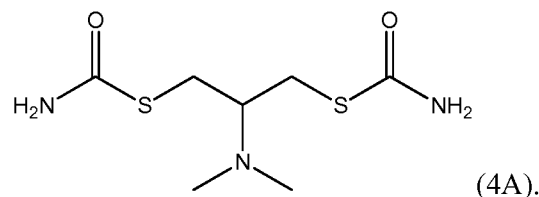
n₁ and n₂ are integers each independently selected from 1, 2 and 3.

In some such embodiments, n₁ is 1.

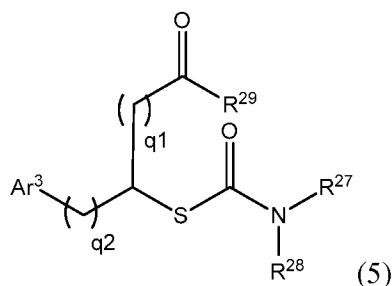
In some such embodiments, n₂ is 1.

In some such embodiments, one or more of, or all of R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ may be H or (C₁-C₁₀)alkyl, *e.g.*, methyl or ethyl. In some embodiments R²¹ or R²² or both may be H. In some embodiments, R²⁵ or R²⁶ or both may be H. In some embodiments R²³ or R²⁴ or both may be (C₁-C₁₀)alkyl, *e.g.*, methyl or ethyl.

The compounds of formula (4) include the compound of the following formula, and pharmaceutically acceptable salts thereof:



The present disclosure also provides a compound of formula (5):



or a pharmaceutically acceptable salt thereof, wherein:

R^{27} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

R^{28} is selected from H and (C_1-C_{10}) alkyl;

5 R^{29} is selected from OR^{30} and $NR^{31}R^{32}$;

R^{30} is selected from H and (C_1-C_{10}) alkyl;

R^{31} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

R^{32} is selected from H and (C_1-C_{10}) alkyl;

q_1 is selected from 0, 1 and 2;

10 q_2 is selected from 0, 1 and 2; and

Ar^3 is selected from substituted or unsubstituted (C_6-C_{14}) aryl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl.

In some embodiments, R^{27} is H. In some embodiments R^{28} is H. In some embodiments, R^{27} and R^{28} are both H.

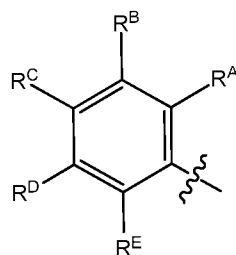
15 In some embodiments, R^{29} is OR^{30} . In some such embodiments, R^{30} may be H. In some such embodiments, R^{30} may be (C_1-C_{10}) alkyl, *e.g.*, methyl or ethyl.

In some embodiments, q_1 is 0.

In some embodiments, q_2 is 1.

In some embodiments, Ar^3 may be an unsubstituted or substituted phenyl ring.

20 In some such embodiments, Ar^3 can be a group of the following formula:



wherein:

R^A , R^B , R^D , and R^E are independently selected from H, halo, (C₁-C₁₀)alkyl, *e.g.*, methyl or ethyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂ and NO₂;

R^C is independently selected from H, halo, (C₁-C₁₀)alkyl, *e.g.*, methyl or ethyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂, NO₂,
 5 -((C₁-C₆)alkylene)Ar⁴, -((C₁-C₆)alkylene)OAr⁴, -O((C₁-C₆)alkylene)Ar⁴, and
 -((C₁-C₃)alkylene)-O((C₁-C₃)alkylene)Ar⁴;

Ar⁴ is selected from unsubstituted (C₆-C₁₄)aryl or (C₄-C₁₂)heteroaryl, and (C₆-C₁₄)aryl or (C₄-C₁₂)heteroaryl substituted with 1, 2, or 3-substituents selected from,
 10 halo, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂ and NO₂; and

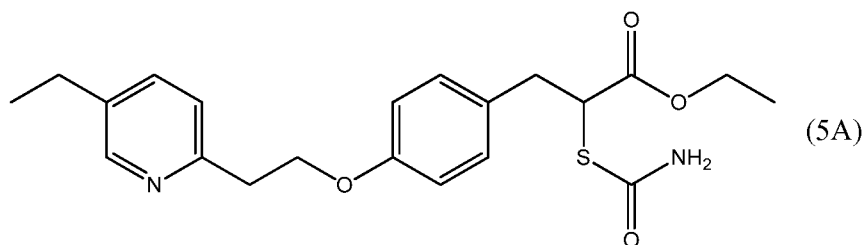
each R^F is independently selected from hydrogen and (C₁-C₁₀)alkyl, *e.g.* methyl or ethyl.

In some such embodiments R^A , R^B , R^D , and/or R^E can be H.

In some embodiments R^C can be H. In some embodiments, R^C can be
 15 -O((C₁-C₆)alkylene)Ar⁴, *e.g.*, -OCH₂CH₂Ar⁴.

In some embodiments Ar⁴ is aryl, *e.g.* phenyl. In some embodiments Ar⁴ is heteroaryl, *e.g.* pyridyl, *e.g.*, 2-pyridyl. In some embodiments Ar⁴ can be monocyclic. In some embodiments, Ar⁴ is unsubstituted. In some embodiments Ar⁴ is substituted,
 20 *e.g.* monosubstituted.

Compounds of formula (5) include compounds of the following formula, and pharmaceutically acceptable salts thereof.



When a compound provided herein is referred in the sections that follow, the compound, unless otherwise clearly indicated the compound can be any of the
 25 compounds defined above, or in the claims, or any embodiment thereof.

III. Synthesis

Compounds provided herein, including salts thereof, can be purchased from commercial suppliers or prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes known to a person of ordinary skill in the art. Suitable synthetic methods may be identified by reference to the literature, including reference sources such as *Comprehensive Organic Synthesis*, Ed. B. M. Trost and I. Fleming (Pergamon Press, 1991), *Comprehensive Organic Functional Group Transformations*, Ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees (Pergamon Press, 1996), *Comprehensive Organic Functional Group Transformations II*, Ed. A. R. Katritzky and R. J. K. Taylor (Editor) (Elsevier, 2nd Edition, 2004), *Comprehensive Heterocyclic Chemistry*, Ed. A. R. Katritzky and C. W. Rees (Pergamon Press, 1984) and *Comprehensive Heterocyclic Chemistry II*, Ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven (Pergamon Press, 1996).

Preparation of the compounds described herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, *e.g.*, in *Protecting Group Chemistry*, 1st Ed., Oxford University Press, 2000; *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th Ed., Wiley-Interscience Publication, 2001; and Petrusson, S. *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 74(11), 1297 (1997) (each of which is incorporated herein by reference in their entirety).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ¹H or ¹³C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS) or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) ("*Preparative LC-MS Purification: Improved Compound Specific Method Optimization*" K.F. Blom, *et al.*,

J. Combi. Chem. 6(6) (2004), which is incorporated herein by reference in its entirety) and normal phase silica chromatography.

IV. Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds described herein can be administered in the form of pharmaceutical compositions, in which an active ingredient is combined with a pharmaceutically acceptable carrier. The active ingredient in such formulations may comprise from 0.1 to 99.99 weight percent. "Pharmaceutically acceptable carrier" means any carrier, diluent or excipient which is compatible with the other ingredients of the formulation and not deleterious to the recipient.

These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral, or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, *e.g.*, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners, and the like may be necessary or desirable. The compositions may contain the compound described in isolated or substantially isolated form (in addition to one or more pharmaceutically acceptable carriers). The compositions may also contain the compound as the sole pharmaceutically active ingredient.

This disclosure also includes pharmaceutical compositions which contain, as the active ingredient, a compound as described herein or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical

administration. In making the compositions described herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, *e.g.*, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which
5 acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, *e.g.*, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged
10 powders.

In preparing a formulation, an active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If an active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If an active compound is substantially water soluble, the particle size can be
15 adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

The compounds described herein may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate)
20 preparations of the compounds described herein can be prepared by processes known in the art, *e.g.*, see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose,
25 water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions described herein can be formulated so as to provide quick, sustained or delayed
30 release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500

mg, of the active ingredient. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

5 In some embodiments, the compositions described herein contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about 30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg
10 of the active ingredient.

 In some embodiments, the compositions described herein contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 50 to about 100, about 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about
15 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

 In some embodiments, the compositions described herein contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compositions containing about 500 to about 550, about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to
20 about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

 Similar dosages of the compounds described herein may be used in the methods and uses described below.

 The active compound can be effective over a wide dosage range and is
25 generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of
30 the patient's symptoms, and the like.

 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound as described herein.

When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit
5 dosage forms of the type described above containing from, *e.g.*, about 0.1 to about 1000 mg of the active ingredient.

The tablets or pills described herein can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the
10 latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with
15 such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions described herein can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut
20 oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are
25 administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from
30 devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, *e.g.*, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol,

white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, *e.g.*, glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, *e.g.*, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound as described herein. The topical formulations can be suitably packaged in tubes of, *e.g.*, 100 g which are optionally associated with instructions for the treatment of the select indication.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to treat or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound described herein can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound in a pharmaceutical composition can vary depending upon a number of factors including

dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds as described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1
5 mg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of
10 administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

V. Methods of Use

The compounds described herein can be used to inhibit insulin-degrading enzyme (IDE) in a patient and/or in a cell. For example, IDE can be inhibited in a
15 patient following administration of a therapeutically effective amount of a compound of formula (1) or (2), or a pharmaceutically acceptable salt thereof.

Further provided herein are methods of treating diabetes in a patient. The method includes administering to the patient a therapeutically effective amount of a compound of formula (1) or (2), or a pharmaceutically acceptable salt thereof.

