



(51) International Patent Classification:

C07D 249/04 (2006.01) **A61P 31/12** (2006.01)
C07D 403/12 (2006.01) **A61P 1/16** (2006.01)
C07D 271/107 (2006.01)

(21) International Application Number:

PCT/US2010/039825

(22) International Filing Date:

24 June 2010 (24.06.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/220,944 26 June 2009 (26.06.2009) US

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

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

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: AMINO ACID DERIVED UREAS

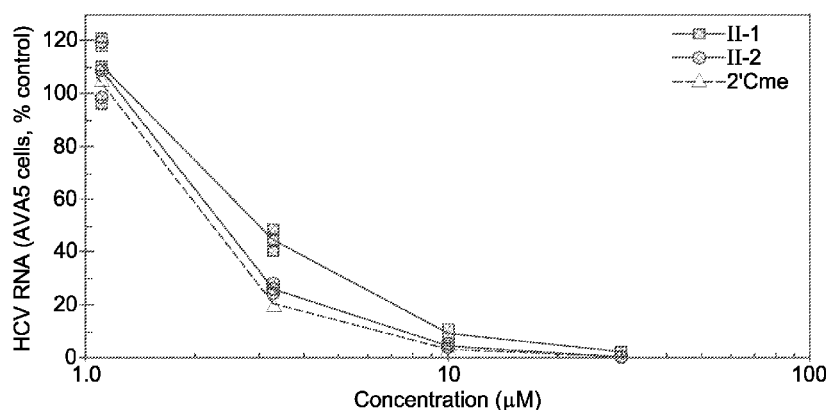


FIG. 1

(57) **Abstract:** Novel classes of amino acid derived urea compounds and compositions are disclosed. These compounds and compositions are useful in treating, preventing, and/or ameliorating viral infections such as, for example, Hepatitis C Virus.

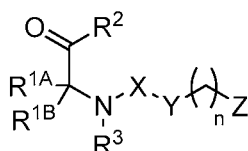
AMINO ACID DERIVED UREAS

BACKGROUND

Viral infections are major causes of morbidity and mortality. For example, chronic infection with hepatitis C virus (HCV) is a major health problem that affects more than 170 million people worldwide and is a causative agent of liver cirrhosis, hepatocellular carcinoma, and liver failure. *Flaviviruses* such as West Nile virus (WNV), Japanese Encephalitis virus, and Dengue virus (e.g., the four known serotypes of Dengue virus (DEN-1-4)) are significant human pathogens that cause millions of infections each year. Currently, there are no approved vaccines or antiviral therapeutics available for either DEN- or WNV-infected human. While there are treatments for HCV, these treatments are plagued by limited efficacy, serious side effects, high expense, and often result in drug resistance.

SUMMARY

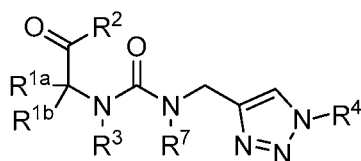
Novel amino acid derived urea compounds and compositions useful in treating, preventing, and/or ameliorating viral infections (e.g., Hepatitis C virus) are disclosed along with methods of making and using them. A first class of amino acid derived urea compounds includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, n is 0 to 5; R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy, alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; R² is OR⁵ or NR⁵R⁶, wherein R⁵ and R⁶ are each independently selected from hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or

unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or
 unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or
 5 unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and
 substituted or unsubstituted heterocycloalkylalkyl; R³ is hydrogen, substituted or
 unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or
 unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or
 unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 10 heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
 arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted
 cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; X is C=O or
 SO₂; Y is NR⁷ or O, wherein R⁷ is hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl,
 substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl,
 15 substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted
 or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or
 unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or
 substituted or unsubstituted heterocycloalkylalkyl; and Z is a substituted or
 20 unsubstituted aryl or substituted or unsubstituted heteroaryl.

A second class of amino acid derived urea compounds includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In this class of
 compounds, R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy,
 alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen,
 substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl,
 30 substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl,
 substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted
 or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted
 or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or

10004-022WO1 / 2009-020

unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl;
R² is OR⁵ or NR⁵R⁶, wherein R⁵ and R⁶ are each independently selected from
hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂
haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂
alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl,
substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,
substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted
heterocycloalkylalkyl; and R³, R⁴, and R⁷ are each independently selected from
hydrogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂
haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂
alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl,
substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,
substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted
heterocycloalkylalkyl.

Also provided herein are novel compositions including the amino acid derived
urea compounds described herein and pharmaceutically acceptable carriers.

A method for the treatment of viral infections, such as Hepatitis C, in a subject
is also provided herein. The method includes administering to the subject a
therapeutically effective amount of the compounds and/or compositions described
herein. A method for the prevention of viral infections is also provided, which
includes administering to the subject a therapeutically effective amount of the
compounds and/or compositions described herein. The methods of treating or
preventing viral infections can further include administering a second compound or
composition, wherein the second compound or composition includes an antiviral
compound (e.g., a nucleoside polymerase inhibitor, a non-nucleoside polymerase
inhibitor, or a protease inhibitor).

DESCRIPTION OF DRAWINGS

Fig. 1 is a graph displaying the dose response inhibition of HCV by
Compounds II-1 and II-2.

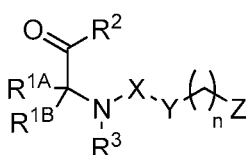
10004-022WO1 / 2009-020

Fig. 2 is a graph displaying the analysis of **Compound II-2** in combination treatments.

DETAILED DESCRIPTION

Described herein are novel amino acid derived urea compounds and compositions useful in treating, preventing, and/or ameliorating viral infections (e.g., Hepatitis C), along with methods of making and using them.

A first class of amino acid derived urea compounds as described herein are represented by **Compound I**:

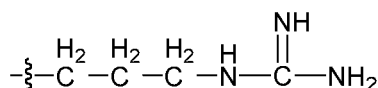
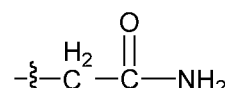
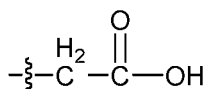
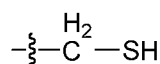
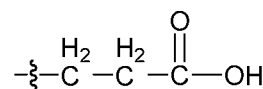
**I**

or pharmaceutically acceptable salts or prodrugs thereof.

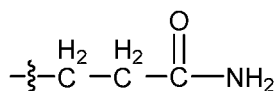
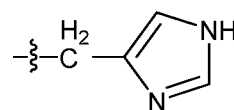
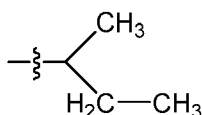
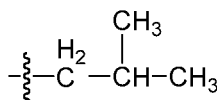
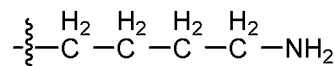
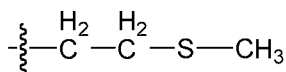
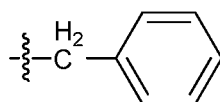
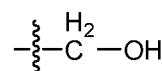
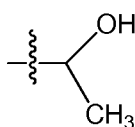
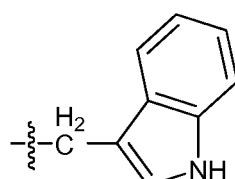
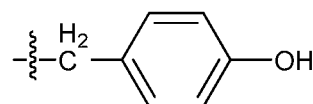
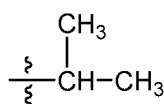
In **Compound I**, n is 0 to 5. In some examples, n is 1.

