HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 61/909,414, filed November 27, 2013, which is incorporated by reference.

BACKGROUND OF THE INVENTION

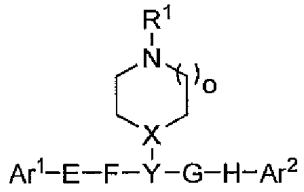
[0002] Hepatitis C virus (HCV) infects about 200 million people in the world. Many infected people progress to chronic liver disease including cirrhosis with a risk of developing liver cancer. To date, there is no effective vaccine for hepatitis C.

[0003] Current standard treatment of chronic hepatitis C, based on combination of peginterferon-α and ribavirin, is only effective in about half of the patients, with significant adverse effects. The fraction of people with HCV who can complete a successful treatment is estimated to be no more than 10 percent. Recent development of direct-acting antivirals against HCV, such as protease and polymerase inhibitors, is promising but still requires combination with peginterferon and ribavirin for maximal efficacy. In addition, these agents are associated with high rate of resistance and many have significant side effects.

[0004] In view of the foregoing, an unmet need exists for novel agents for treating or preventing viral infection.

BRIEF SUMMARY OF THE INVENTION

[0005] The invention provides a compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups, are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$ or $-SO_2-$,

G is absent or is $(CH_2)_r$,

H is absent or is $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

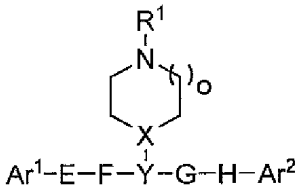
o is 0, 1, or 2,

X is CH,

Y is N

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof.

[0006] The disclosure also provides a method of treating or preventing hepatitis C comprising administering to a mammal in need thereof an effective amount of a compound of formula (I):



(I)

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl C_1-C_{10} alkyl, C_6-C_{10} aryl, C_6-C_{10} aryl C_1-C_{10} alkyl, C_6-C_{10} aryl C_3-C_{10} cycloalkyl, heteroaryl, heterocyclyl, $C_{6\text{-}10}$ arylsulfonyl, $C_{6\text{-}10}$ arylcarbonyl, C_1-C_{10} alkylcarbonyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl, aryl, or heteroaryl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 and Ar^2 are the same or different and are independently selected from C_6-C_{10} aryl, heteroaryl, and heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CR^{13}R^{14})_m$, NH, or S,

F is absent or is $(CR^{15}R^{16})_n$, C=O, or $-SO_2-$,

G is absent or is $(CR_{17}CR_{18})_r$,

H is absent or is C=O, or $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

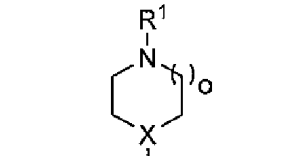
o is 0, 1, or 2,

X and Y are independently CH or N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof.

[0006]a The invention also provides pharmaceutical composition comprising a compound, salt, stereoisomers, and mixtures comprising stereoisomers as used herein and a pharmaceutically acceptable carrier.

[0006]b The invention also provides the use of a compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$ or $-SO_2-$,

G is absent or is $(CH_2)_r$,

H is absent or is $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

X is CH,

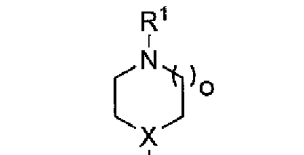
Y is N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

in the manufacture of a medicament for treating or preventing a viral infection in a mammal in need thereof or for use in synergistically enhancing the antiviral effect of an anti-hepatitis C compound in a mammal undergoing treatment with the anti-hepatitis C compound, wherein the medicament is to be administered to the mammal in combination with the anti-hepatitis C compound,

wherein the anti-hepatitis C compound is selected from include ribavirin, interferon-α, telaprevir, cyclosporin A, Asunaprevir (BMS-650032), Boceprevir, GS-9451, GS-9256, ABT-450, Danoprevir (RG7227), Faldaprevir (BI 201335), IDX320, MK-5172, Simeprevir (TMC435), Sovaprevir (ACH-1625), ABT-267, ACH-3102, BMS-791325, Daclatasvir (BMS-790052), GSK2336805, IDX719, JNJ-47910382, Ledipasvir (GS-5885), MK-8742, PPI-461, PPI-668, ABT-333, ALS-002200, BI 207127, IDX184, INX-08189, Mericitabine (RO5024048), PPI-383, PSI-352938, Setrobuvir (ANA-598), Sofosbuvir (PSI-7977 or GS-7977), Tegobuvir (GS-9190), TMC647055, Filibuvir (PF-00868554), GS-9669, GSK2878175, VX-135, VX-222, Algeron (Cepeginterferon Alfa-2b), BIP 48 (Peginterferon alfa 2b 48kDA), Pegylated interferon alfa 2b, Pegylated interferon lambda (BMS-914143), Pegylated-P-Interferon-alpha-2b (P1101), and Alisporivir (DEB025).