20 Diabetes includes disorders such as diabetes mellitus and/or any of a group of related disorders in which there is a defect in the regulation of circulating and/or intracellular glucose (sugar) levels. Diabetic patients include those with abnormally high levels of blood sugar (hyperglycemia) or abnormally low levels of blood sugar (hypoglycemia), and can also include patients with glucose intolerance. Non-limiting
25 examples of diabetic conditions are described in the following paragraphs.

Diabetes mellitus ("diabetes") is a highly debilitating and increasingly common disorder that is typically associated with impaired insulin signaling. The major types of diabetes are:

Type 1 diabetes results from the body's impairment of insulin production due
30 to loss of pancreatic beta cells. Type 1 diabetes is usually diagnosed in children and young adults, and was previously known as juvenile diabetes. Conditions associated with type 1 diabetes include hyperglycemia, hypoglycemia, ketoacidosis, and celiac

disease. Some complications of type 1 diabetes include: heart disease (cardiovascular disease), blindness (retinopathy), nerve damage (neuropathy), and kidney damage (nephropathy).

5 Type 2 diabetes results from insulin resistance (a condition in which the body fails to properly use insulin, *i.e.*, cellular sensitivity to circulating insulin is impaired), combined with relative insulin deficiency. Type 2 diabetes increases the risk for many serious complications including heart disease (cardiovascular disease), blindness (retinopathy), nerve damage (neuropathy), and kidney damage (nephropathy).

10 Hyperosmolar Hyperglycemic Nonketotic Syndrome, or HHNS, is a serious condition most frequently seen in older persons. HHNS can happen to people with either type 1 or type 2 diabetes, but it occurs more often in people with type 2. HHNS is usually brought on by something else, such as an illness or infection. In HHNS, blood sugar levels rise (over 600 mg/dl), and the body tries to eliminate the excess sugar by passing it into urine. If HHNS continues, the severe dehydration will lead to
15 seizures, coma and eventually death. HHNS may take days or even weeks to develop.

Gestational diabetes affects about 4% of all pregnant women - about 135,000 cases in the United States each year. Pregnant women who have never had diabetes before but who have high blood sugar (glucose) levels during pregnancy are said to have gestational diabetes.

20 Pre-diabetes is a condition that occurs when a subject's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes. It is estimated that before subjects develop type 2 diabetes, they almost always have “pre-diabetes” — blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. Recent research has shown that some long-term damage
25 to the body, especially the heart and circulatory system, may already be occurring during pre-diabetes.

The term “diabetes” also refers to a patient having ketoacidosis - a serious condition where the body has dangerously high levels of ketones or acids that build up in the blood, and it can lead to diabetic coma (passing out for a long time) or even
30 death.

There are tests routinely used by those of ordinary skill in the art to establish if a patient requires treatment for diabetes. Two different tests include: the fasting plasma glucose test (FPG) or the oral glucose tolerance test (OGTT). The blood

glucose levels measured after these tests can be used to determine whether a patient has a normal metabolism, or whether a patient has pre-diabetes or diabetes.

The compounds of formula (1) and (2) can also be used in additional methods of treatment. For example, a compound as described herein can be used to promote wound healing in a patient; the method comprising administering to the patient a therapeutically effective amount of a compound of formula (1) or (2), or a pharmaceutically acceptable salt thereof.

The compounds described herein can also be used to improve memory in a patient. The method comprises administering to the patient a therapeutically effective amount of a compound of formula (1) or (2), or a pharmaceutically acceptable salt thereof. Improvements in memory can be evaluated by methods known to those of skill in the art. For example, as described in Dhamoon, M.S. *et al.*, (2009) *Neurology* 72(3):292-3; author reply 293-4.

Improvements in memory can be beneficial for patients suffering from a variety of disorders including dementing illnesses. Individuals with dementing illnesses usually present with gradual loss of memory followed by progressive deterioration of thought, judgment, language skills, visual-spatial perception, mood, and the ability to manage personal affairs. These patients become severely demented and typically die of intercurrent medical illnesses, such as pneumonia. There are many causes of dementia including primary cortical degenerative disorders (Alzheimer's disease, Pick's disease, and Lewy body disorders), cerebrovascular disease (multi-infarct dementia), sub-cortical degenerative disorders (Multiple System Atrophy, Huntington's disease and Progressive Supranuclear Palsy), infections (Neurosyphilis, AIDS), prion disorders, toxic and metabolic disorders (alcohol, hypothyroidism), tumors, and brain injury.

As one example, Alzheimer's disease is characterized by the progressive and severe accumulation in the brain of the amyloid β -protein ($A\beta$) (Selkoe (1999) *Nature* 399:A23-A31). Little is known, however, about how $A\beta$, after being secreted, is degraded and cleared from tissues. Defective degradation of $A\beta$ would be expected to be a risk factor for the development of Alzheimer's disease.

It has been suggested that insulin-degrading enzyme (IDE) may be involved in the degradation of endogenous brain-derived $A\beta$ peptides (Kurochkin and Goto (1994) *FEBS Lett* 345:33-37; McDermott and Gibson (1996) *D. NeuroReport* 7:2163-

2166; Qiu et al. (1998) *J Biol. Chem.* 273:32730-32738). It has also been shown that intact IDE, like A β , can be released into the extracellular fluid by healthy cultured microglial (BV-2) cells and is also present in normal CSF (Qui et al. (1998) *J Biol. Chem.* 273:32730-32738). In addition, it has been demonstrated that neuronal-type
 5 cells exhibit significant extracellular A β -degrading activity that is inhibited by competitive IDE substrates and other IDE inhibitors (Vekrellis, et al. (2000) *J Neurosci* 20(5):1657-1665).

In some embodiments, the methods described herein can be used *in vitro*, e.g., inhibiting IDE in a cell. Such *in vitro* methods can be performed by contacting a cell
 10 with an effective amount of a compound of formula (1) or formula (2). Uses of such *in vitro* methods include, but are not limited to, use in a screening assay (e.g., wherein the compound is used as a positive control or standard compared to compounds of unknown activity or potency in inhibiting IDE).

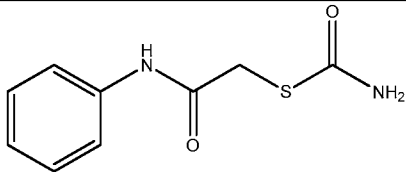
EXAMPLES

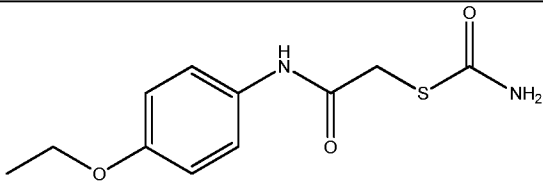
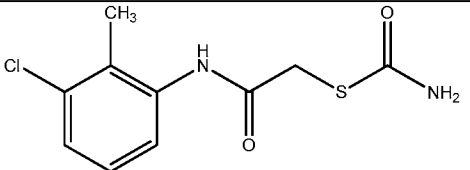
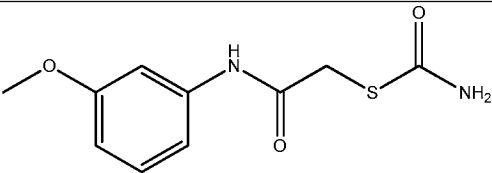
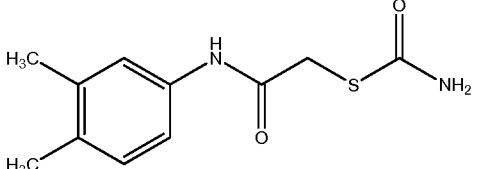
15 Example 1 – Inhibition of IDE by thiocarbamate compounds

The inhibitory potency of individual compounds was assessed by monitoring the hydrolysis of fluorogenic peptide, FRET1, (7-methoxycoumarin-4-yl)acetic acid-GGFLRKVGQK(2,4-dinitrophenyl) (FRET1; 5 μ M), (excitation = 335 nm, emission = 395 nm) by recombinant human IDE in assay buffer (50 mM HEPES, 100 mM
 20 NaCl, 10 mM MgCl₂, 0.1% bovine serum albumin, pH 7.4) in the presence of varying concentrations of compounds using the methods described in Cabrol *et al.*, (2009) *PLoS ONE* 4(4): e5274.

The data is summarized in Table 1 and FIG. 1.

Table 1

Compound Number	Compound	IC ₅₀ (μ M)		k _i (μ M)	
		mean	s.d	mean	s.d.
1A		4.6	4.3	2.7	2.6

Compound Number	Compound	IC ₅₀ (μM)		k _i (μM)	
		mean	s.d.	mean	s.d.
1B		5.0	5.8	3.0	3.4
1C		3.7	3.5	2.2	2.1
1D		5.1	5.2	3.0	3.0
1E		1.7	1.4	0.9	0.8

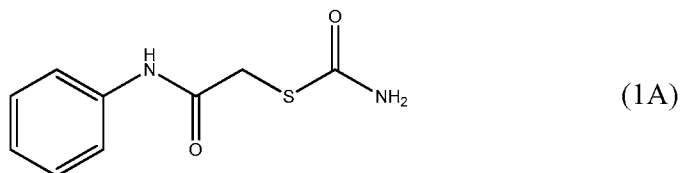
Example 2 – Inhibition of IDE by thiocarbamate compounds

