

achieve substantial viral load reductions (Fraser, IP *et al.*, Abstract #48, HEP DART 2011, Koloa, HI, December 2011.)

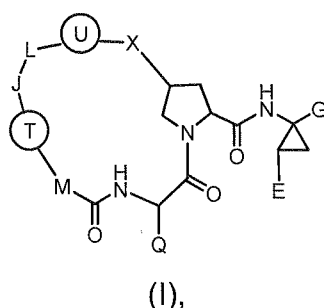
Antiviral agents that are less susceptible to viral resistance are also needed. For example, resistance mutations at positions 155 and 168 in the HCV protease frequently cause a substantial decrease in antiviral efficacy of HCV protease inhibitors (Mani, N. *Ann Forum Collab HIV Res.*, 2012, 14, 1-8; Romano, KP *et al*, *PNAS*, 2010, 107, 20986-20991; Lenz O, *Antimicrobial agents and chemotherapy*, 2010, 54,1878–1887.)

In view of the limitations of current HCV therapy, there is a need to develop more effective anti-HCV therapies. It would also be useful to provide therapies that are effective against multiple HCV genotypes and subtypes.

SUMMARY

Novel compounds that inhibit the hepatitis C virus (HCV) NS3 protease are disclosed. In certain embodiments, the compounds disclosed inhibit multiple genotypes of the hepatitis C virus. These compounds are useful for the treatment of HCV infection and the related symptoms.

In ~~one embodiment~~ an aspect, there is provided a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof. In certain embodiments:

$\textcircled{\text{T}}$ is T^1 , T^2 , T^3 , T^4 , T^5 , or T^6 ;

L is L^1 , L^2 , L^3 , L^4 , L^5 , L^6 , L^7 , L^8 , L^9 , L^{10} , L^{11} or L^{12} ;

X is -O-, -CH₂-, -OC(O)-, -C(O)O-, -C(O)-, -SO₂-, -S(O)-, -N(R¹⁶)-, -S-, =N-

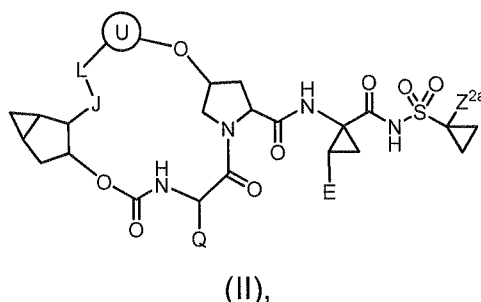
O- or a bond;

M is a bond, C₁-C₆ alkylene, -O-, or -N(R¹⁶)-;

Q is Q¹, Q², Q³, Q⁴, Q⁵, Q⁶ or Q⁷;

E is E¹, E², E³, E⁴, E⁵, or E⁶;

In another embodiment aspect, there is provided a compound of formula (II):



or a pharmaceutically acceptable salt thereof. In certain embodiments, in the compound of formula II:

L is L¹, L², L³, L⁴, L⁵, L⁶, L⁷, L⁸, L⁹, L¹⁰, L¹¹ or L¹²;

Q is Q¹, Q², Q³, Q⁴, Q⁵, Q⁶ or Q⁷;

E is E¹, E², E³, E⁴, E⁵, or E⁶;

J is -CH₂- or -CF₂-;

Ⓢ is U¹, U², U³, U⁴, U⁵, U⁶, U⁷ or U⁸;

L¹ is C₁-C₈ alkylene or C₂-C₈ alkenylene;

L² is C₁-C₈ alkylene or C₂-C₈ alkenylene wherein said C₁-C₈ alkylene or said C₂-C₈ alkenylene is substituted with 1-4 halogen atoms;

L³ is C₁-C₈ alkylene or C₂-C₈ alkenylene wherein said C₁-C₈ alkylene or said C₂-C₈ alkenylene is substituted with 1-4 Z³ groups and wherein said C₁-C₈ alkylene or C₂-C₈ alkenylene is optionally substituted with 1-4 halogen atoms;

L⁴ is C₁-C₈ alkylene or C₂-C₈ alkenylene substituted with two geminal C₁-C₄ alkyl groups that come together to form a spiro C₃-C₈ carbocyclyl group, wherein L⁴ is optionally substituted with 1-4 Z¹ groups;

L⁵ is C₁-C₈ alkylene or C₂-C₈ alkenylene substituted with two geminal Z¹ groups that come together to form a spiro 4-8 membered heterocyclyl group, wherein L⁵ is optionally substituted with 1-4 additional Z¹ groups;

L⁶ is 2-8 membered heteroalkylene or 4-8 membered heteroalkenylene;