[0007] The disclosure further provides a method for synergistically enhancing the antiviral effect of an anti-hepatitis C compound in a mammal undergoing treatment with the anti-hepatitis C compound, comprising administering to the mammal a compound of the formula (I):



(I)

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl C_1-C_{10} alkyl, C_6-C_{10} aryl, C_6-C_{10} aryl C_1-C_{10} alkyl, C_6-C_{10} aryl C_3-C_{10} cycloalkyl, heteroaryl, heterocyclyl, C_{6-10} arylsulfonyl, C_{6-10} arylcarbonyl, C_1-C_{10} alkylcarbonyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl, aryl, or heteroaryl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 and Ar^2 are the same or different and are independently selected from C_6-C_{10} aryl, heteroaryl, and heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CR^{13}R^{14})_m$, NH, or S,

F is absent or is $(CR^{15}R^{16})_n$, C=O, or –SO2-,

G is absent or is $(CR^{17}CR^{18})_r$,

H is absent or is C=O, or –SO2-,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

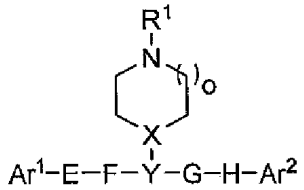
X and Y are independently CH or N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

in combination with the anti-hepatitis C compound.

[0008] The invention additionally provides a kit comprising:

(a) a compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl, aryl, or heteroaryl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$, C=O, or –SO2-,

G is absent or is $(CH_2)_r$,

H is absent or is –SO2-,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

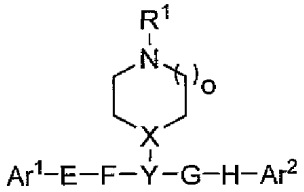
X is CH,

Y is N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, and

(b) an anti-hepatitis C compound other than a compound of formula (II).

[0008]a The invention additionally provides a compound of formula (I):



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

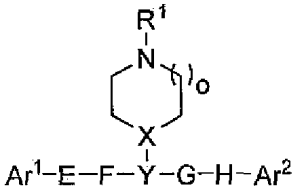
Ar^2 is phenyl or 4-chlorophenyl, and

o is 0 or 1,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

with the proviso that (i) when o is 1 and R^1 is hydrogen, ethyl, or isopropyl, the compound is a single enantiomer at the carbon bearing Ar^1 and Ar^2.

[0008b] The invention additionally provides a compound of formula (I):



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

Ar^2 is phenyl or 4-chlorophenyl,

D is NR^8R^9,

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive, and

o is 0 or 1,

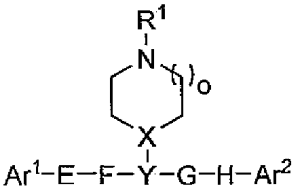
or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

for use in treating or preventing a viral infection in a mammal in need thereof or for use in synergistically enhancing the antiviral effect of an anti-hepatitis C compound, wherein the medicament is to be administered to the mammal in combination with the anti-hepstitis C compound,

wherein the anti-hepatitis C compound is selected from include ribavirin, interferon-α, telaprevir, cyclosporin A, Asunaprevir (BMS-650032), Boceprevir, GS-9451, GS-9256, ABT-450, Danoprevir (RG7227), Faldaprevir (BI 201335), IDX320, MK-5172, Simeprevir (TMC435), Sovaprevir (ACH-1625), ABT-267, ACH-3102, BMS-791325, Daclatasvir (BMS-790052), GSK2336805, IDX719, JNJ-47910382, Ledipasvir (GS-5885), MK-8742, PPI-461, PPI-668, ABT-333, ALS-002200, BI 207127, IDX184, INX-08189, Mericitabine (RO5024048), PPI-383, PSI-352938, Setrobuvir (ANA-598), Sofosbuvir (PSI-7977 or GS-7977), Tegobuvir (GS-9190), TMC647055, Filibuvir (PF-00868554), GS-9669,

GSK2878175, VX-135, VX-222, Algeron (Cepeginterferon Alfa-2b), BIP 48 (Peginterferon alfa 2b 48kDA), Pegylated interferon alfa 2b, Pegylated interferon lambda (BMS-914143), Pegylated-P-Interferon-alpha-2b (P1101), and Alisporivir (DEB025).