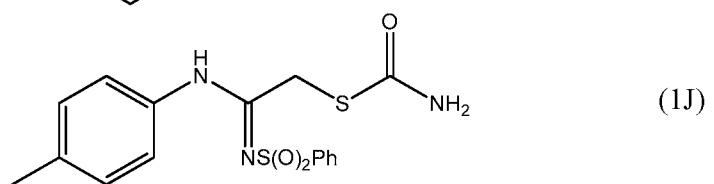
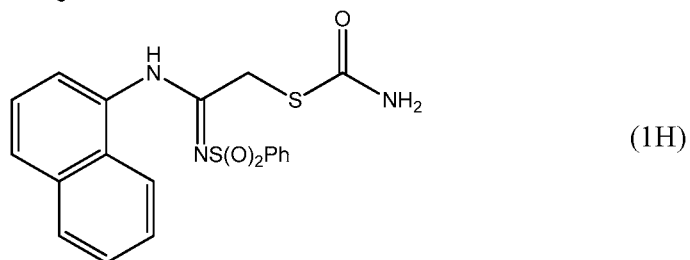
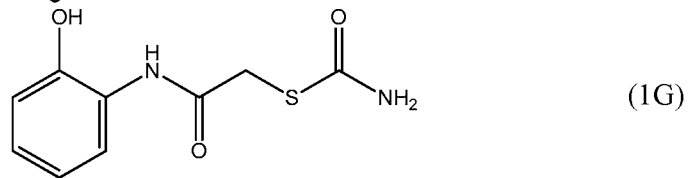
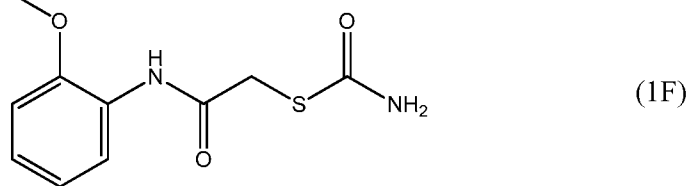
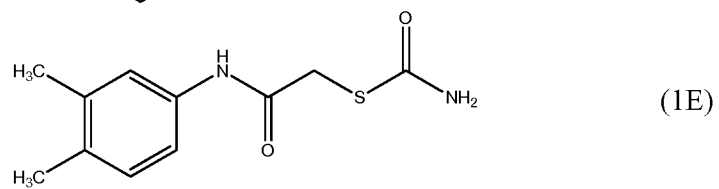
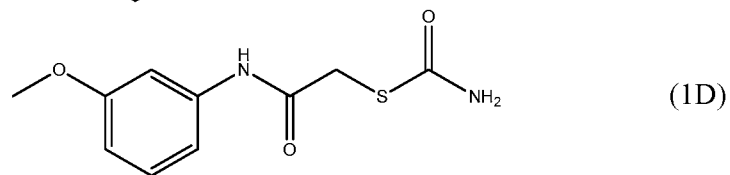
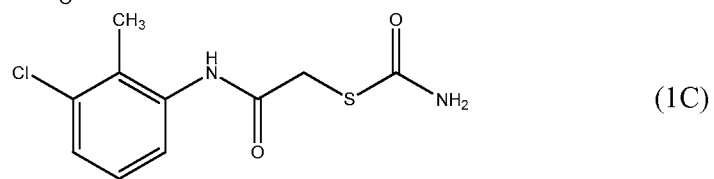
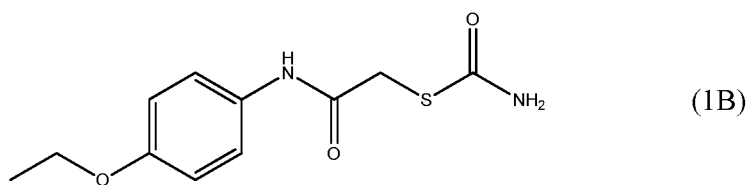
The inhibitory potency of individual compounds was assessed by monitoring the hydrolysis of fluorogenic peptide, FRET1, (7-methoxycoumarin-4-yl)acetic acid-GGFLRKVGQK(2,4-dinitrophenyl) (FRET1; 5 μM), (excitation = 335 nm, emission = 395 nm) by recombinant human IDE in assay buffer (50 mM HEPES, 100 mM NaCl, 10 mM MgCl₂, 0.1% bovine serum albumin, pH 7.4) in at 1 μM using the methods described in Cabrol *et al.*, (2009) *PLoS ONE* 4(4): e5274. In addition, a dose-response was measured for one compound, 5A, which was found to have a k_i of 76.4 nM.

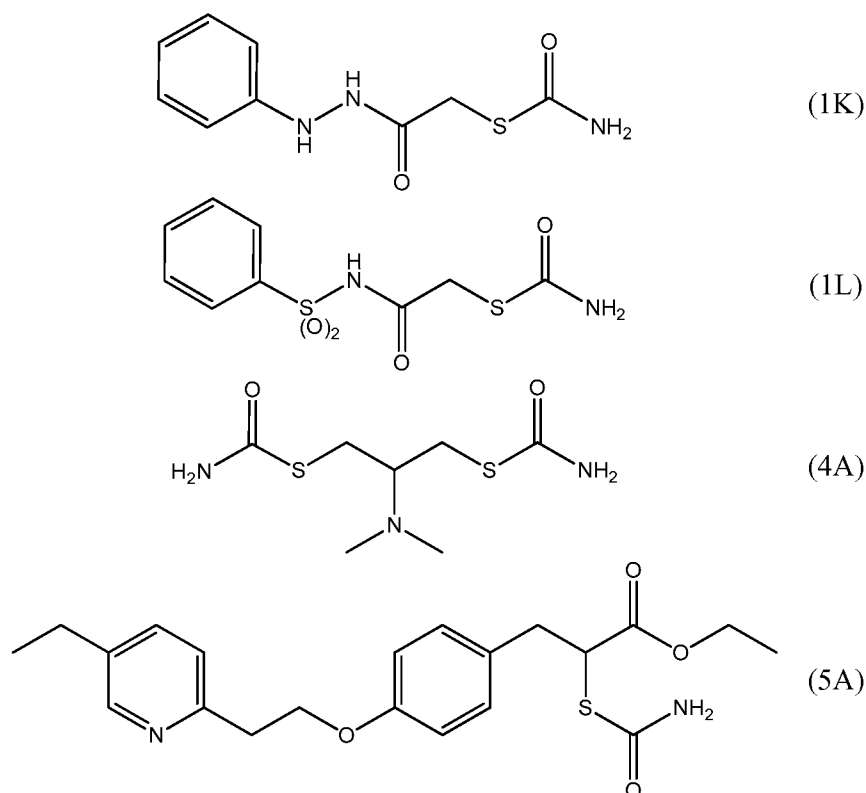
The percentage inhibition observed for various compounds is summarized FIG. 2.

The dose-curve obtained for compound 5A is shown in FIG.3.

The compounds tested are as shown below:







Example 3 – Inhibition of IDE does not occur through interaction with cysteines

To determine whether the thiocarbamate compounds exert their inhibitory effect by irreversible binding to cysteine residues within IDE, the activity of Compounds 1E and 1F was tested using cysteine-free IDE (CF-IDE); that is, a mutant form of recombinant IDE in which all cysteine residues were mutated to serines (Neant-Fert *et al.*, (2008) *PNAS* 105(28): 9582-9587). Using the hydrolysis of FRET1 as a measure of IDE activity, Compounds 1D and 1E were found to inhibit CF-IDE and wild-type IDE (non-mutated IDE containing cysteines) with similar potencies, demonstrating that the ability of these compounds to inhibit IDE does not involve interactions with cysteines. Specifically, Compound 1E inhibited CF-IDE and wild-type IDE with an IC_{50} of 2.8 ± 1.9 and 1.3 ± 2.0 μ M, respectively while Compound 1F inhibited CF-IDE and wild-type IDE with an IC_{50} of 3.3 ± 1.8 and 3.1 ± 2.1 μ M, respectively.

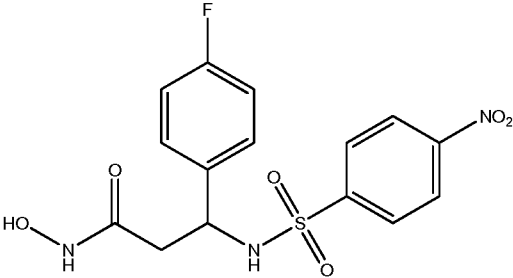
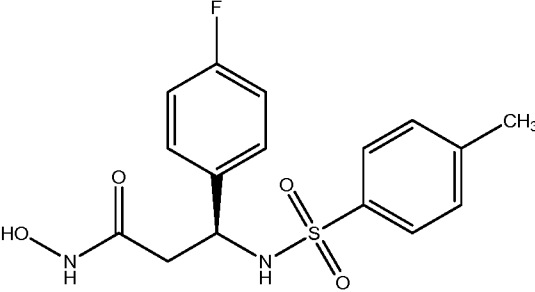
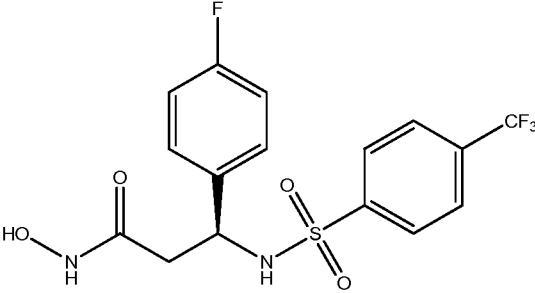
FIG. 4 summarizes the results of this experiment. The data for compound 1E are shown in FIG. 4A and the data for compound 1F are shown in FIG. 4B.