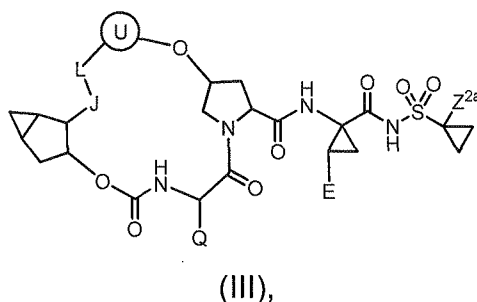
L⁷ is 2-8 membered heteroalkylene or 4-8 membered heteroalkenylene, wherein the carbon atoms of said heteroalkylene or heteroalkenylene is substituted with 1-4 halogen atoms;

bicyclic carbocyclyl, aryl, heteroaryl or heterocyclyl portion of Z^2 is optionally substituted with 1-4 Z^{2a} groups;

each Z^{2a} is independently selected from hydrogen, oxo, halogen, C_1 - C_8 alkyl, C_2 - C_8 alkynyl, C_3 - C_8 carbocyclyl, C_5 - C_{10} bicyclic carbocyclyl, C_1 - C_8 haloalkyl, C_6 - C_{10} aryl, 5-14 membered heteroaryl, 4-10 membered heterocyclyl, $-(C_2-C_8 \text{ alkynyl})\text{aryl}$, $-(C_2-C_8 \text{ alkynyl})\text{heteroaryl}$, $-\text{CN}$, $-\text{C}(\text{O})(C_1-C_6 \text{ alkyl})$, $-\text{C}(\text{O})\text{O}(C_1-C_6 \text{ alkyl})$, $-\text{C}(\text{O})\text{N}(C_1-C_6 \text{ alkyl})_2$, $-\text{NH}_2$, $-\text{NH}(C_1-C_6 \text{ alkyl})$, $-\text{N}(C_1-C_6 \text{ alkyl})_2$, $-\text{NHC}(\text{O})\text{O}(C_1-C_6 \text{ alkyl})$, $-\text{NHC}(\text{O})(C_1-C_6 \text{ alkyl})$, $-\text{NHC}(\text{O})\text{NH}(C_1-C_6 \text{ alkyl})$, $-\text{OH}$, $-\text{O}(C_1-C_6 \text{ alkyl})$, halo(C_1 - C_6 alkoxy), C_3 - C_8 cycloalkoxy, $-\text{S}(C_1-C_6 \text{ alkyl})$, or $-\text{SO}_2\text{N}(C_1-C_6 \text{ alkyl})_2$; wherein any alkyl, alkynyl, carbocyclyl, cycloalkoxy, bicyclic carbocyclyl, aryl, heteroaryl or heterocyclyl portions of Z^{2a} is optionally substituted with 1-4 halogen or C_1 - C_6 alkoxy groups;