[0008c] The invention additionally provides a kit comprising:



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, and C_3-C_{10} cycloalkyl, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

Ar^2 is phenyl or 4-chlorophenyl, and

o is 0 or 1,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

with the proviso that (i) when o is 1 and R^1 is hydrogen, methyl, ethyl, or isopropyl, the compound is a single enantiomer at the carbon bearing Ar^1 and Ar^2,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, and

(b) an anti-hepatitis C compound other than a compound of formula (I).

[0009] In accordance with an example, extracellular and intracellular viral RNA levels were reduced with the treatment of compounds of the invention.

[0010] In accordance with an example, inhibition of viral entry is not the mechanism of anti-HCV action of compounds of the invention.

[0011] In accordance with an example, compounds of the invention exhibit synergistic antiviral effect of chlorcyclizine ("CCZ") with current anti-HCV drugs, either approved or under clinical trial.

[0012] In accordance with an example, compounds of the invention exhibit a lack of long-term in vitro cytotoxicity of chlorcyclizine hydrochloride.

[0013] In accordance with an example, compounds of formula (I), for example, NCGC00345021, target the late stage of the HCV life cycle.

[0014] In accordance with an example, inhibition of Dengue virus infection is produced by a compound of formula (I).

[0015] In accordance with an example, inhibition of HCV genotype 1b and 2a infections *in vivo* is produced by a compound of formula (I) without clear evidence of drug resistance.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

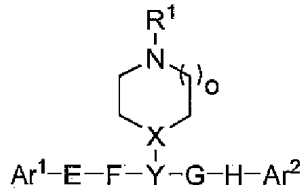
[0016] Figures 1A and 1B illustrate the reduction of extracellular and intracellular viral RNA levels, respectively, upon treatment with DMSO (vehicle), racemic chlorcyclizine hydrochloride ("CCZ"), (R)-CCZ, and (S)-CCZ. Cyclosporin A is included as a comparison. A = DMSO; B = racemic CCZ; C = (R)-CCZ; D = (S)-CCZ; E = Cyclosporin A.

[0017] Figure 2A illustrates luciferase activity of Huh 7.5.1 cells that were inoculated with the infectious HCVsc virus together with DMSO (vehicle), racemic CCZ, (R)-CCZ, and (S)-CCZ, and Cyclosporin A. A = DMSO; B = racemic CCZ; C = (R)-CCZ; D = (S)-CCZ; E = Cyclosporin A.

[0018] Figure 2B illustrates luciferase activity of HCV replicon GT 1b and 2a cells and transient replicon GT 1a cells that were treated with DMSO (vehicle), racemic CCZ,

[0100] CLAIM(S):

1. A compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$ or $-SO_2-$,

G is absent or is $(CH_2)_r$,

H is absent or is $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

X is CH,

Y is N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof.

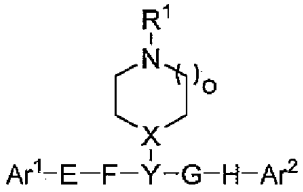
2. The compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 1, wherein E is $(CH_2)_m$, F is absent, m is 2, G is $(CH_2)_r$, H is absent, and r is 1.

3. The compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 1, wherein Ar^1 and Ar^2 are both phenyl.

4. The compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 1 or 2, wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 2-phenylethyl, 4-methoxycarbonylbenzyl, and (benzo-1,4-dioxane-6-yl)methyl.

5. A pharmaceutical composition comprising a compound, salt, stereoisomers, and mixtures comprising stereoisomers of any one of claims 1-14 and a pharmaceutically acceptable carrier.