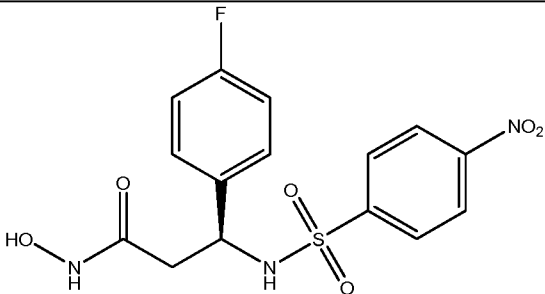
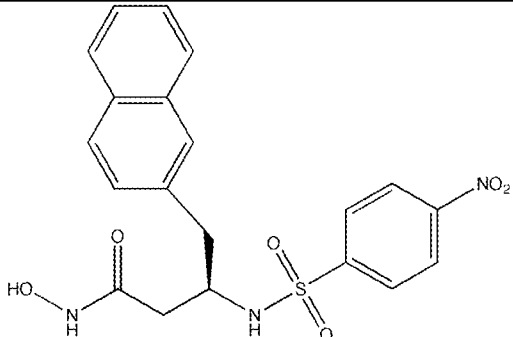
Example 4 - Inhibition of IDE by sulfonamide hydroxamate compounds

The inhibitory potency of individual compounds was assessed by monitoring the hydrolysis of fluorogenic peptide, FRET1, (7-methoxycoumarin-4-yl)acetic acid-GGFLRKVGQK(2,4-dinitrophenyl) (FRET1; 5 μ M), (excitation = 335 nm, emission = 395 nm) by recombinant human IDE in assay buffer (50 mM HEPES, 100 mM NaCl, 10 mM MgCl₂, 0.1% bovine serum albumin, pH 7.4) in the presence of varying concentrations of compounds using the methods described in Cabrol *et al.*, (2009) *PLoS ONE* 4(4): e5274.

The data is summarized in Table 2 and FIG. 5.

10 **Table 2.**

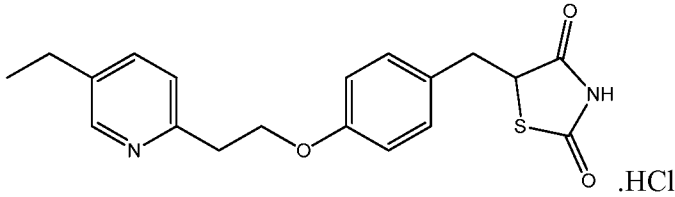
Compound Number	Compound	IC ₅₀ (μ M)		k _i (μ M)	
		mean	s.d.	mean	s.d.
2A (racemic)		4.6	4.3	2.7	2.6
2B		5.0	5.8	3.0	3.4
2C		3.7	3.5	2.2	2.1

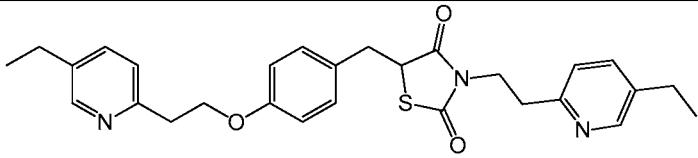
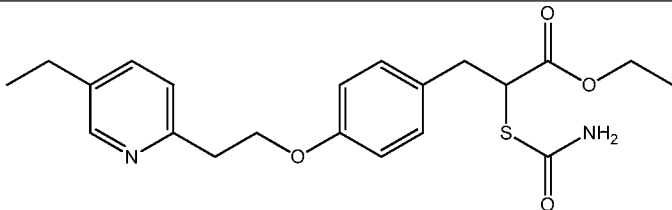
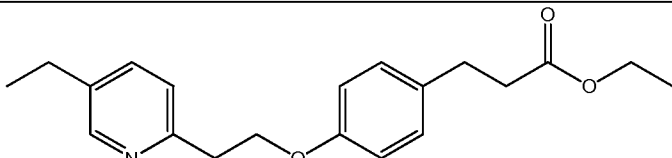
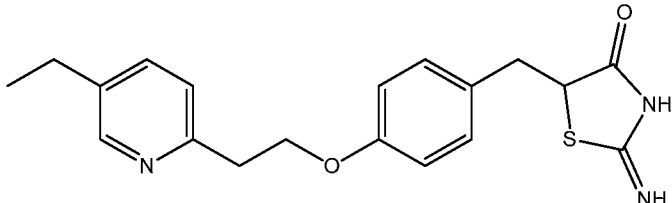
Compound Number	Compound	IC ₅₀ (μM)		k _i (μM)	
		mean	s.d.	mean	s.d.
2A		5.1	5.2	3.0	3.0
3A		2.1	0.6	1.4	0.4

Example 5 - Inhibition of IDE by Pioglitazone Analogs

The inhibitory potency of five pioglitazone analogs was tested at 10μM using a β-amyloid-based IDE assay as described by Leissring *et al.*, *J. Biol. Chem.*, 2003, 278, 37314-37320. The results are shown in FIG. 6. In FIG. 6, bars B to F show the percentage inhibition at 10μM by various compounds (whose structures are shown below). Bar A is a DMSO vehicle control (no enzyme inhibitor) while Bar G is a control run with no IDE enzyme present. Compounds tested are summarized in Table 3.

Table 3. Percentage Inhibition of IDE at 10μM by Pioglitazone Analogues

Entry (Bar of FIG. 6)	Compound	% Inhibition at 10μM
B	 Pioglitazone	+

C		+
D	 (5A)	+++
E		-
F		+

Less than 10% inhibition: -

10-40% inhibition at 10 μ M: +

40-60% inhibition at 10 μ M: ++

More than 60% inhibition at 10 μ M: +++

5 Example 6. Test to Evaluate In Vivo Anti-Diabetic Properties of IDS Inhibitors.

Groups of mice are fasted for 6 hours. An IDE inhibitor is administered, *e.g.*, orally, intranasally, intravenously, subcutaneously, intramuscularly, subcutaneously, or intraperitoneally, or via other routes) at a range of concentrations, *e.g.*, 0.1, 1, 10, 100 mg/kg. After administration of inhibitor, or at the same time insulin is also

10 administered to the mice via any of the above routes, at a dose sufficient to induce a partial drop in blood sugar (*e.g.*, 0.5 U/kg administered subcutaneously) relative to the levels measured before insulin administration. Control mice are not administered any inhibitor, or are administered vehicle alone. Before and administration of insulin,

blood samples are taken from the mice and glucose levels of the blood samples are measured.

Relative to mice administered no inhibitor, or vehicle alone, mice receiving an IDE inhibitors are predicted to show significantly larger drops in blood sugar.

5

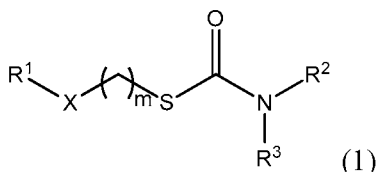
OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages and modifications are within the scope of the following claims.

10

WHAT IS CLAIMED IS:

1. A method for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl;

X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -NHNHC(O)-, -NH(C=NR^a)-, -S(O)₂NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

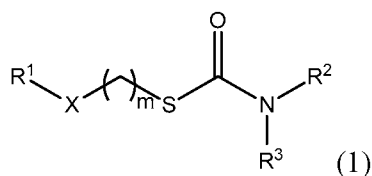
R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R^a is selected from H, OH, (C₁-C₁₀)alkyl, substituted or unsubstituted (C₆-C₁₄)aryl, and S(O)₂R^b;

R^b is selected from (C₁-C₁₀)alkyl and substituted or unsubstituted (C₆-C₁₄)aryl;
and

m is an integer selected from 1, 2 and 3.

2. A method for inhibiting insulin-degrading enzyme in a cell, the method comprising contacting the cell with an effective amount of the compound of formula (1):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl;

X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -NHNHC(O)-, -NH(C=NR^a)-, -S(O)₂NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R^a is selected from H, OH, (C₁-C₁₀)alkyl, substituted or unsubstituted (C₆-C₁₄)aryl, and S(O)₂R^b;

R^b is selected from (C₁-C₁₀)alkyl and substituted or unsubstituted (C₆-C₁₄)aryl; and

m is an integer selected from 1, 2 and 3.

3. The method of any one of claims 1 or 2, wherein the compound is a compound of formula (1) or a pharmaceutically acceptable salt thereof, wherein:

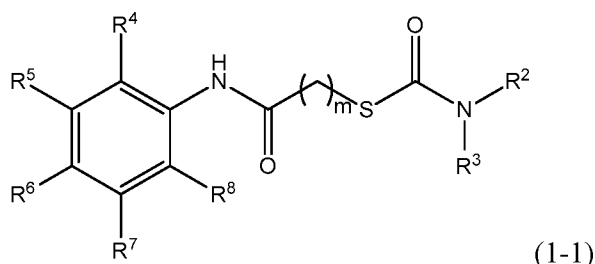
R¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl;

X is a chemical moiety linking R¹ to the remainder of the molecule selected from -NHC(O)-, -O-, -S-, -S(O)₂-, -C(O)-, -C(S)-, -NH-, -NHS(O)₂-, -(1,2,3-triazolyl)-, -(1,2,4-triazolyl)-, or a pharmaceutically acceptable bioisostere of any of the preceding;

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and

m is an integer selected from 1, 2 and 3.