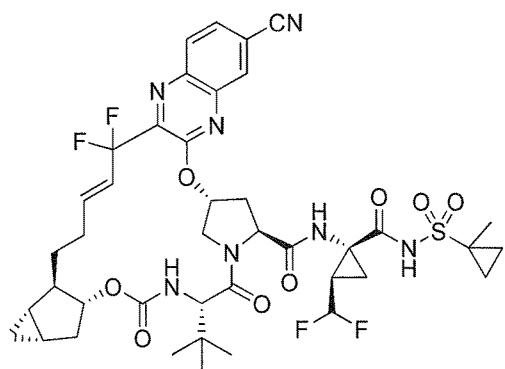
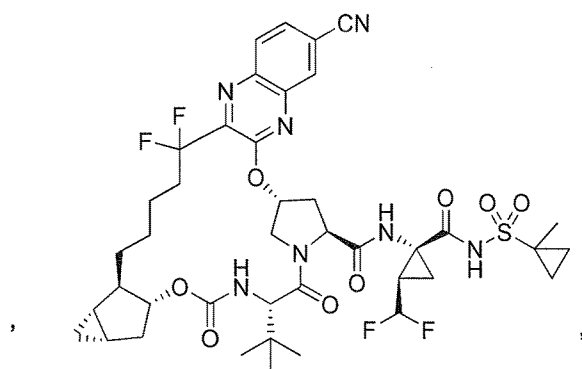
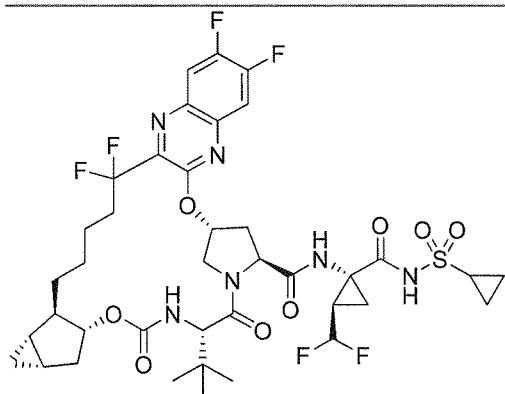
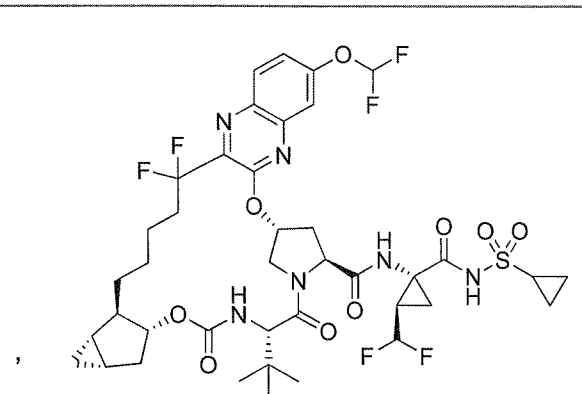
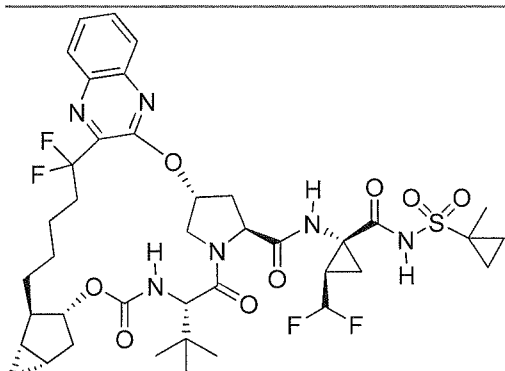
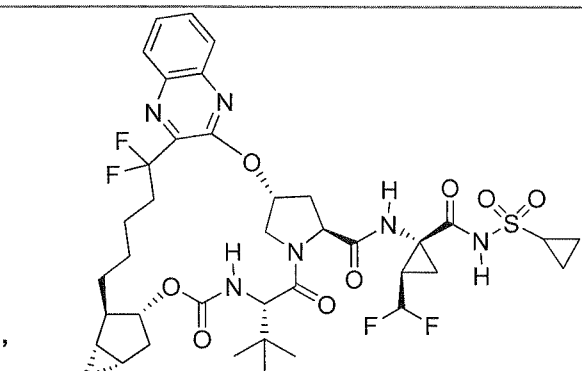
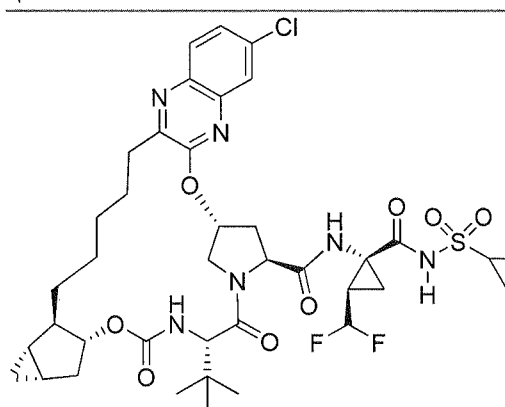
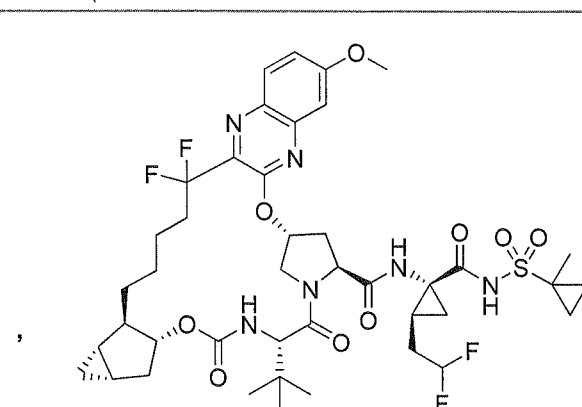
each Z^3 is independently selected from oxo, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 carbocyclyl, C_5 - C_{10} bicyclic carbocyclyl, C_1 - C_8 haloalkyl, C_6 - C_{10} aryl, 5-14 membered heteroaryl, 4-10 membered heterocyclyl, $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^{16}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{NR}^{17}\text{R}^{18}$, $-\text{NR}^{16}\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{OR}^{16}$, $-\text{SR}^{16}$ or $-\text{SO}_2\text{R}^{16}$, wherein any alkenyl, alkynyl, carbocyclyl, aryl, heteroaryl or heterocyclyl portion of Z^3 is optionally substituted with 1-4 halogen.