Also in **Compound I**, R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy, alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

The R^{1a} and R^{1b} groups of **Compound I** can be, for example, hydrogen, n-propyl, benzyl, or one of the following **Structures A1-A19**:

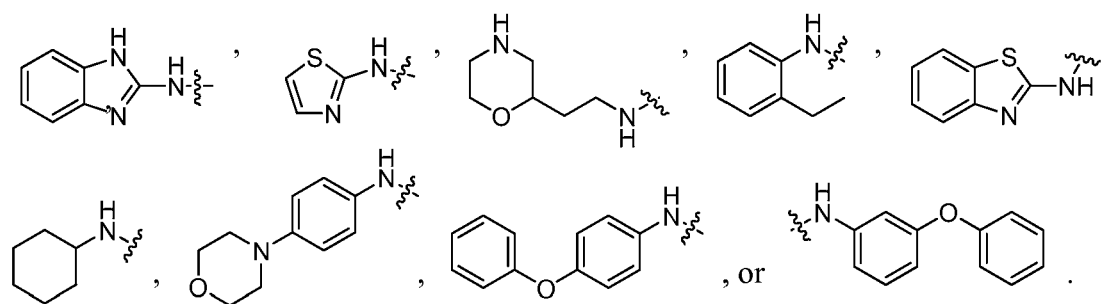
**A1****A2****A3****A4****A5****A6**

10004-022WO1 / 2009-020

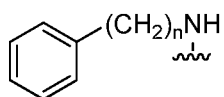
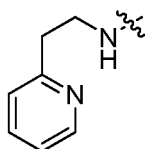
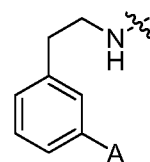
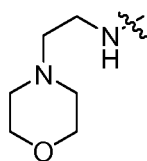
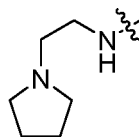
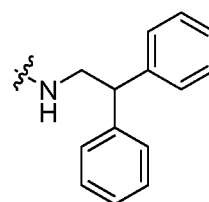
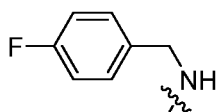
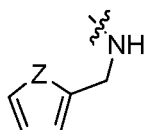
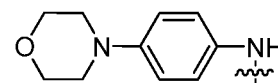
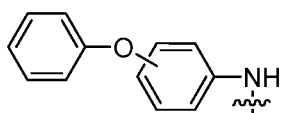
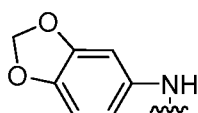
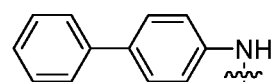
**A7****A8****A9****A10****A11****A12****A13****A14****A15****A16****A17****A18****A19**

Additionally in **Compound I**, R^2 is OR^5 or NR^5R^6 , wherein R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl. In some examples, R^2 is hydroxy, methoxy, or ethoxy. In some examples, R^2 is NHR^6 . NHR^6 can be, for example,

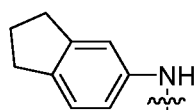
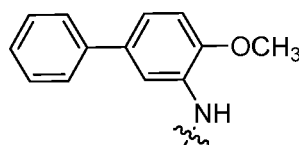
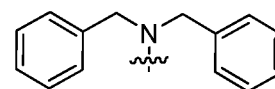
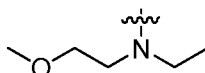
10004-022WO1 / 2009-020



5 In some examples of **Compound I**, R^2 is NR^5R^6 . The $-NR^5R^6$ group can have, for example, one of the following **Structures B1–B16**:

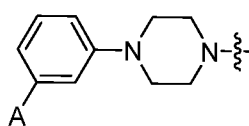
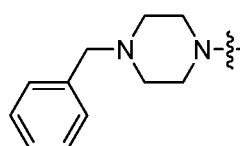
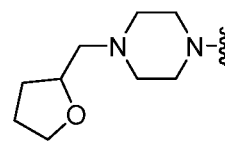
**B1****B2****B3****B4****B5****B6****B7****B8****B9****B10****B11****B12**

10004-022WO1 / 2009-020

**B13****B14****B15****B16**

In **Structure B1**, n is 0, 1, or 2. In **Structure B3**, A is F or OCH_3 . In **Structure B8**, Z is O or NH. As shown in **Structure B10**, the phenoxy group can be in the *ortho*, *meta*, or *para* position.

In **Compound I** wherein R^2 is $-NR^5R^6-$, the R^5 and R^6 groups can be combined to form substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl groups. For example, R^5 can be a propyl amine group and R^6 can be an ethyl group that combine to form a piperidine group. Further examples of the $-NR^5R^6-$ group of **Compound I** wherein R^2 is $-NR^5R^6-$, and R^5 and R^6 combine are shown in the following **Structures B17–B19**:

**B17****B18****B19**

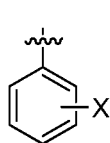
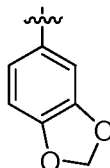
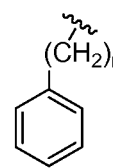
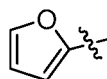
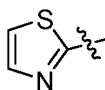
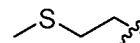
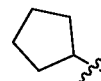
In **Structure B17**, A is H, OCH_3 , or CF_3 .

Also in **Compound I**, R^3 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl. In some examples, R^3 is hydrogen.

10004-022WO1 / 2009-020

In **Compound I**, one of R^{1a} or R^{1b} can be combined with R^3 to form substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl groups. For example, R^{1a} can be an ethyl group and R^3 can be a methyl group that combine to form a substituted heterocycloalkyl group.

In **Compound I**, R^3 can have, for example, one of the following **Structures C1–C8**:

**C1****C2****C3****C4****C5****C6****C7****C8**

In **Structure C1**, X is OCH_3 , OPh , F, CN, OCH_2Ph , or Ph. In **Structure C3**, n is 0, 1, or 2.

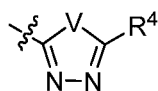
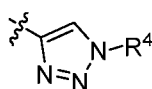
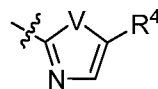
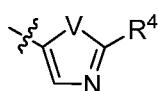
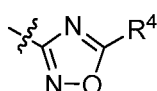
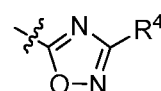
Additionally in **Compound I**, X is C=O or SO_2 .

Further in **Compound I**, Y is NR^7 or O, wherein R^7 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

Also in **Compound I**, Z is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In some examples, Z is a substituted or unsubstituted triazole or a substituted or unsubstituted oxadiazole.

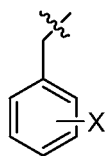
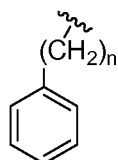
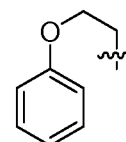
10004-022WO1 / 2009-020

In some examples of **Compound I**, Z can have, for example, one of the following **Structures D1–D6**:

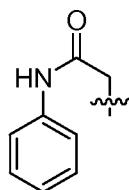
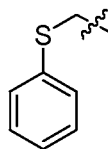
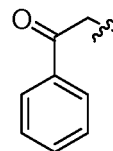
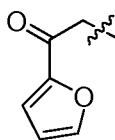
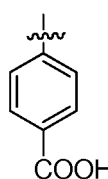
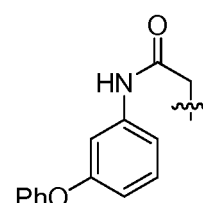
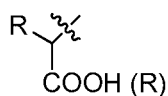
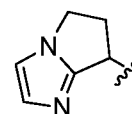
**D1****D2****D3****D4****D5****D6**

In **Structures D1–D6**, R^4 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl. In **Structure D1**, V is O, S, or NH. In **Structures D3 and D4**, V is O or S.

In **Structures D1–D6** of **Compound I**, R^4 can be, for example, a substituted or unsubstituted benzyl (e.g., *p*-methoxy benzyl) or one of the following **Structures E1–E12**:

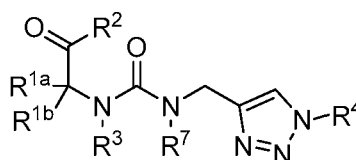
**E1****E2****E3**

10004-022WO1 / 2009-020

**E4****E5****E6****E7****E8****E9****E10****E11****E12**

In **Structure E1**, X is H, *para*- or *meta*-fluoro, *para*-methoxy, or *meta*-C(O)OCH₃. In **Structure E2**, n is 2 or 3. In Structure E11, R is a substitution group as defined herein.