4. The method of any one of claims 1 to 3, wherein R¹ is a substituted or unsubstituted (C₆-C₁₄)aryl.
5. The method of any one of claims 1 to 4, wherein m is 1.
6. The method of any one of claims 1 to 5, wherein R² and R³ are H.
7. The method of any one of claims 1 to 6, wherein X is -NH₂C(O)-.
8. The method of claim 7, wherein the compound is a compound of formula (1-1):



or a pharmaceutically acceptable salt thereof, wherein:

R² and R³ are independently selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

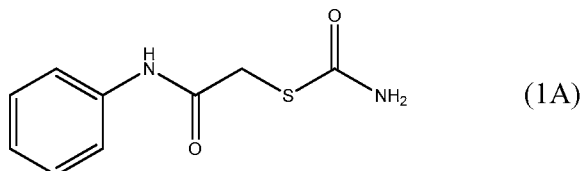
R⁴, R⁵, R⁶, R⁷, and R⁸ are independently selected from H, halo, OH, O(C₁-C₁₀)alkyl, NR⁹R¹⁰, NO₂, (C₁-C₁₀)haloalkyl, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or

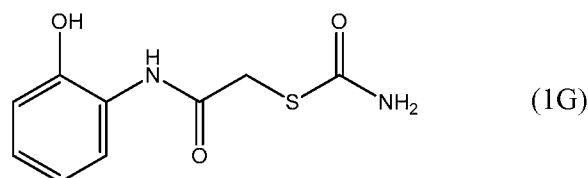
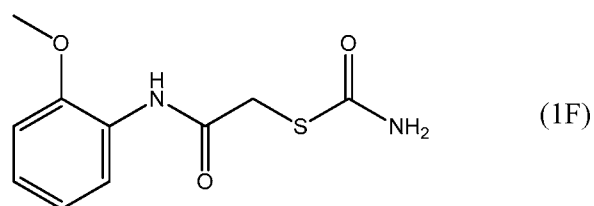
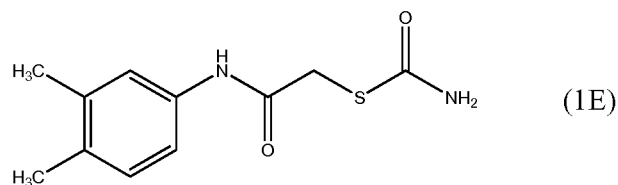
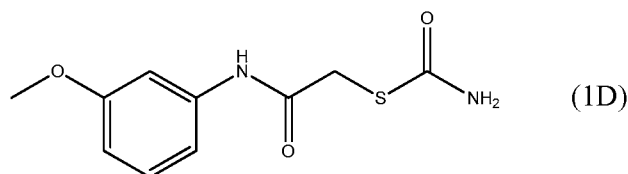
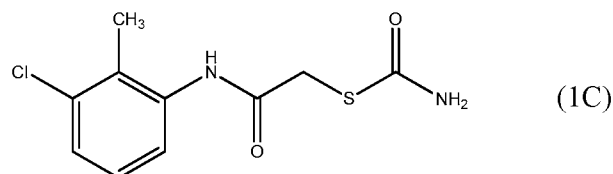
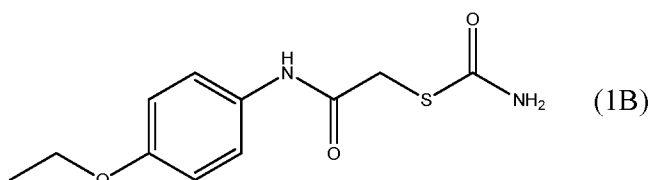
unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R⁹ and R¹⁰ are independently selected from H and (C₁-C₁₀)alkyl; and

m is an integer selected from 1, 2 and 3.

9. The method of claim 8, wherein R² and R³ are H.
10. The method of claim 8 or 9, wherein m is 1.
11. The method of any one of claims 8 to 10, wherein R⁷ and R⁸ are H.
12. The method of any one of claims 8 to 11, wherein R⁴ is H, substituted or unsubstituted (C₁-C₁₀)alkyl or -O-(C₁-C₁₀)alkyl.
13. The method of any one of claims 8 to 11, wherein R⁴ is H or substituted or unsubstituted (C₁-C₁₀)alkyl.
14. The method of any one of claims 8 to 11, wherein R⁴ is CH₃.
15. The method of any one of claims 8 to 11, wherein R⁴ is OCH₃.
16. The method of any one of claims 8 to 15, wherein R⁵ is selected from H, halo, -O-(C₁-C₁₀)alkyl, and substituted or unsubstituted (C₁-C₁₀)alkyl.
17. The method of any one of claims 8 to 15, wherein R⁵ is selected from H, halo, -OCH₃, and CH₃.
18. The method of any one of claims 8 to 17, wherein R⁶ is selected from H, -O-(C₁-C₁₀)alkyl, and substituted or unsubstituted (C₁-C₁₀)alkyl.
19. The method of any one of claims 8 to 17, wherein R⁶ is selected from H, -OCH₂CH₃, and CH₃.
20. The method of any one of claims 8 to 17, wherein R⁶ is H.
21. The method of claim 11, wherein the compound is selected from compounds of the following formulae:

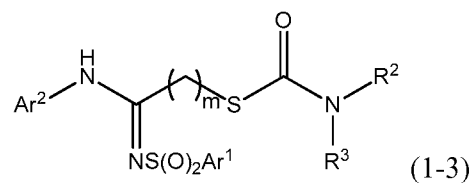




or a pharmaceutically acceptable salt thereof.

22. The method of any one of claims 1 to 6, wherein X is -NH(C=NR^a)-.

23. The method of claim 22, wherein the compound is a compound of formula (1-3):



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

Ar^1 is unsubstituted (C_6-C_{14}) aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

Ar^2 is unsubstituted (C_6-C_{14}) aryl, or aryl substituted with 1, 2 or 3 substituents independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and

m is an integer selected from 1, 2 and 3.

24. The method of claim 23, wherein R^2 and R^3 are H.

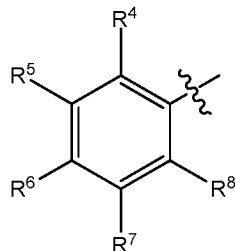
25. The method of claim 23 or 24, wherein m is 1.

26. The method of any one of claims 23 to 25, wherein Ar^1 is unsubstituted phenyl.

27. The method of any one of claims 23 to 25, wherein Ar^1 is para-substituted phenyl.

28. The method of claim 27, wherein Ar^1 is 4-tolyl or 4-halosubstituted phenyl.

29. The method of any one of claims 23 to 28, wherein Ar^2 is a group of the following formula:

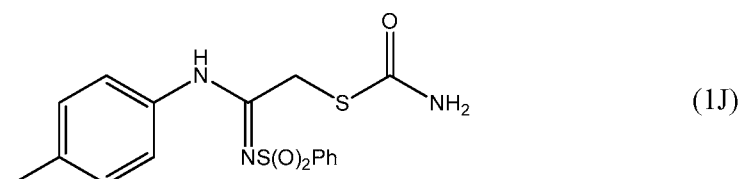
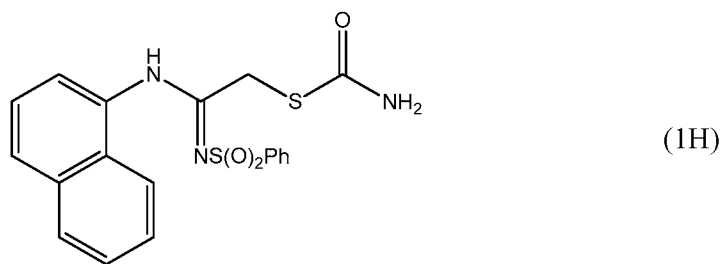


wherein:

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, O(C₁-C₁₀)alkyl, NR⁹R¹⁰, NO₂, (C₁-C₁₀)haloalkyl, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl; and

R^9 and R^{10} are independently selected from H and (C₁-C₁₀)alkyl.

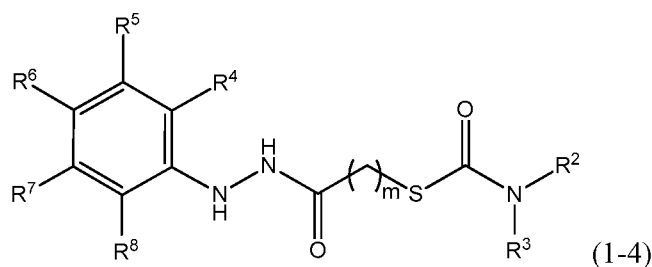
30. The method of claim 29, wherein R^7 and R^8 are H.
31. The method of claim 29 or claim 30, wherein R^4 is H, substituted or unsubstituted (C₁-C₁₀)alkyl or -O-(C₁-C₁₀)alkyl.
32. The method of any one of claims 29 to 31, wherein R^4 is H or substituted or unsubstituted (C₁-C₁₀)alkyl.
33. The method of any one of claims 29 to 31, wherein R^4 is CH₃ or OCH₃.
34. The method of any one of claims 29 to 33, wherein R^5 is selected from H, halo, -O-(C₁-C₁₀)alkyl, and substituted or unsubstituted (C₁-C₁₀)alkyl.
35. The method of any one of claims 29 to 33, wherein R^5 is selected from H, halo, -OCH₃, and CH₃.
36. The method of any one of claims 29 to 35, wherein R^6 is selected from H, -O-(C₁-C₁₀)alkyl, and substituted or unsubstituted (C₁-C₁₀)alkyl.
37. The method of any one of claims 29 to 35, wherein R^6 is selected from H, -OCH₂CH₃, and CH₃.
38. The method of any one of claims 29 to 35, wherein R^6 is H.
39. The method of any one of claims 23 to 29, wherein Ar² is 1-naphthyl.
40. The method of any one of claims 23 to 29, wherein Ar² is 2-naphthyl.
41. The method of claim 23, wherein the compound is selected from compounds of the following formulae:



or a pharmaceutically acceptable salt thereof.

42. The method of any one of claims 1 to 6, wherein X is -NHNHC(O)-.

43. The method of claim 42, wherein the compound is a compound of formula (1-4):



or a pharmaceutically acceptable salt thereof, wherein:

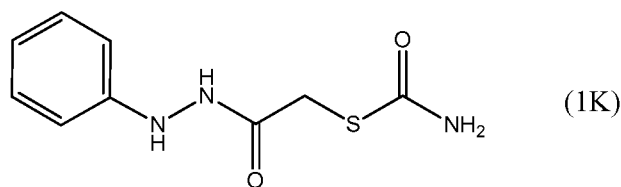
R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^9 and R^{10} are independently selected from H and (C_1-C_{10}) alkyl; and

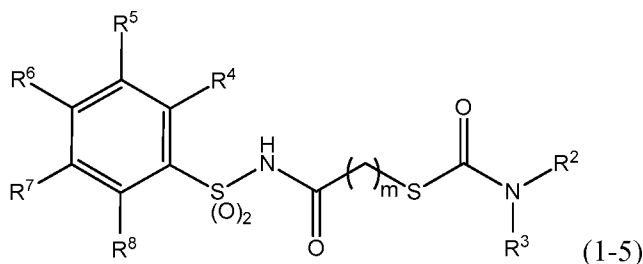
m is an integer selected from 1, 2 and 3.