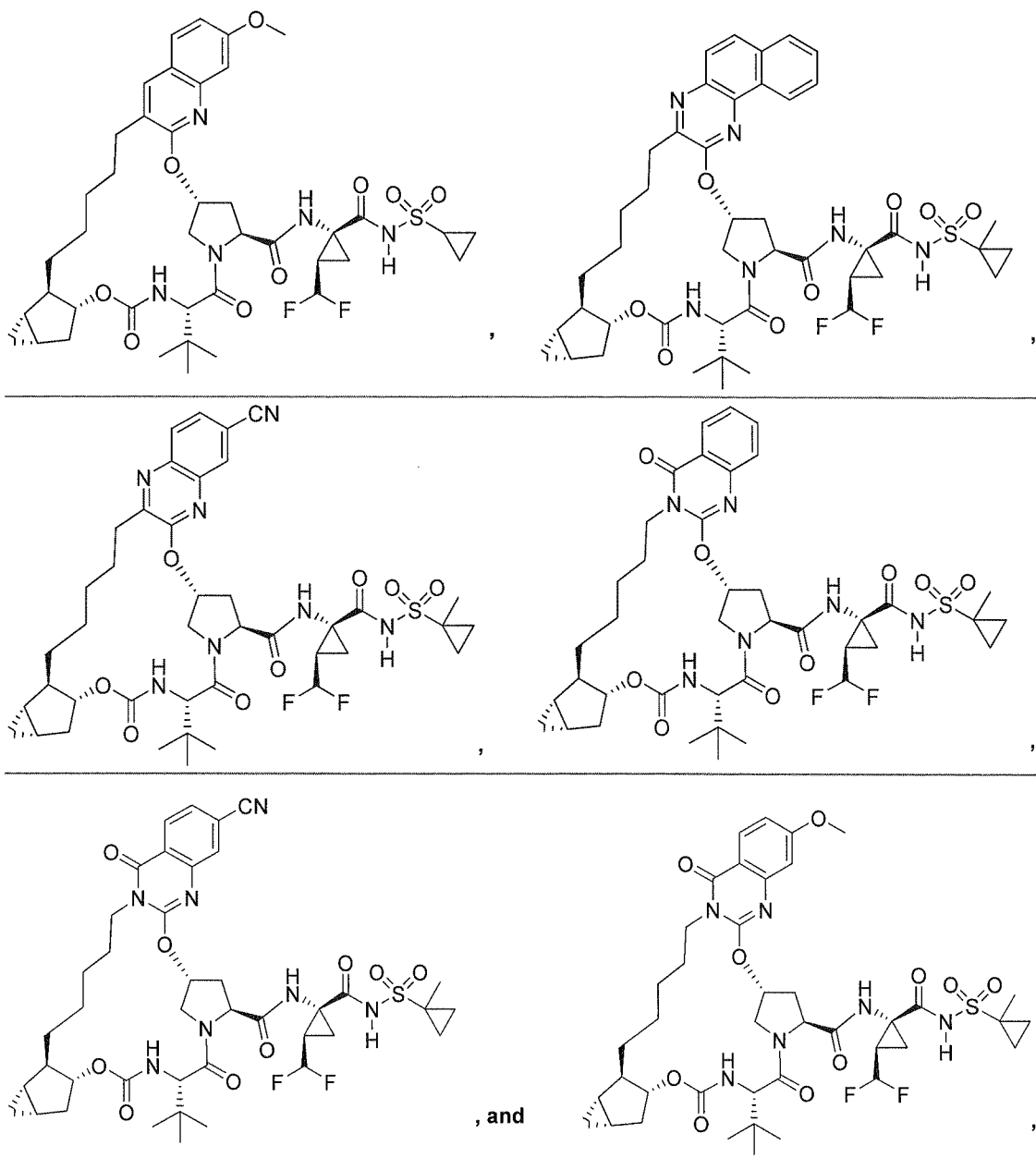
In another embodiment aspect, there is provided a compound of formula (III):



or a pharmaceutically acceptable salt thereof. In certain embodiments:

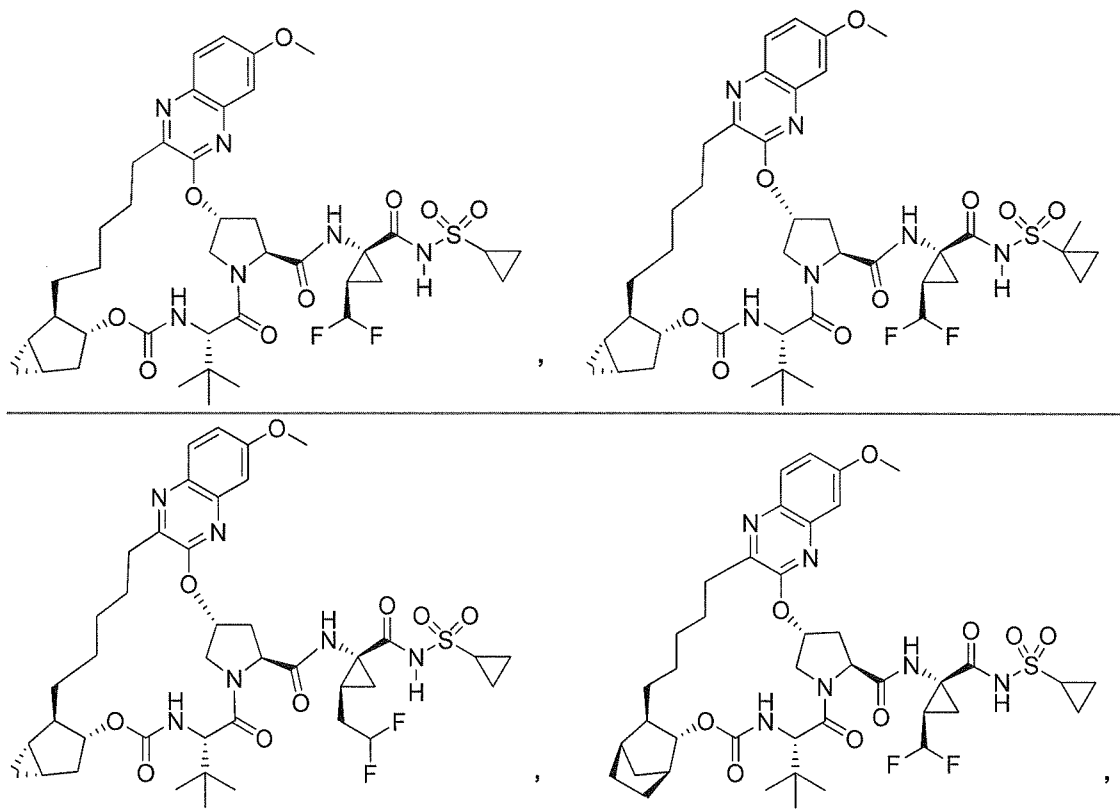
L is C_1 - C_8 alkylene or C_2 - C_8 alkenylene wherein said C_1 - C_8 alkylene or said C_2 - C_8 alkenylene is optionally substituted with one or more R^{25} , wherein each R^{25} is independently selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_6 carbocyclyl, 3 to 6 membered heteroalkyl, $-\text{OH}$, or $-\text{O}(C_1-C_4 \text{ alkyl})$, or oxo;