A second class of amino acid derived urea compounds as described herein are represented by **Compound II**:



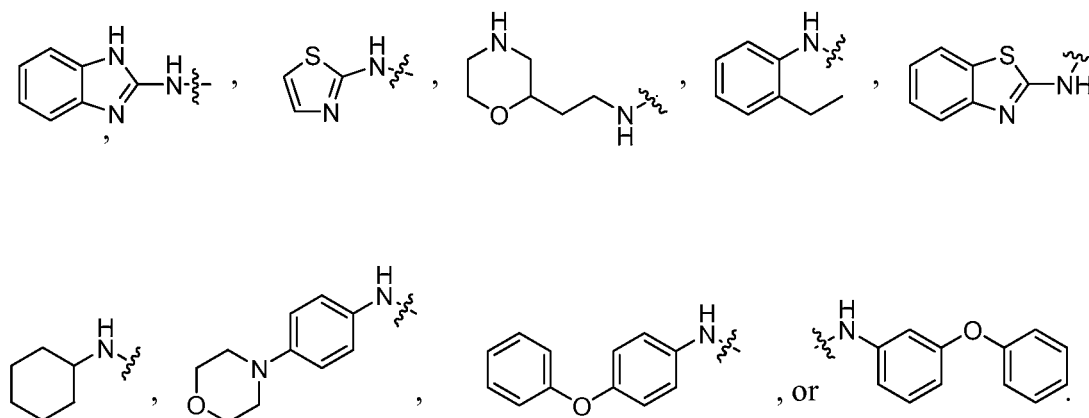
or pharmaceutically acceptable salts or prodrugs thereof.

In **Compound II**, R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy, alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen, substituted or unsubstituted C₁₋₁₂ alkyl, substituted or unsubstituted C₁₋₁₂ haloalkyl, substituted or unsubstituted C₂₋₁₂ alkenyl, substituted or unsubstituted C₂₋₁₂

10004-022WO1 / 2009-020

alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl. In some examples, R^{1a} or R^{1b} is hydrogen, propyl, or benzyl. The R^{1a} and R^{1b} groups of **Compound II** can have, for example, one of the **Structures A1–A19** (see pages 4-7).

Also in **Compound II**, R² is OR⁵ or NR⁵R⁶, wherein R⁵ and R⁶ are each independently selected from hydrogen, substituted or unsubstituted C_{1–12} alkyl, substituted or unsubstituted C_{1–12} haloalkyl, substituted or unsubstituted C_{2–12} alkenyl, substituted or unsubstituted C_{2–12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl. In some examples, R² is hydroxy, methoxy, or ethoxy. In some examples, R² is NR⁵R⁶. The NR⁵R⁶ group of **Compound II** can have, for example, one of the **Structures B1–B19** (see pages 7-11). In some examples, R² is NHR⁶. NHR⁶ can be, for example,

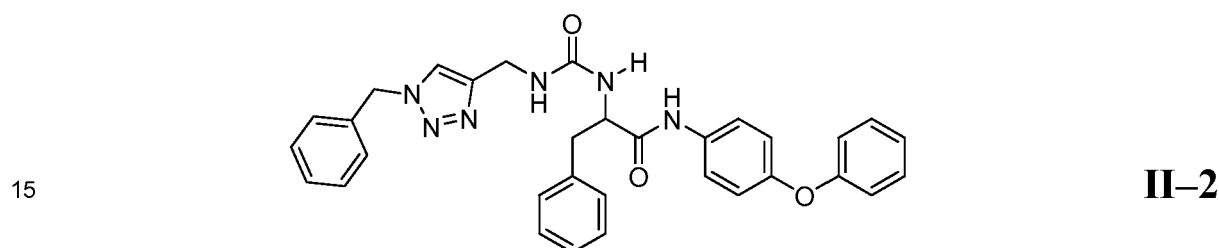
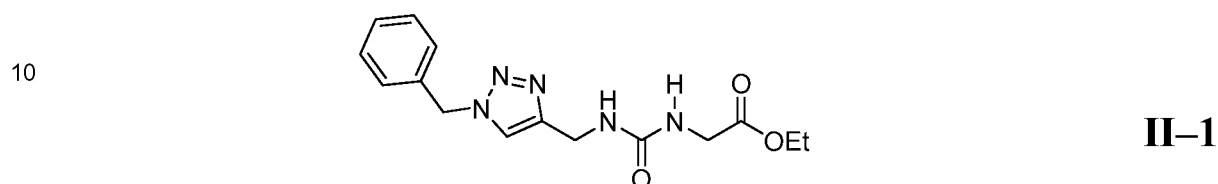


Further in **Compound II**, R³, R⁴, and R⁷ are each independently selected from hydrogen, substituted or unsubstituted C_{1–12} alkyl, substituted or unsubstituted C_{1–12} haloalkyl, substituted or unsubstituted C_{2–12} alkenyl, substituted or unsubstituted C_{2–12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl,

10004-022WO1 / 2009-020

substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl. In some examples, R³ is hydrogen. The R³ group of **Compound II** can have, for example, one of the **Structures C1–C8** (see pages 11-12). In some examples, R⁴ is a substituted or unsubstituted benzyl (e.g., *p*-methoxy benzyl). The R⁴ group of **Compound II** can have, for example, one of the **Structures D1–D12** (see pages 13-15). In some examples, R⁷ is hydrogen.

Examples of **Compound II** are as follows:



As used herein, the terms alkyl, alkenyl, and alkynyl include straight- and branched-chain monovalent substituents. Examples include methyl, ethyl, isobutyl, 3-butynyl, and the like. Heteroalkyl, heteroalkenyl, and heteroalkynyl are similarly defined but may contain O, S, or N heteroatoms or combinations thereof within the backbone. The term cycloalkyl as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term heterocycloalkyl is a type of cycloalkyl group as defined above, and is included within the meaning of the term cycloalkyl, where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus.

Aryl molecules include, for example, cyclic hydrocarbons that incorporate one or more planar sets of, typically, six carbon atoms that are connected by delocalized electrons numbering the same as if they consisted of alternating single and double covalent bonds. An example of an aryl molecule is benzene. Heteroaryl molecules

include substitutions along their main cyclic chain of atoms such as O, N, or S. When heteroatoms are introduced, a set of five atoms, e.g., four carbons and a heteroatom, can create an aromatic system. Examples of heteroaryl molecules include furan, pyrrole, thiophene, imidazole, oxazole, pyridine, and pyrazine. Aryl and heteroaryl molecules can also include additional fused rings, for example, benzofuran, indole, benzothiophene, naphthalene, anthracene, and quinoline.

The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, and heteroaryl molecules used herein can be substituted or unsubstituted. As used herein, the term substituted includes the addition of an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, or heteroaryl group (as described herein) to a position attached to the main chain of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, or heteroaryl, e.g., the replacement of a hydrogen by one of these molecules. Examples of substitution groups include, but are not limited to, hydroxyl, halogen (e.g., F, Br, Cl, or I), and carboxyl groups. Conversely, as used herein, the term unsubstituted indicates the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, or heteroaryl has a full complement of hydrogens, i.e., commensurate with its saturation level, with no substitutions, e.g., linear decane ($(\text{CH}_2)_9\text{--CH}_3$).

The compounds described herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and is contemplated. Enantiomeric resolution may, for example, be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

In the case of amino acid residues, such residues may be of either the L- or D-form. As used herein, the term amino acid refers to α -amino acids which are racemic, or of either the D- or L-configuration. The designation "L" preceding an amino acid refers to the L-isomer of the amino acid. The designation "DL" preceding an amino acid designation refers to a mixture of the L- and D-isomers of the amino acid. The chiral centers of the compounds provided herein may undergo epimerization *in vivo*.

10004-022WO1 / 2009-020

As such, the administration of a compound in its (L) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (D) form.

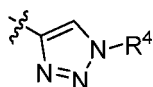
The compounds described herein can be prepared in a variety of ways. The compounds can be synthesized using synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art. The compounds described herein can be prepared from readily available starting materials. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Variations on **Compound I** and **Compound II** include the addition, subtraction, or movement of the various constituents as described for each compound. Similarly, as described above, when one or more chiral centers is present in a molecule the chirality of the molecule can be changed. Additionally, compound synthesis can involve the protection and deprotection of various chemical groups. The use of protection and deprotection, and the selection of appropriate protecting groups can be determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, *Protective Groups in Organic Synthesis*, 4th Ed., Wiley & Sons, 2006, which is incorporated herein by reference in its entirety. The synthesis and subsequent testing of various compounds as described by **Compound I** and **Compound II** to determine efficacy is contemplated.