44. The method of claim 43, wherein R^2 and R^3 are H.
45. The method of claim 43 or 44, wherein m is 1.
46. The method of any one of claims 43 to 45, wherein R^4 and R^5 are H.
47. The method of any one of claims 43 to 46, wherein R^7 and R^8 are H.
48. The method of any one of claims 43 to 47, wherein R^6 is H, (C_1-C_{10}) alkyl or halogen.
49. The method of any one of claims 43 to 47, wherein R^6 is H.
50. The method of claim 43, wherein the compound is a compound of the following formula:



or a pharmaceutically acceptable salt thereof.

51. The method of any one of claims 1 to 6, wherein X is $-S(O)_2NHC(O)-$.
52. The method of claim 51, wherein the compound is a compound of formula (1-5):



or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are independently selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, NR^9R^{10} , NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or

unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl;

R⁹ and R¹⁰ are independently selected from H and (C₁-C₁₀)alkyl; and

m is an integer selected from 1, 2 and 3.

53. The method of claim 52, wherein R² and R³ are H.

54. The method of claim 52 or 53, wherein m is 1.

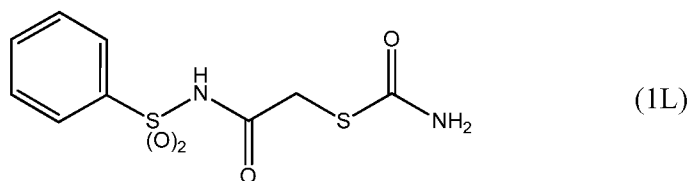
55. The method of any one of claims 52 to 54, wherein R⁴ and R⁵ are H.

56. The method of any one of claims 52 to 55, wherein R⁷ and R⁸ are H.

57. The method of any one of claims 52 to 56, wherein R⁶ is H, (C₁-C₁₀)alkyl or halogen.

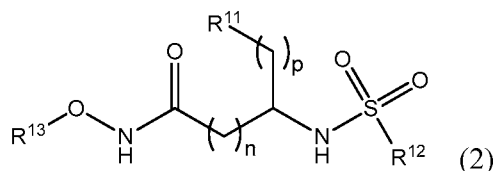
58. The method of any one of claims 52 to 56, wherein R⁶ is H.

59. The method of claim 52, wherein the compound is selected from compounds of the following formulae:



or a pharmaceutically acceptable salt thereof.

60. A method for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (2):



or a pharmaceutically acceptable salt thereof, wherein:

R¹¹ is selected from H, OH, SH, NH₂, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted (C₂-C₁₀)alkenyl, substituted or unsubstituted (C₂-C₁₀)alkynyl, substituted or unsubstituted (C₃-C₁₂)cycloalkyl, substituted or unsubstituted (C₆-C₁₄)aryl, substituted or unsubstituted (C₃-C₁₂)heterocycloalkyl, substituted or unsubstituted (C₄-C₁₂)heteroaryl, and an amino acid side chain;

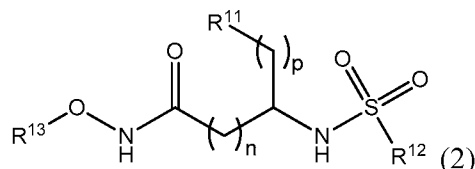
R^{12} is selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, substituted or unsubstituted (C_4-C_{12}) heteroaryl, and an amino acid side chain;

R^{13} is H or substituted or unsubstituted (C_1-C_{10}) alkyl;

n is an integer from 0 to 3; and

p is an integer from 0 to 3.

61. A method for inhibiting insulin-degrading enzyme in a cell, the method comprising contacting the cell with an effective amount of the compound of formula (2):



or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, substituted or unsubstituted (C_4-C_{12}) heteroaryl, and an amino acid side chain;

R^{12} is selected from H, OH, SH, NH_2 , substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, substituted or unsubstituted (C_4-C_{12}) heteroaryl, and an amino acid side chain;

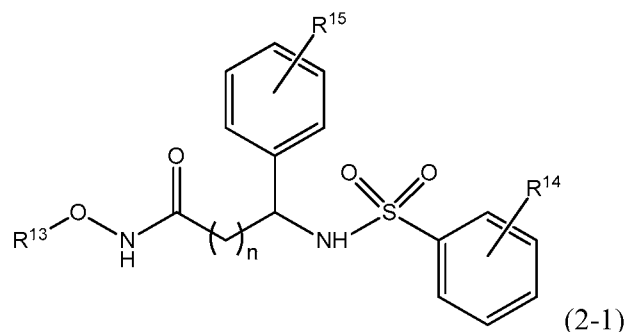
R^{13} is H or substituted or unsubstituted (C_1-C_{10}) alkyl;

n is an integer from 0 to 3; and

p is an integer from 0 to 3.

62. The method of claim 60 or 61, wherein R^{11} is a substituted or unsubstituted (C_6-C_{14}) aryl.
63. The method of claim 62, wherein R^{11} is a substituted phenyl.
64. The method of any one of claims 60 to 63, wherein R^{12} is a substituted or unsubstituted (C_6-C_{14}) aryl.

65. The method of claim 64, wherein R^{12} is a substituted phenyl.
66. The method of any one of claims 60 to 65, wherein R^{13} is H.
67. The method of any one of claims 60 to 66, wherein n is 1.
68. The method of any one of claims 60 to 67, wherein p is 0.
69. The method of any one of claims 60 to 68, wherein the compound is a compound of formula (2-1):



or a pharmaceutically acceptable salt thereof, wherein:

R^{13} is H or substituted or unsubstituted (C_1-C_{10}) alkyl;

R^{14} is selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, $NR^{16}R^{17}$, NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

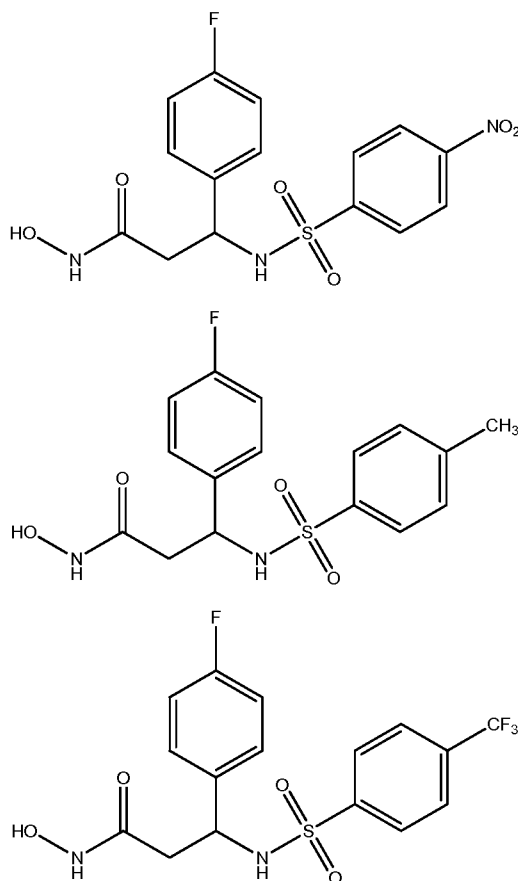
R^{15} is selected from H, halo, OH, $O(C_1-C_{10})$ alkyl, $NR^{16}R^{17}$, NO_2 , (C_1-C_{10}) haloalkyl, substituted or unsubstituted (C_1-C_{10}) alkyl, substituted or unsubstituted (C_2-C_{10}) alkenyl, substituted or unsubstituted (C_2-C_{10}) alkynyl, substituted or unsubstituted (C_3-C_{12}) cycloalkyl, substituted or unsubstituted (C_6-C_{14}) aryl, substituted or unsubstituted (C_3-C_{12}) heterocycloalkyl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl;

R^{16} and R^{17} are independently selected from H and substituted or unsubstituted (C_1-C_{10}) alkyl; and

n is an integer from 1 to 10.

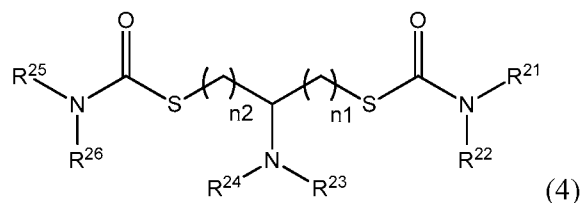
70. The method of claim 69, wherein R^{13} is H.
71. The method of claim 69 or 70, wherein R^{14} is selected from NO_2 , (C_1-C_{10}) haloalkyl, and (C_1-C_{10}) alkyl.

72. The method of any one of claims 69 to 71, wherein R^{15} is halo.
73. The method of claim 72, wherein R^{15} is F.
74. The method of claim 69, wherein the compound is selected from compounds of the following formulae:



or a pharmaceutically acceptable salt thereof.

75. A method for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (4):

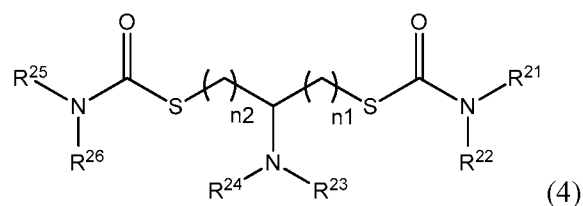


or a pharmaceutically acceptable salt thereof, wherein:

R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are independently selected from H and substituted or unsubstituted (C₁-C₁₀)alkyl; and

n1 and n2 are integers each independently selected from 1, 2 and 3.

76. A method for inhibiting insulin-degrading enzyme in a cell, the method comprising contacting the cell with an effective amount of a compound of formula (4):



or a pharmaceutically acceptable salt thereof, wherein:

R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are independently selected from H and substituted or unsubstituted (C₁-C₁₀)alkyl; and

n1 and n2 are integers each independently selected from 1, 2 and 3.