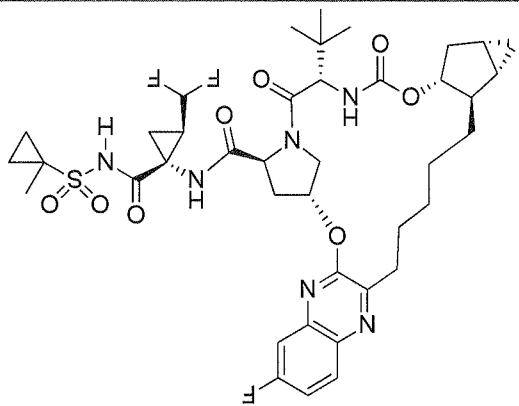
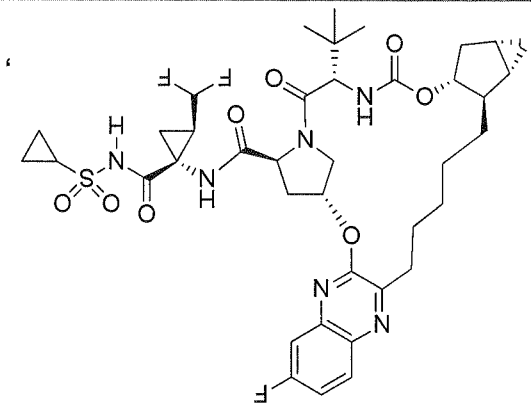
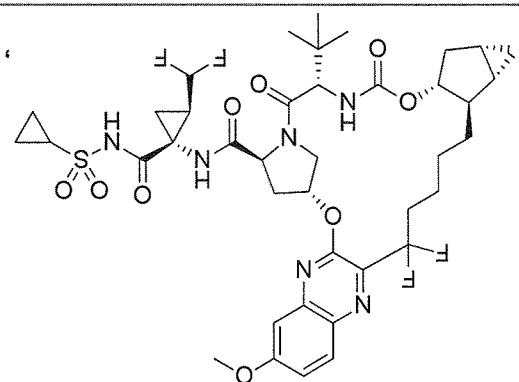
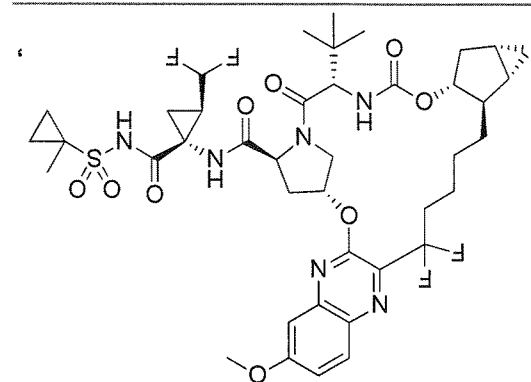
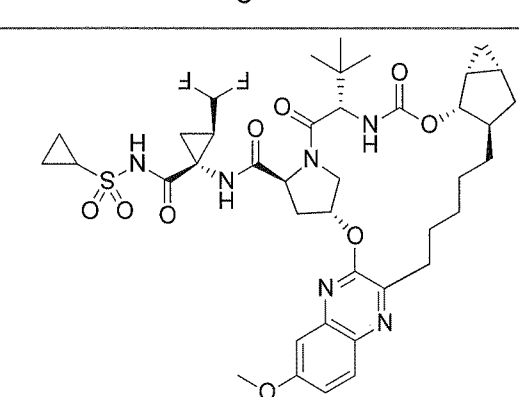
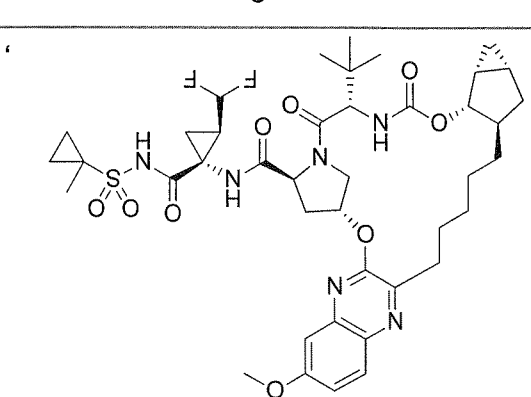
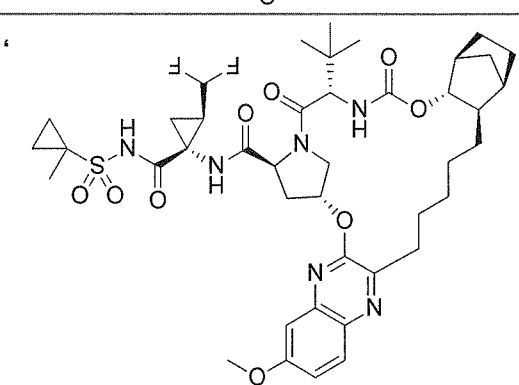
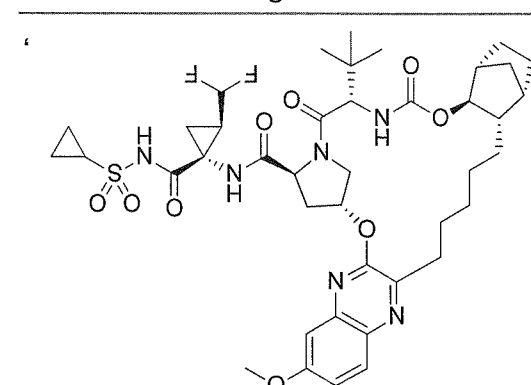