Reactions to produce the compounds described herein can be carried out in solvents which can be selected by one of skill in the art of organic synthesis. Solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products under the conditions at which the reactions are carried out, i.e., temperature and pressure. Reactions can be carried out in one solvent or a mixture of more than one solvent. Product or intermediate formation 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), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

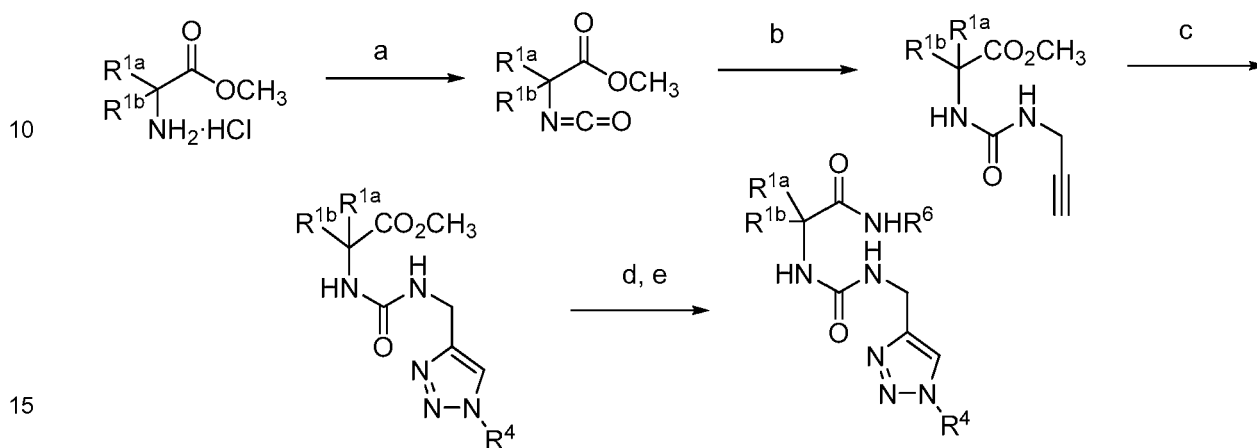
10004-022WO1 / 2009-020

Examples of compounds described by **Compound I**, wherein Z is



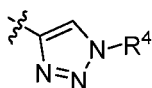
R^2 is NHR^6 , and R^3 is H; or **Compound II**, and pharmaceutically acceptable salts and prodrugs thereof can be made in solution phase using the methods shown in Scheme 1.

Scheme 1:



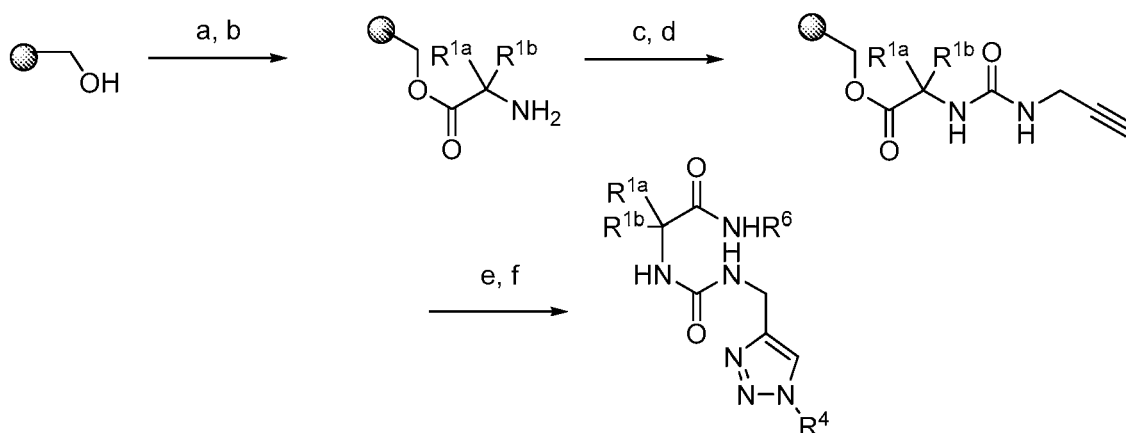
a. $ClCO_2CCl_3$, dioxane, reflux; b. propargylamine, CH_2Cl_2
 c. R^4-N_3 , $CuSO_4$ hydrate, sodium ascorbate; d. $LiOH$, aq. THF;
 e. EDCI/DMF, then R^6NH_2

Additionally, compounds described herein can be prepared using solid-phase synthetic procedures. Examples of synthesizing compounds described by **Compound I**, wherein Z is



R^2 is NHR^6 , and R^3 is H; or **Compound II**, and pharmaceutically acceptable salts and prodrugs thereof using solid phase synthesis techniques is shown in Scheme 2.

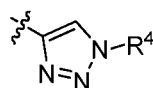
10004-022WO1 / 2009-020

Scheme 2:

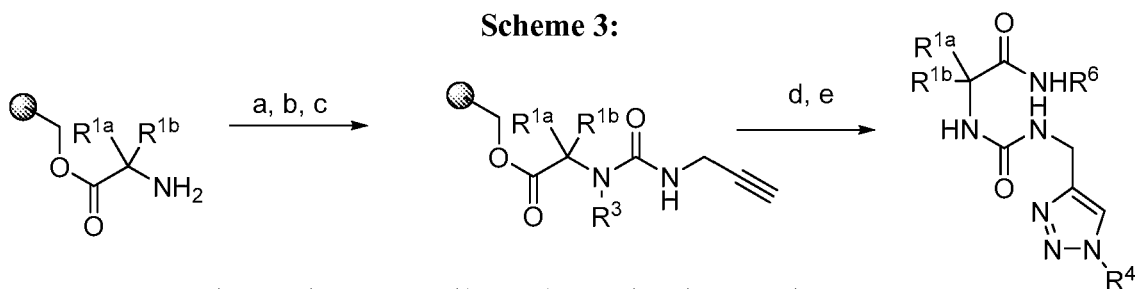
- a. FmocNHCR^{1a}R^{1b}CO₂H, N,N'-diisopropylcarbodiimide, DMAP, CH₂Cl₂;
 b. Piperidine/DMF; c. ClCO₂CCl₃, dioxane; d. propargylamine;
 e. R⁴-N₃, CuSO₄, ascorbate, t-butanol; f. R⁶NH₂

An example of synthesizing compounds described by **Compound I**, wherein

Z is



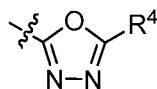
and R² is NHR⁶; or **Compound II**, and pharmaceutically acceptable salts and prodrugs thereof using solid phase synthesis techniques is shown in Scheme 3.

Scheme 3:

- a. RCHO/HOAc/NaCNBH₃/((CH₃O)₃CH; b. ClCO₂CCl₃;
 c. propargylamine; d. R⁴-N₃, CuSO₄, ascorbate, t-butanol; e. R⁶NH₂

An example of synthesizing compounds described by **Compound I**, wherein

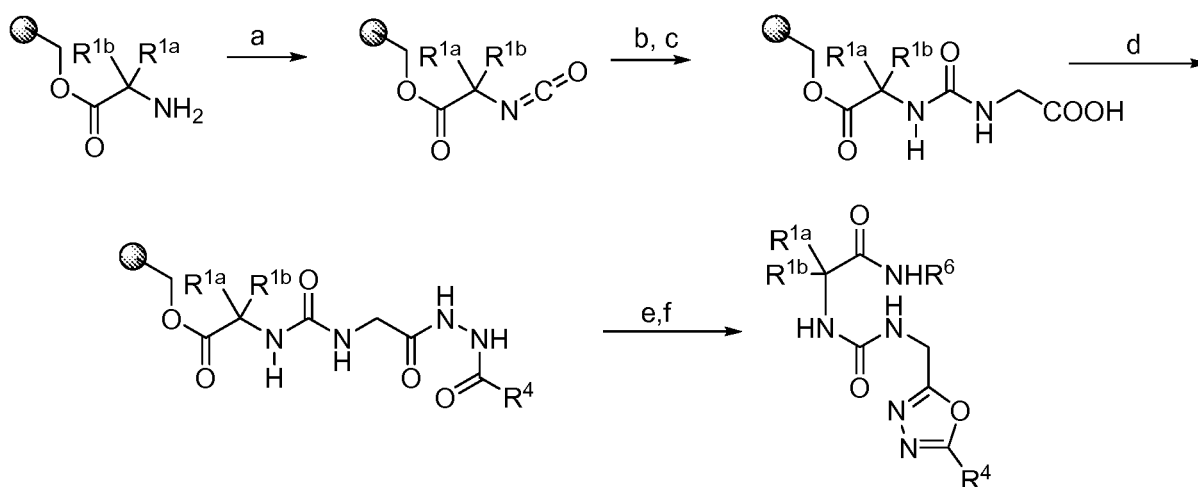
Z is



and R³ is H; and pharmaceutically acceptable salts and prodrugs thereof using solid phase synthesis techniques is shown in Scheme 4.