6. Use of a compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups are optionally substituted with one or more substituents selected from halo,

C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$, or $-SO_2-$,

G is absent or is $(CH_2)_r$,

H is absent or is $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

X is CH,

Y is N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

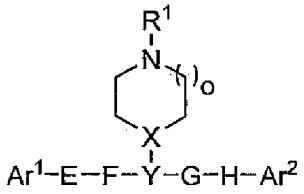
in the manufacture of a medicament for treating or preventing a viral infection in a mammal in need thereof or for use in synergistically enhancing the antiviral effect of an anti-hepatitis C compound in a mammal undergoing treatment with the anti-hepatitis C compound, wherein the medicament is to be administered to the mammal in combination with the anti-hepatitis C compound,

wherein the anti-hepatitis C compound is selected from include ribavirin, interferon-α, telaprevir, cyclosporin A, Asunaprevir (BMS-650032), Boceprevir, GS-9451, GS-9256, ABT-450, Danoprevir (RG7227), Faldaprevir (BI 201335), IDX320, MK-5172, Simeprevir (TMC435), Sovaprevir (ACH-1625), ABT-267, ACH-3102, BMS-791325, Daclatasvir (BMS-790052), GSK2336805, IDX719, JNJ-47910382, Ledipasvir (GS-5885), MK-8742, PPI-461, PPI-668, ABT-333, ALS-002200, BI 207127, IDX184, INX-08189, Mericitabine (RO5024048), PPI-383, PSI-352938,

Setrobuvir (ANA-598), Sofosbuvir (PSI-7977 or GS-7977), Tegobuvir (GS-9190), TMC647055, Filibuvir (PF-00868554), GS-9669, GSK2878175, VX-135, VX-222, Algeron (Cepeginterferon Alfa-2b), BIP 48 (Peginterferon alfa 2b 48kDA), Pegylated interferon alfa 2b, Pegylated interferon lambda (BMS-914143), Pegylated-P-Interferon-alpha-2b (P1101), and Alisporivir (DEB025).

7. A kit comprising:

(a) a compound of formula (I):



(I)

wherein R^1 is selected from sec-butyl, isopropyl, n-butyl, trideuteromethyl, 2,2,2-trideuteroethyl, 2,2,2-trifluoroethyl, benzyl, 4-methylbenzyl, 4-chlorobenzyl, 4-trifluorobenzyl, phenyl, 4-phenylbenzyl, 4-iodobenzyl, 3-methoxybenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-methoxycarbonylbenzyl, (benzo-1,4-dioxane-6-yl)methyl, $-(CH_2)_xA(CH_2)_yB$, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl, aryl, or heteroaryl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 and Ar^2 are the same or different and are independently C_6-C_{10} aryl, wherein the aryl groups are optionally substituted with one or more substituents selected from halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

A is O, S, or N,

x and y are independently 1-4, inclusive,

B is selected from OR^4, $COOR^5$, and $CONR^6R^7$,

wherein R^4, R^5, R^6, and R^7 are independently selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and C_6-C_{10} aryl,

D is NR^8R^9, OH, or OR^{12},

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive,

E is absent or is $(CH_2)_m$, NH, or S,

F is absent or is $(CH_2)_n$ or $-SO_2-$,

G is absent or is $(CH_2)_r$,

H is absent or is $-SO_2-$,

m, n, and r are independently 0, 1, 2, 3, or 4,

o is 0, 1, or 2,

X is CH,

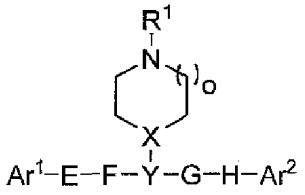
Y is N,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, and

(b) an anti-hepatitis C compound other than a compound of formula (I).

8. Use of a compound of claim1 or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, in the manufacture of a medicament for treating or preventing cancer in a mammal in need thereof.

9. A compound of formula (I):



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

Ar^2 is phenyl or 4-chlorophenyl, and

o is 0 or 1,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

with the proviso that (i) when o is 1 and R^1 is hydrogen, ethyl, or isopropyl, the compound is a single enantiomer at the carbon bearing Ar^1 and Ar^2.

10. A compound of claim 8 wherein:

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is hydrogen, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is ethyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is n-propyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is isopropyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is 2-methyl-2-propyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is cyclopentyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is cyclohexyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is acetyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is 2,4-dimethoxybenzyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is CD_3, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is CD_3CD_2, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is CF_3CH_2, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $CH_2CH_2OCH_2CH_2NH_2$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $(CH_2CH_2O)_4CH_2CH_2NH_2$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $(CH_2CH_2O)_4CH_2CH_2NHC(=O)Me$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $(CH_2CH_2O)_4CH_2CH_2NHC(=O)t\text{-}Bu$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is 4-chlorophenyl, R^1 is hydrogen, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is 4-chlorophenyl, R^1 is ethyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is 4-bromophenyl, R^1 is ethyl, and o is 1, and

Ar^1 is 4-chlorophenyl, Ar^2 is 4-chlorophenyl, R^1 is $(CH_2CH_2O)_4CH_2CH_2NH_2$, and o is 1,

or a pharmaceutically acceptable salt, stereoisomer, and mixture thereof.