77. The method of claim 75 or 76, wherein n1 is 1.

78. The method of any one of claims 75 to 77, wherein n2 is 1.

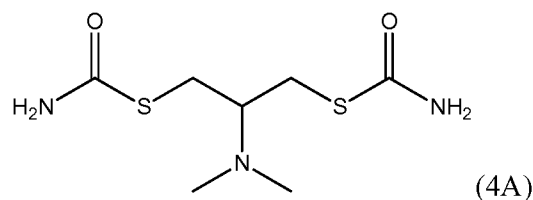
79. The method of any one of claims 75 to 78, wherein R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are independently selected from H and (C₁-C₁₀)alkyl.

80. The method of any one of claims 75 to 79, wherein R^{21} and R^{22} are H.

81. The method of any one of claims 75 to 80, wherein R^{25} and R^{26} are H.

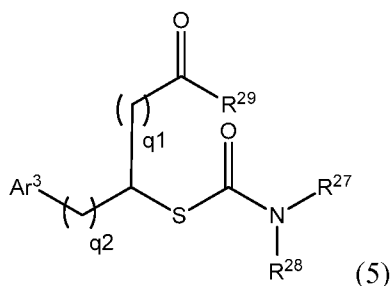
82. The method of any one of claims 75 to 81, wherein R^{23} and R^{24} are (C₁-C₁₀)alkyl.

83. The method of claim 75 or 76, wherein the compound is a compound of the following formula:



or a pharmaceutically acceptable salt thereof,

84. A method for inhibiting insulin-degrading enzyme, treating diabetes, promoting wound healing, or improving memory in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (5):



or a pharmaceutically acceptable salt thereof, wherein:

R^{27} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

R^{28} is selected from H and (C_1-C_{10}) alkyl;

R^{29} is selected from OR^{30} and $NR^{31}R^{32}$;

R^{30} is selected from H and (C_1-C_{10}) alkyl;

R^{31} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

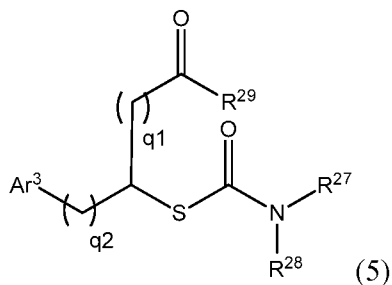
R^{32} is selected from H and (C_1-C_{10}) alkyl;

q_1 is selected from 0, 1 and 2;

q_2 is selected from 0, 1 and 2; and

Ar^3 is selected from substituted or unsubstituted (C_6-C_{14}) aryl, and substituted or unsubstituted (C_4-C_{12}) heteroaryl.

85. A method for inhibiting insulin-degrading enzyme in a cell, the method comprising contacting the cell with an effective amount of a compound of formula (5):



or a pharmaceutically acceptable salt thereof,

wherein:

R^{27} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

R^{28} is selected from H and (C_1-C_{10}) alkyl;

R^{29} is selected from OR^{30} and $NR^{31}R^{32}$;

R^{30} is selected from H and (C_1-C_{10}) alkyl;

R^{31} is selected from H, OH, NH_2 , and (C_1-C_{10}) alkyl;

R^{32} is selected from H and (C_1-C_{10}) alkyl;

q1 is selected from 0, 1 and 2;

q2 is selected from 0, 1 and 2; and

Ar³ is selected from substituted or unsubstituted (C₆-C₁₄)aryl, and substituted or unsubstituted (C₄-C₁₂)heteroaryl.

86. The method of claim 84 or 85, wherein R²⁷ is H.

87. The method of any one of claims 84 to 86, wherein R²⁸ is H.

88. The method of any one of claims 84 to 87, wherein R²⁹ is OR³⁰.

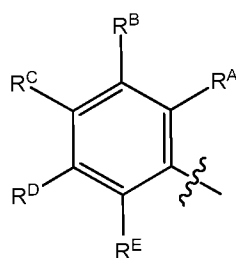
89. The method of claim 88, wherein R³⁰ is (C₁-C₁₀)alkyl.

90. The method of any one of claims 84 to 89, wherein q1 is 0.

91. The method of any one of claims 84 to 90, wherein q2 is 1.

92. The method of any one of claims 84 to 91, wherein Ar³ is a phenyl ring.

93. The method of claim 92, wherein Ar³ is a group of the following formula:



wherein:

R^A, R^B, R^D, and R^E are independently selected from H, halo, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂ and NO₂;

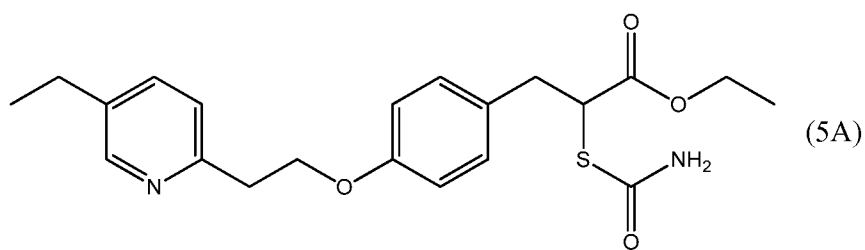
R^C is independently selected from H, halo, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂, NO₂, -((C₁-C₆)alkylene)Ar⁴, -((C₁-C₆)alkylene)OAr⁴, -O((C₁-C₆)alkylene)Ar⁴, and -((C₁-C₃)alkylene)-O((C₁-C₃)alkylene)Ar⁴;

Ar⁴ is selected from unsubstituted (C₆-C₁₄)aryl or (C₄-C₁₂)heteroaryl, and (C₆-C₁₄)aryl or (C₄-C₁₂)heteroaryl substituted with 1, 2, or 3-substituents selected from, halo, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)haloalkyl, OR^F, NR^F₂ and NO₂; and

each R^F is independently selected from hydrogen and (C₁-C₁₀)alkyl;

94. The method of claim 93, wherein R^A, R^B, R^D, and R^E are hydrogen.

95. The method of claim 93 or 94, wherein R^C is $-O((C_1-C_6)\text{alkylene})Ar^4$.
96. The method of claim 93 or 94, wherein R^C is $-OCH_2CH_2Ar^4$.
97. The method of any one of claims 93 to 96, wherein Ar^4 is a pyridyl.
98. The method of claim 97, wherein Ar^4 is a 2-pyridyl.
99. The method of any one of claims 93 to 97, wherein Ar^4 is unsubstituted or monosubstituted.
100. The method of claim 84 or 85, wherein the compound is a compound of the following formula:



or a pharmaceutically acceptable salt thereof.