10004-022WO1 / 2009-020

Scheme 4:



a. $\text{ClCO}_2\text{CCl}_3$; b. EDCI/DMF, then Gly-Ot-Bu; c. TFA/ CH_2Cl_2
 d. EDCI/DMF, then $\text{NH}_2\text{NH}(\text{C}=\text{O})\text{R}^6$; e. TsCl/ Et_3N ; f. $\text{R}^4\text{-NH}_2$

15 The compounds described herein or pharmaceutically acceptable salts or prodrugs thereof can be provided in a pharmaceutical composition. Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid, or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit

20 dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the compounds described herein or a pharmaceutically acceptable salt or prodrug thereof in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically acceptable

25 is meant a material that is not biologically or otherwise undesirable, which can be administered to an individual along with the selected substrate without causing significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

30 As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and

formulations containing these materials is described in, *e.g.*, Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers such as phosphate buffers, citrate buffer, and
5 buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose,
10 or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN[®] (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICS[™] (BASF; Florham Park, NJ).

Compositions containing the compounds described herein or pharmaceutically
15 acceptable salts or prodrugs thereof suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol,
20 polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

25 These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged
30 absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration of the compounds described herein or a pharmaceutically acceptable salt or prodrug thereof include capsules, tablets,

pills, powders, and granules. In such solid dosage forms, the compounds described herein or a pharmaceutically acceptable salt or prodrug thereof is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration of the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-

butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

5 Besides such inert diluents, the composition can also include adjuvants, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

 Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-
10 agar and tragacanth, or mixtures of these substances, and the like.

 Compositions of the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof for rectal administrations are preferably suppositories which can be prepared by mixing the compounds with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a
15 suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

 Dosage forms for topical administration of the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof include ointments, powders,
20 sprays, and inhalants. The compounds described herein or pharmaceutically acceptable salts or prodrugs thereof are admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, ointments, powders, and solutions are also contemplated as being within the scope of the compositions.

25 The term pharmaceutically acceptable salt as used herein refers to those salts of the compounds described herein that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic
30 forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds described herein. These salts can be prepared *in situ* during the isolation and purification of the compounds or by separately reacting the purified compound in its

free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See Stahl and Wermuth, *Pharmaceutical Salts: Properties, Selection, and Use*, Wiley-VCH, 2008, which is incorporated herein by reference in its entirety, at least, for compositions taught therein.)

The compounds and compositions described above are useful in treating viral infections in humans, e.g., including pediatric and geriatric populations, and animals, e.g., veterinary applications. Methods of using the compounds and compositions described herein comprise administering to a subject a therapeutically effective amount of the compounds or compositions described herein or a pharmaceutically acceptable salt or prodrug thereof. Viral infections include, for example, Hepatitis C Virus and *Flavivirus* infections. Flavivirus infections include, for example, West Nile Virus, Dengue Virus, and Japanese Encephalitis Virus. Several serotypes of Dengue Virus have been identified such as, for example, serotype DEN-1, serotype DEN-2, serotype DEN-3, and serotype DEN-4. As used herein the term treating or treatment includes prevention; delay in onset; diminution, eradication, or delay in exacerbation of signs or symptoms after onset; and prevention of relapse.

The methods and compounds or compositions as described herein are useful for both prophylactic and therapeutic treatment of viral infections. For prophylactic use, a therapeutically effective amount of the compounds or compositions described herein are administered to a subject prior to exposure (e.g., before or when traveling to a location where viral infections are possible), during a period of potential exposure to viral infections, or after a period of potential exposure to viral or fungal infections. Prophylactic administration can occur for several days to weeks prior to potential exposure, during a period of potential exposure, and for a period of time, e.g., several

days to weeks, after potential exposure. Therapeutic treatment involves administering to a subject a therapeutically effective amount of the compounds or compositions described herein after a viral infection is diagnosed.

Administration of compounds or compositions described herein or
5 pharmaceutically acceptable salts or prodrugs thereof can be carried out using therapeutically effective amounts of the compounds or compositions described herein or pharmaceutically acceptable salts or prodrugs thereof for periods of time effective to treat viral infections. The effective amount of the compounds or compositions described herein or pharmaceutically acceptable salts or prodrugs thereof may be
10 determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to about 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.05 to about 75 mg/kg of body weight of active compound
15 per day, about 0.5 to about 50 mg/kg of body weight of active compound per day, about 0.5 to about 25 mg/kg of body weight of active compound per day, about 1 to about 20 mg/kg of body weight of active compound per day, about 1 to about 10 mg/kg of body weight of active compound per day, about 20 mg/kg of body weight of active compound per day, about 10 mg/kg of body weight of active compound per
20 day, or about 5 mg/kg of body weight of active compound per day. Those of skill in the art will understand that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of
25 the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

In these methods, a viral infection, for example, can be further treated with one or more additional agents. For example, the methods of treating and preventing viral infections as described herein can further include administering a second
30 compound or composition to the subject. The second compound or composition can include an antiviral compound or mixtures of antiviral compounds (e.g., pegylated interferon- α , ribavirin, and mixtures thereof). Antiviral compounds that can be used in combination with the compounds described herein include, for example, nucleoside

polymerase inhibitors, non-nucleoside polymerase inhibitors, protease inhibitors, nucleoside or nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, entry inhibitors, assembly inhibitors, integrase inhibitors, kinase inhibitors, enzyme inhibitors, maturation inhibitors, M2 inhibitors, and neuraminidase inhibitors. Examples of such additional antiviral compounds include, but are not limited to amantadine, rimantadine, oseltamivir (Tamiflu®, Roche Laboratories, Nutley, NJ), zanamivir (Relenza®, GlaxoSmithKline, Philadelphia, PA), peramivir, raltegravir, Maraviros, enfuvirtide, bevirimat, Vivecon™ (Myriad Genetics, Salt Lake City, UT), Combivir® (zidovudine + lamivudine, AZT + 3TC) (GlaxoSmithKline, Philadelphia, PA), Emtriva® (emtricitabine, FTC) (Gilead Sciences, Foster City, CA), Epivir® (lamivudine, 3TC) (GlaxoSmithKline, Philadelphia, PA), Epzicom® (Kivexa, abacavir + lamivudine, ABC + 3TC) (GlaxoSmithKline, Philadelphia, PA), Retrovir® (zidovudine, AZT, ZDV) (GlaxoSmithKline, Philadelphia, PA), Trizivir® (abacavir + zidovudine + lamivudine, ABC + AZT + 3TC) (GlaxoSmithKline, Philadelphia, PA), Truvada® (tenofovir DF + emtricitabine, TDF + FTC) (Gilead Sciences, Foster City, CA), Videx® & Videx EC® (didanosine, ddI) (Bristol-Myers Squibb, Princeton, NJ), Viread® (tenofovir disoproxil fumarate, TDF) (Gilead Sciences, Foster City, CA), Zerit® (stavudine, d4T) (Bristol-Myers Squibb, Princeton, NJ), Ziagen® (abacavir, ABC) (GlaxoSmithKline, Philadelphia, PA), Racivir™ (RCV) (Pharmasset, Princeton, NJ), Amdoxovir™ (AMDx, DAPD) (RFS Pharma, Tucker, GA), apricitabine (SPD754, AVX754), elvucitabine (ACH-126,443, Beta-L-Fd4C), Immunitin® (HE2000, alpha-epibromide) (Hollis-Eden Pharmaceuticals, San Diego, CA), Proleukin® (aldesleukin, Interleukin-2, IL-2) (Chiron Corporation, Emeryville, CA), Remune® (HIV-1 Immunogen, Salk vaccine) (Orchestra Therapeutics, Carlsbad, CA), BAY 50-4798, IR103, Intelence™ (etravirine, TMC-125) (Tibotec Therapeutics, Irvine, CA), Rescriptor® (delavirdine, DLV) (Pfizer, New York, NY), Sustiva® (Stocrin, efavirenz, EFV) (Bristol-Myers Squibb, Princeton, NJ), Viramune® (nevirapine, NVP) (Boehringer Ingelheim, Ridgefield, CT), rilpivirine (TMC-278), Agenerase® (amprenavir, APV) (GlaxoSmithKline, Philadelphia, PA), Aptivus® (tipranavir, TPV) (Boehringer Ingelheim, Ridgefield, CT), Crixivan® (indinavir, IDV) (Merck, Whitehouse Station, NJ), Invirase® (saquinavir, SQV) (Roche Laboratories, Nutley, NJ), Kaletra® (Aluvia®, lopinavir/ritonavir, LPV/r) (Abbott Laboratories, Abbott