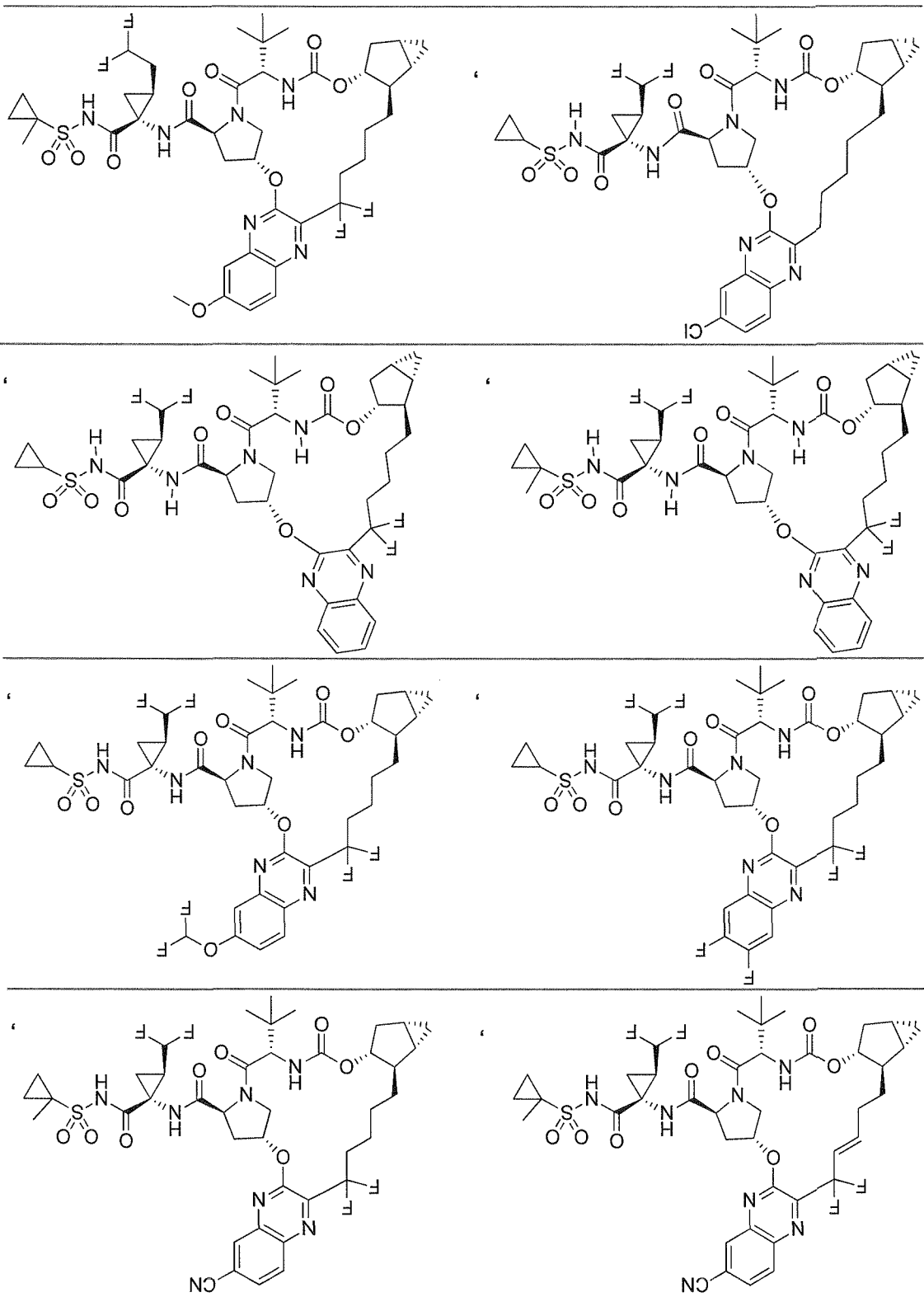


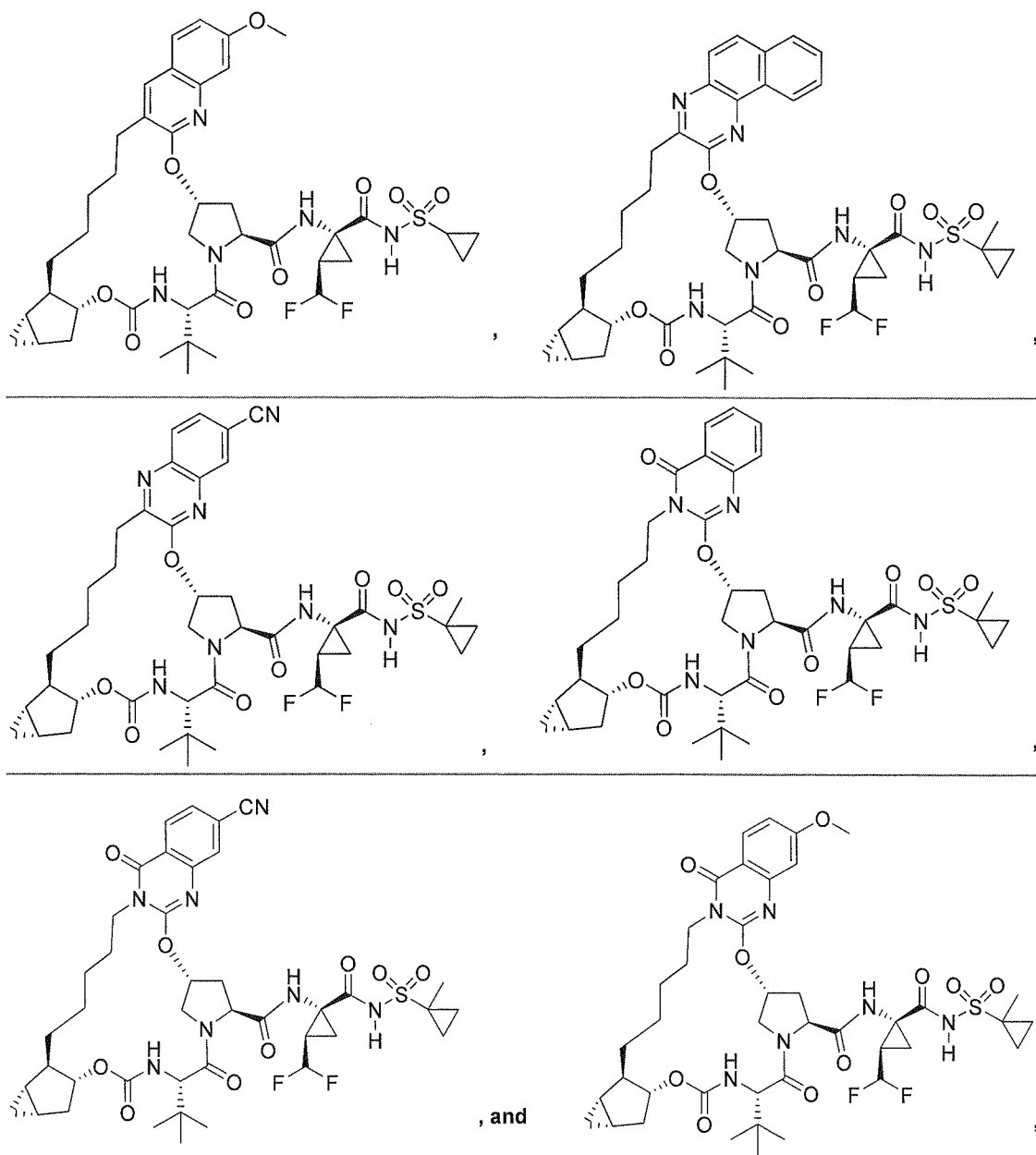
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound selected from the group consisting of:



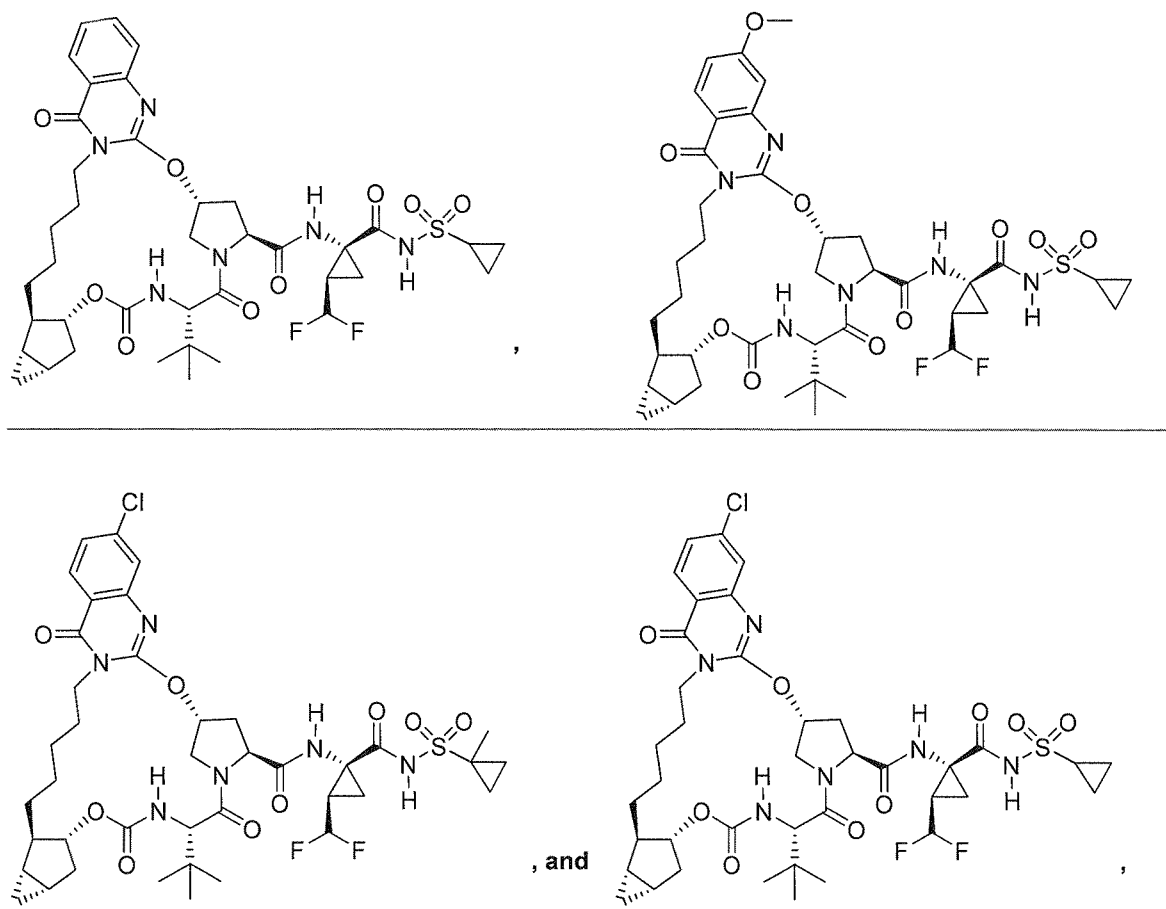






or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, and a pharmaceutically acceptable excipient.

One embodiment provides a pharmaceutical composition comprising a compound of Formula I, II, or III, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

One embodiment provides a method for treating a *Flaviviridae* viral infection (e.g., an HCV viral infection) in a patient in need thereof (e.g., mammal such as a human). The method includes administering a compound of Formula I, II or III, or a pharmaceutically acceptable salt thereof, to the patient.

In another aspect, there is provided the use of a compound as defined above or pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of hepatitis C virus (HCV).

One embodiment provides a method for inhibiting the proliferation of the HCV virus, treating HCV or delaying the onset of HCV symptoms in a patient in need thereof (e.g., mammal such as a human). The method includes administering a compound of Formula I, II, or III or a pharmaceutically acceptable salt thereof, to the patient.

One embodiment provides a compound of Formula I, II, or III or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating a *Flaviviridae* viral infection such as an HCV viral infection or in treating the proliferation of the HCV virus or delaying the onset of HCV symptoms in a patient in need thereof (e.g., mammal such as a human)).

One embodiment provides a compound of Formula I, II, or III or a pharmaceutically acceptable salt thereof for use in the manufacture of a

60. A pharmaceutical composition comprising a compound of any of claims 1-59, and a pharmaceutically acceptable excipient.

61. Use of A method of treating HCV in a patient in need thereof, comprising administering to said patient a compound of any of claims 1-59 or pharmaceutical composition of claim 60 in the manufacture of a medicament for the treatment of hepatitis C virus (HCV).