1/6

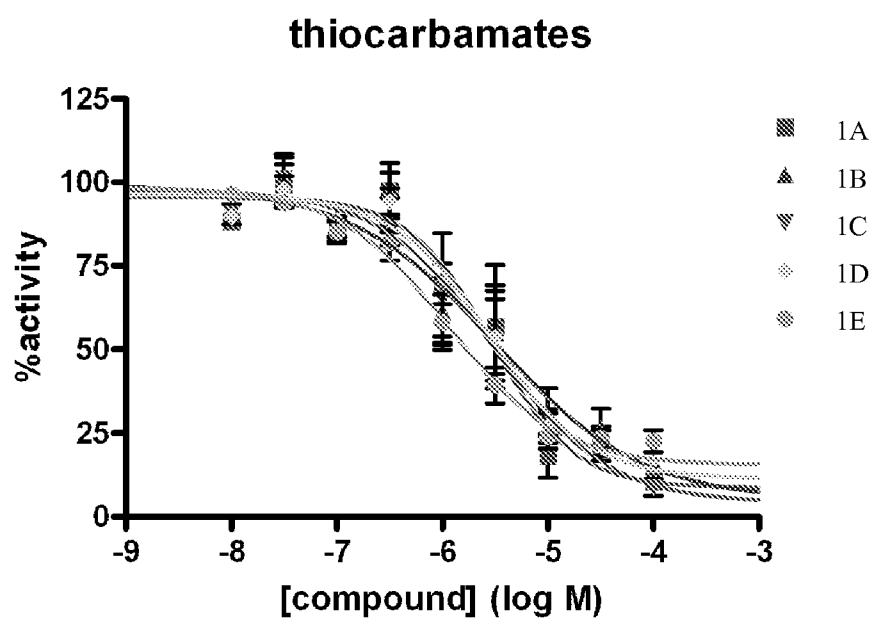


FIG. 1

2/6

Inhibition of insulin degradation by IDE by thiocarbamates at 1 μ M

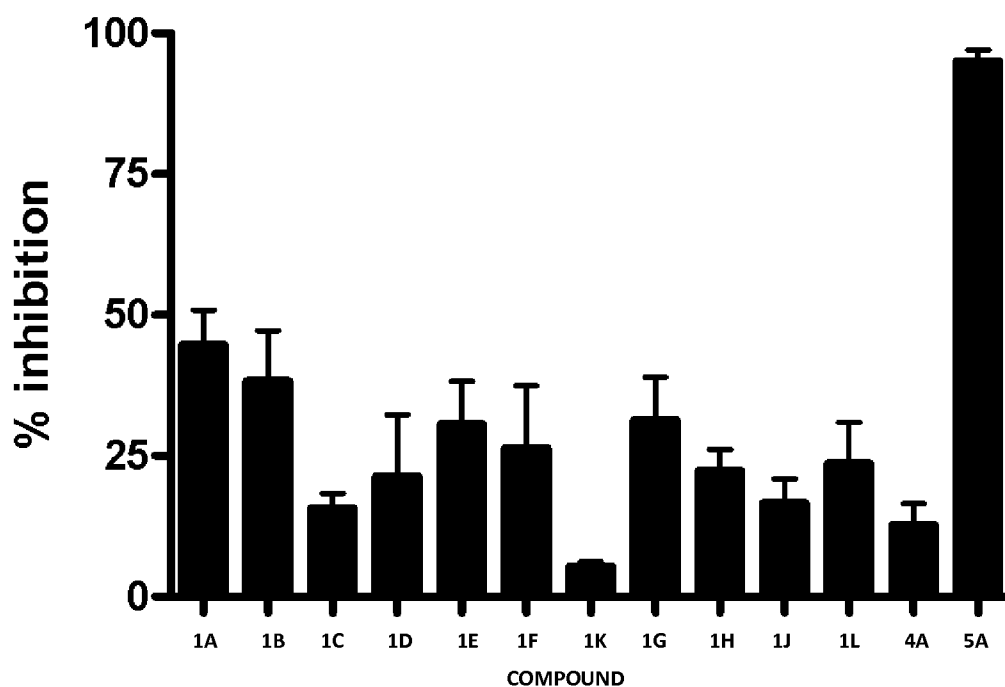


FIG. 2

3/6

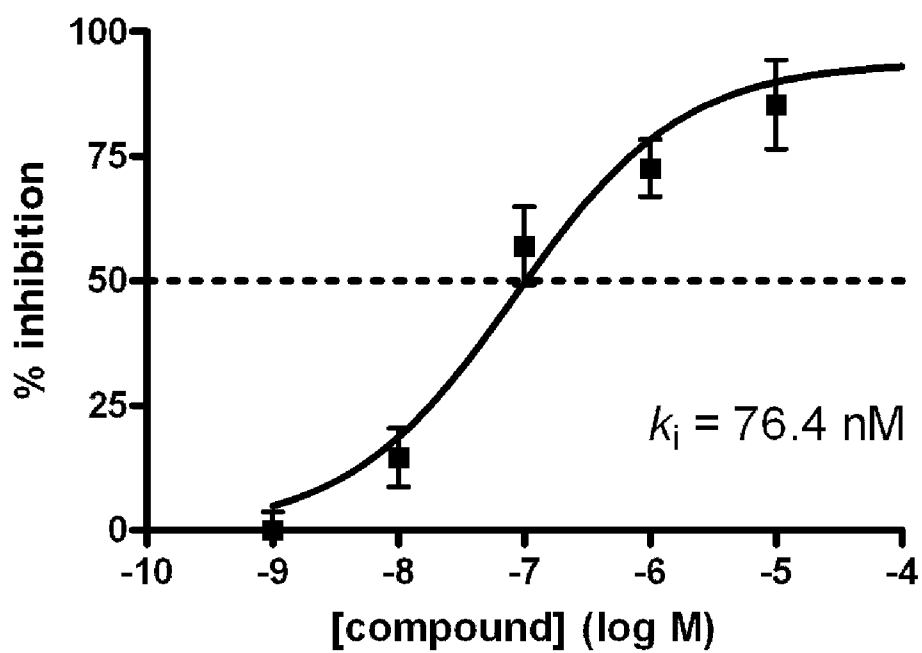


FIG. 3

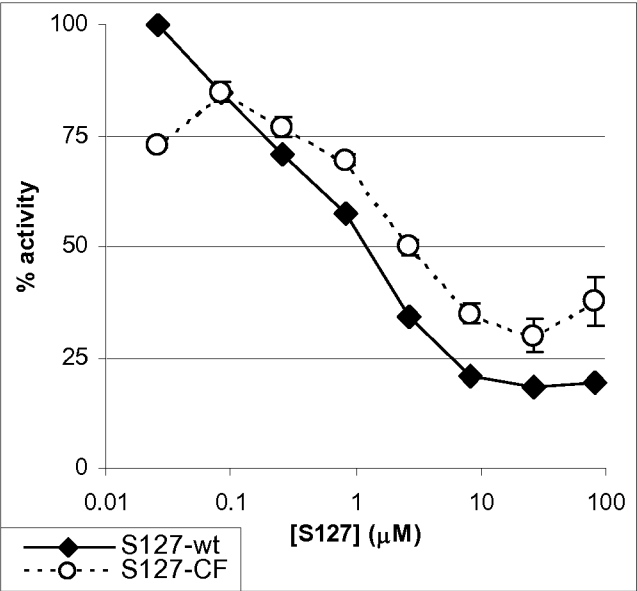


FIG. 4A

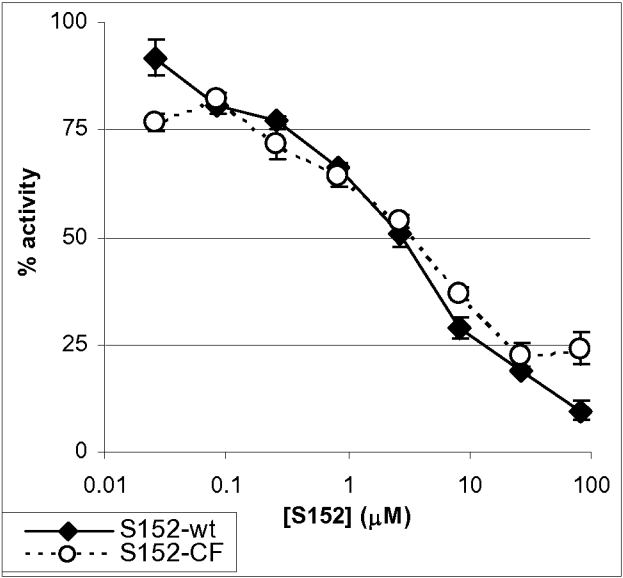


FIG. 4B

5/6

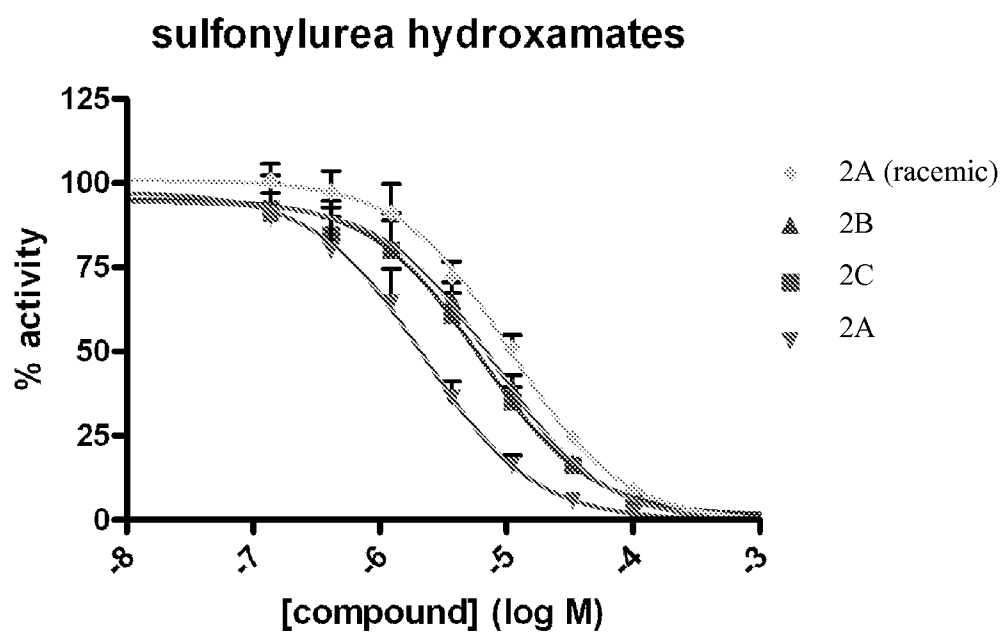


FIG. 5

6/6

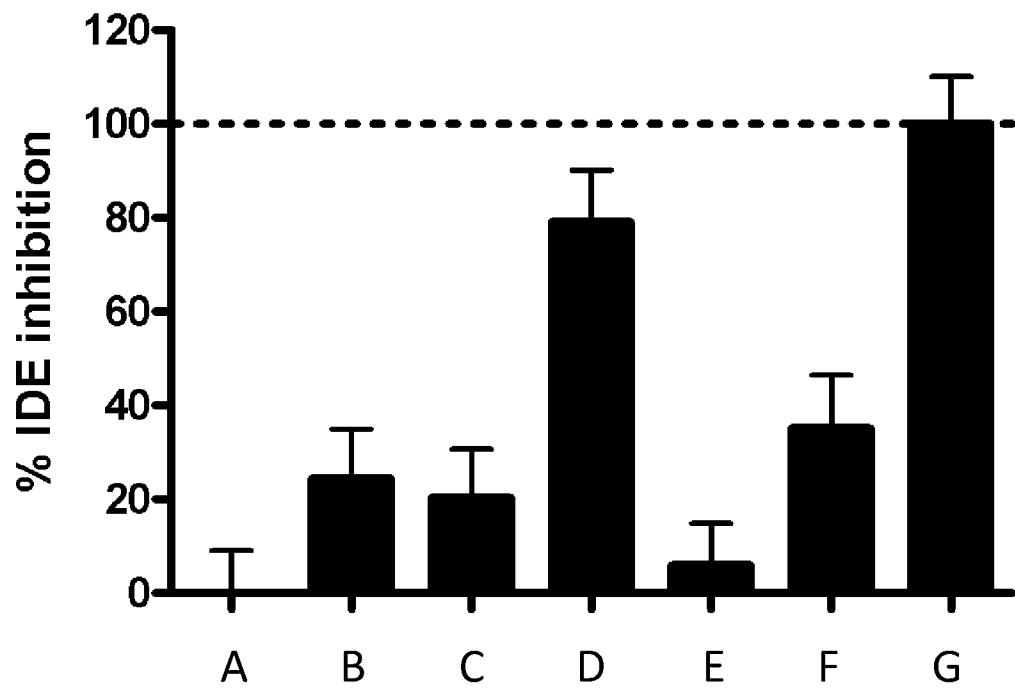


FIG. 6