Park, IL), Lexiva® (Telzir®, fosamprenavir, FPV) (GlaxoSmithKline, Philadelphia, PA), Norvir® (ritonavir, RTV) (Abbott Laboratories, Abbott Park, IL), Prezista® (darunavir, DRV) (Tibotec Therapeutics, Irvine, CA), Reyataz® (atazanavir, ATV) (Bristol-Myers Squibb, Princeton, NJ), Viracept® (nelfinavir, NFV) (Pfizer, Inc., New York, NY), Fuzeon® (enfuvirtide, ENF, T-20) (Roche Laboratories, Inc., Nutley, NJ), Selzentry® (Celsentri®, maraviroc, UK-427,857) (Pfizer, Inc., New York, NY), Vicriviroc® (SCH-417690, SCH-D) (Schering-Plough, Kenilworth, NJ), PRO 140 (Progenics Pharmaceuticals, Tarrytown, NY), TNX-355 (Tanox, Inc., Houston, TX), Isentress® (raltegravir, MK-0518) (Merck, Whitehouse Station, NJ), Elvitegravir™ (GS-9137) (Gilead Sciences, Foster City, CA), Bevirimat™ (PA-457) (Panacos Pharmaceuticals, Inc., Watertown, MA), and Droxia® or Hydrea® (hydroxyurea, HU) (Bristol-Myers Squibb, Princeton, NJ).

The one or more additional agents and the compounds or compositions described herein or a pharmaceutically acceptable salt or prodrug thereof can be administered in any order, including simultaneous administration, as well as temporally spaced order of up to several days apart. The methods may also include more than a single administration of the one or more additional agents and/or the compounds or compositions described herein or a pharmaceutically acceptable salt or prodrug thereof. The administration of the one or more additional agent and the compounds or compositions described herein or a pharmaceutically acceptable salt or prodrug thereof may be by the same or different routes and concurrently or sequentially.

The examples below are intended to further illustrate certain aspects of the methods, compounds, and compositions described herein, and are not intended to limit the scope of the claims.

Examples

Example 1: Anti-HCV Activity of Compounds

The antiviral activities of **Compound II-1** and **II-2** were assessed in a 3-day assay using the stably-expressing HCV replicon cell lines, AVA5 (sub-genomic CON1, genotype 1b) and APC103 (genomic H77, genotype 1a) maintained as sub-confluent cultures on 96-well plates. Antiviral activity was determined by blot hybridization analysis of intracellular HCV RNA (normalized to the level of cellular

B-actin RNA in each culture sample). See Table 1 (SI refers to Selectivity Index). A 3-fold suppression of HCV RNA and less than 2-fold suppression of cellular B-actin RNA was used as the cutoff. Cytotoxicity was assessed by neutral red dye uptake after 3 days of treatment. Dose response inhibition of HCV was also determined (Figure 1). The nucleoside analogue 2'C-methyl cytidine (2'CmeC) was used as an assay activity control. EC₅₀, EC₉₀ and CC₅₀ values (+/- standard deviation [S.D.]) were calculated by linear regression analysis. EC₅₀ and EC₉₀ are drug concentrations at which a 2-fold, or a 10-fold depression of intracellular HBV DNA or HCV RNA (relative to the average levels in untreated cultures), respectively, was observed. CC₅₀ is the drug concentration at which a 2-fold lower level of neutral red dye uptake (relative to the average levels in untreated cultures) was observed.

Table 1: HCV Inhibition by Compounds II-1 and II-2

Compound	CC ₅₀ (μM ± SD)		EC ₅₀ (μM ± SD)		EC ₉₀ (μM ± SD)		SI (CC ₅₀ /EC ₅₀)	
	AVA5	APC103	AVA5	APC103	AVA5	APC103	AVA5	APC103
GH-I-51	26 ± 1.1	27 ± 1.4	2.3 ± 0.3	8.7 ± 0.8	2.7 ± 0.2	9.9 ± 0.5	11	10
GH-I-151	45 ± 1.6	53 ± 1.7	2.0 ± 0.3	6.8 ± 0.4	2.2 ± 0.2	7.4 ± 0.5	>42	>35
2'CmeC	>300	>300	2.0 ± 0.1	5.8 ± 0.4	2.2 ± 0.2	6.4 ± 0.6	>150	>136

Example 2: Anti-HCV Activity of Compound II-2 in Drug Combinations

Compound II-2 was utilized in combination treatments with interferon (with and without RBV), and several representative STAT-C agents including 2'CmeC (nucleoside analogue), HCV-796 (non-nucleoside polymerase inhibitor), and VX-950 (protease inhibitor) (Table 2). For these studies, the compounds were mixed at equipotent (not necessarily equimolar) concentrations based on the monotherapy EC₉₀ values. The mixtures were then serially diluted for dose response analysis keeping the molar ratios constant. Corresponding monotherapies were also included. # Ribavirin (RBV) was held at a constant concentration of 30uM for all serial dilutions of this combination. The overall type of interaction as determined by analysis with CalcuSyn (Biosoft, Inc.; Cambridge, UK) for each combination is indicated next to the corresponding EC₅₀ and EC₉₀ values in Table 2.

Table 2: Effect of Combination Treatments on HCV Replication

Compound/Drug used for Combination	Molar Ratio	Compound II-2(μ M)		Type of Interaction
		EC ₅₀	EC ₉₀	
None (monotherapy)	N/A	2.4 \pm 0.2	9.3 \pm 0.6	N/A
IFN	1:1	0.8 \pm 0.1	2.8 \pm 0.2	S
IFN + 30 μ M RBV [#]	1:1	0.8 \pm 0.1	2.2 \pm 0.2	S
2'CmcC	1:1	0.6 \pm 0.1	3.1 \pm 0.3	A/S
HCV-796	1:100	0.3 \pm 0.03	0.9 \pm 0.1	S
VX-950	1:10	0.1 \pm 0.01	0.3 \pm 0.02	S

S, synergistic; A/S, Additive to Synergistic over the dilution series

Analysis of combination therapies was performed using CalcsynTM software (Biosoft, Inc.; Cambridge, UK). Two types of evaluations were performed (see Figure 2). The top panels of Figure 5 present CI-Fa (Combination Index-Fraction (of virus) affected) plots). For these plots, a combination index [CI] greater than 1.0 indicates antagonism and a CI less than 1.0 indicates synergism. Evaluations of synergy, additivity (summation), or antagonism at different levels of virus inhibition (e.g. 5% (Fa=0.5) to 99% (Fa=0.99)) were performed and are provided by the plotted lines and points. Dotted lines denoting 1.96 standard deviations for significance evaluations can be added but are not included in this example for clarity of presentation. The bottom panels present conservative isobolograms. For these plots, ED₅₀, ED₇₅, and ED₉₀ (50%, 75%, and 90% effective antiviral dose) values for the combination treatments are displayed as single points. Three lines radiating out from the axes denote the expected (e.g., additive) EDC₅₀, EDC₇₅, and EDC₉₀ values for drug combinations as calculated from the monotherapies. ED₅₀, ED₇₅, and ED₉₀ values for the combinations that plot to the left (e.g., less than) of the corresponding lines indicate synergy, and values plotting to the right (e.g., greater than) of the corresponding lines indicate antagonism.

Compound II-2 interacted favorably with interferon, ribavirin, and the STAT-C agents as shown in Table 2 and Figure 2. Various degrees of synergy were observed for the different combinations with the candidate compound (see Figure 2 for an example). The addition of ribavirin (RBV) to the interferon combination did not lessen observed antiviral potencies, indicating that adverse interactions with this nucleoside are unlikely. **Compound II-2** acted equally well with interferon and HCV-796, but more favorably with VX-950.

The compounds and methods of the appended claims are not limited in scope by the specific compounds and methods described herein, which are intended as illustrations of a few aspects of the claims and any compounds and methods that are functionally equivalent are within the scope of this disclosure. Various modifications of the compounds and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Further, while only certain representative compounds, methods, and aspects of these compounds and methods are specifically described, other compounds and methods are intended to fall within the scope of the appended claims. Thus a combination of steps, elements, components, or constituents may be explicitly mentioned herein; however, all other combinations of steps, elements, components, and constituents are included, even though not explicitly stated.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

n is 0 to 5;

R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy, alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl;

R^2 is OR^5 or NR^5R^6 , wherein R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl;

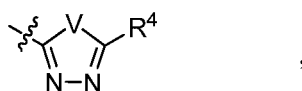
R^3 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl;

X is C=O or SO_2 ;

Y is NR^7 or O, wherein R^7 is hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and

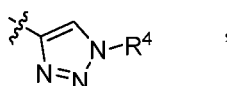
Z is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

2. The compound of claim 1, wherein X is $\text{C}=\text{O}$.
3. The compound of claim 1 or 2, wherein Z is a substituted or unsubstituted triazole.
4. The compound of claim 1 or 2, wherein Z is a substituted or unsubstituted oxadiazole.
5. The compound of claim 1 or 2, wherein Z is



wherein R^4 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and V is O, S, or NH.

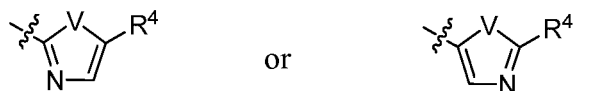
6. The compound of claim 5, wherein V is O.
7. The compound of claim 1 or 2, wherein Z is



wherein R^4 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or

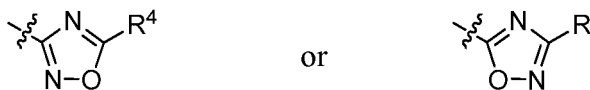
unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

8. The compound of claim 1 or 2, wherein Z is



wherein R^4 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl; and V is O or S.

9. The compound of claim 1 or 2, wherein Z is



wherein R^4 is hydrogen, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocycloalkylalkyl.

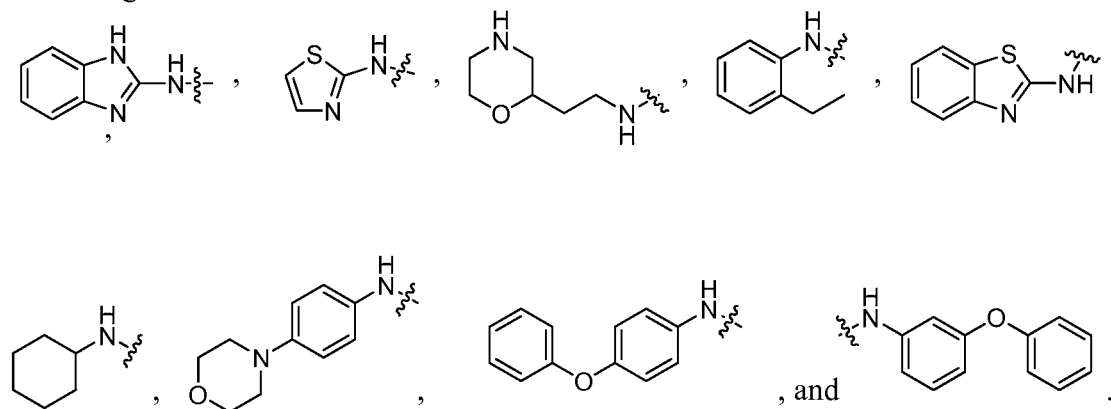
10. The compound of any of claims 5–9, wherein R^4 is a substituted or unsubstituted benzyl.

11. The compound of claim 10, wherein the substituted benzyl is *p*-methoxy benzyl.

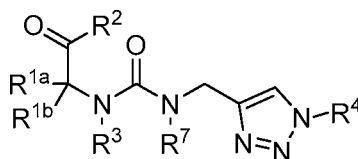
12. The compound of any of claims 1–11, wherein R^{1a} or R^{1b} is selected from the group consisting of hydrogen, propyl, and benzyl.

13. The compound of any of claims 1–12, wherein R^2 is selected from the group consisting of hydroxy, methoxy, and ethoxy.

14. The compound of any of claims 1–12, wherein R^2 is NHR^6 .
15. The compound of claim 14, wherein NHR^6 is selected from the group consisting of:



16. The compound of any of claims 1–15, wherein R^3 is hydrogen.
17. The compound of any of claims 1–16, wherein n is 1.
18. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^{1a} and R^{1b} are each independently selected from hydrogen, hydroxy, alkoxy, substituted or unsubstituted amino, substituted or unsubstituted thio, halogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl;

R^2 is OR^5 or NR^5R^6 , wherein R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl,

substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl; and

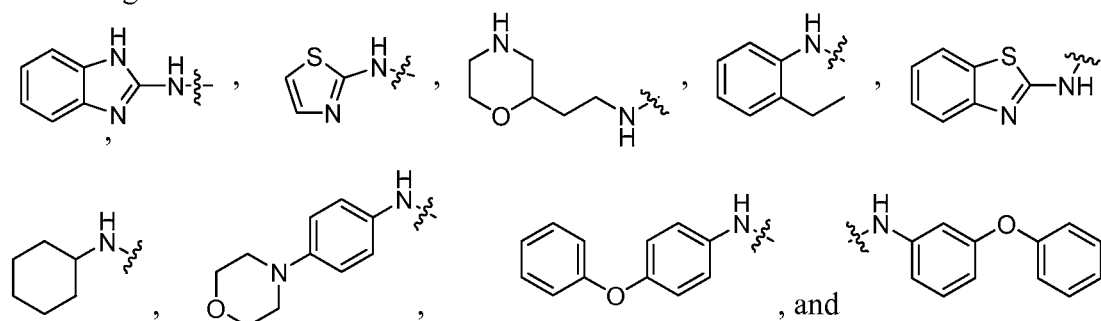
R^3 , R^4 , and R^7 are each independently selected from hydrogen, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{1-12} haloalkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, and substituted or unsubstituted heterocycloalkylalkyl.

19. The compound of claim 18, wherein R^{1a} or R^{1b} is selected from the group consisting of hydrogen, propyl, and benzyl.

20. The compound of claim 18 or 19, wherein R^2 is selected from the group consisting of hydroxy, methoxy, and ethoxy.

21. The compound of claim 18 or 19, wherein R^2 is NHR^6 .

22. The compound of claim 21, wherein NHR^6 is selected from the group consisting of:



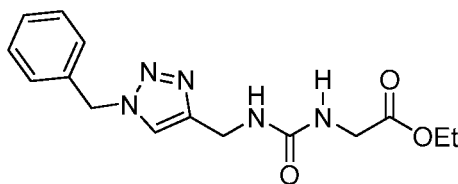
23. The compound of any of claims 18–22, wherein R^3 is hydrogen.

24. The compound of any of claims 18–23, wherein R^4 is a substituted or unsubstituted benzyl.

25. The compound of claim 24, wherein the substituted benzyl is *p*-methoxy benzyl.

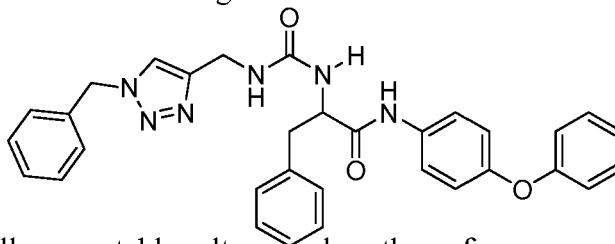
26. The compound of any of claims 18–25, wherein R^7 is hydrogen.

27. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof.

28. A compound of the following formula:



or a pharmaceutically acceptable salt or prodrug thereof.

29. A composition comprising a compound of any one of claims 1–28 and a pharmaceutically acceptable carrier.
30. A method of treating a viral infection in a subject comprising administering to the subject a therapeutically effective amount of the compounds or compositions of claims 1–29.
31. The method of claim 30, wherein the viral infection is Hepatitis C Virus.
32. The method of claim 30 or 31, further comprising administering a second compound or composition, wherein the second compound or composition includes an antiviral compound.
33. The method of claim 32, wherein the second compound or composition is a nucleoside polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a protease inhibitor.
34. The method of claim 32, wherein the second compound or composition includes pegylated interferon- α , ribavirin, or a mixture thereof.
35. A method of preventing a viral infection in a subject comprising administering to the subject a therapeutically effective amount of the compound or compositions of claims 1–29.
36. The method of claim 35, wherein the viral infection is Hepatitis C Virus.

37. The method of claim 35 or 36, further comprising administering a second compound or composition, wherein the second compound or composition includes an antiviral compound.
38. The method of claim 37, wherein the second compound or composition is a nucleoside polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a protease inhibitor.
39. The method of claim 37, wherein the second compound or composition includes pegylated interferon- α , ribavirin, or a mixture thereof.

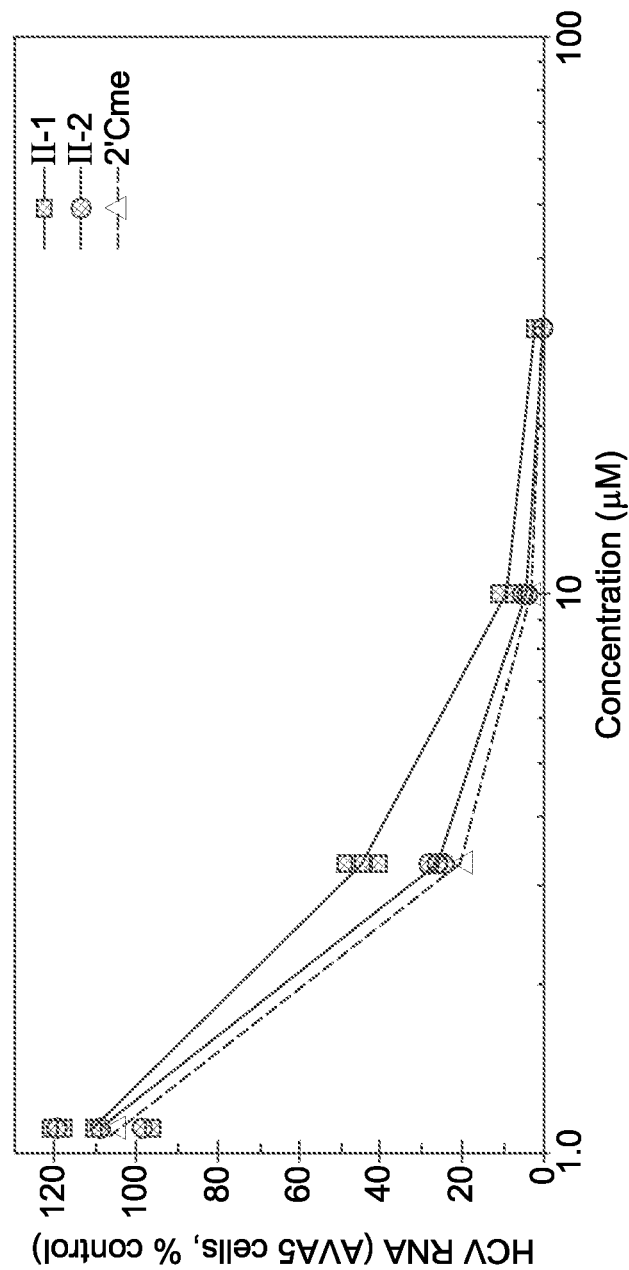


FIG. 1

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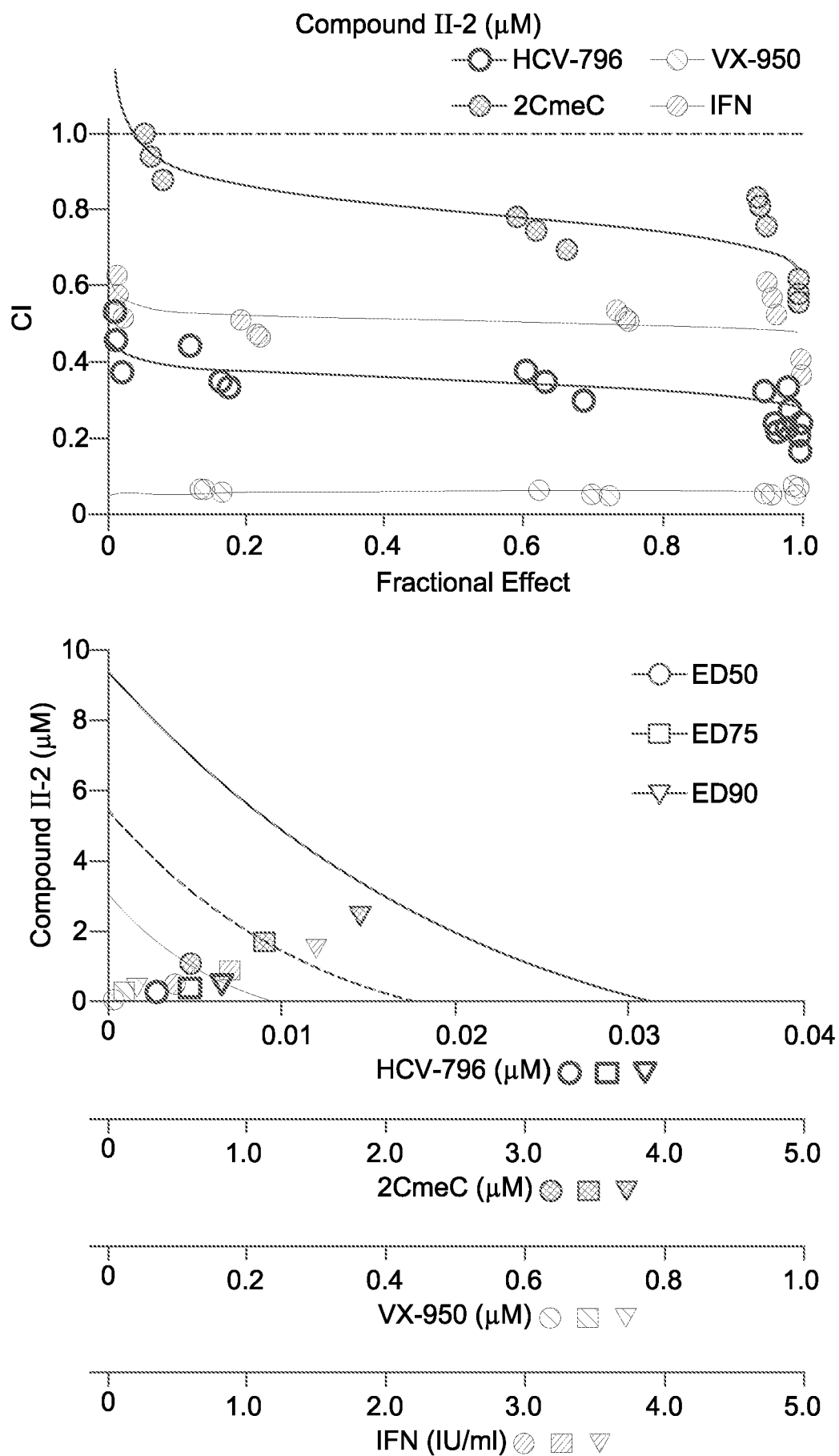


FIG. 2