11. The compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 8, wherein:

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is methyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is hydrogen, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is ethyl, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $CH_2CH_2OCH_2CH_2NH_2$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is phenyl, R^1 is $(CH_2CH_2O)_4CH_2CH_2NH_2$, and o is 1,

Ar^1 is 4-chlorophenyl, Ar^2 is 4-chlorophenyl, R^1 is methyl, and o is 1,

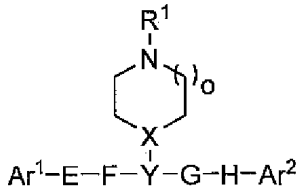
Ar^1 is 4-chlorophenyl, Ar^2 is 4-chlorophenyl, R^1 is hydrogen, and o is 1, and

Ar^1 is 4-bromophenyl, Ar^2 is phenyl, R^1 is ethyl, and o is 1.

12. The compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 8, wherein the compound is a single enantiomer at the carbon bearing Ar^1 and Ar^2.

13. A pharmaceutical composition comprising a compound, salt, stereoisomers, and mixtures comprising stereoisomers of claim 8 and a pharmaceutically acceptable carrier.

14. A compound of formula (I):



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, and $-(CH_2CH_2O)_p(CH_2CH_2)_qD$, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

Ar^2 is phenyl or 4-chlorophenyl,

D is NR^8R^9,

R^8 and R^9 are independently selected from hydrogen, COR^{10}, and $COOR^{11}$,

R^{10} and R^{11} are hydrogen or C_1-C_{10} alkyl,

p and q are independently 1-4, inclusive, and

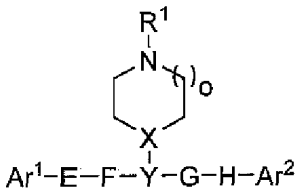
o is 0 or 1,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

for use in treating or preventing a viral infection in a mammal in need thereof or for use in synergistically enhancing the antiviral effect of an anti-hepatitis C compound, wherein the medicament is to be administered to the mammal in combination with the anti-hepstitis C compound,

wherein the anti-hepatitis C compound is selected from include ribavirin, interferon-α, telaprevir, cyclosporin A, Asunaprevir (BMS-650032), Boceprevir, GS-9451, GS-9256, ABT-450, Danoprevir (RG7227), Faldaprevir (BI 201335), IDX320, MK-5172, Simeprevir (TMC435), Sovaprevir (ACH-1625), ABT-267, ACH-3102, BMS-791325, Daclatasvir (BMS-790052), GSK2336805, IDX719, JNJ-47910382, Ledipasvir (GS-5885), MK-8742, PPI-461, PPI-668, ABT-333, ALS-002200, BI 207127, IDX184, INX-08189, Mericitabine (RO5024048), PPI-383, PSI-352938, Setrobuvir (ANA-598), Sofosbuvir (PSI-7977 or GS-7977), Tegobuvir (GS-9190), TMC647055, Filibuvir (PF-00868554), GS-9669, GSK2878175, VX-135, VX-222, Algeron (Cepeginterferon Alfa-2b), BIP 48 (Peginterferon alfa 2b 48kDA), Pegylated interferon alfa 2b, Pegylated interferon lambda (BMS-914143), Pegylated-P-Interferon-alpha-2b (P1101), and Alisporivir (DEB025).

15. A kit comprising:



(I)

wherein E, F, G, and H are all absent,

X is N,

Y is CH,

wherein R^1 is selected from hydrogen, C_1-C_{10} alkyl, and C_3-C_{10} cycloalkyl, wherein the alkyl part of R^1 is optionally substituted with one or more substituents selected from deuterium, halo, C_1-C_{10} alkyl, C_6-C_{10} aryl, trifluoromethyl, C_1-C_{10} alkoxy, cyano, alkylenedioxy, C_1-C_{10} alkylcarbonyl, and C_1-C_{10} alkoxycarbonyl,

Ar^1 is 4-chlorophenyl,

Ar^2 is phenyl or 4-chlorophenyl, and

o is 0 or 1,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof,

with the proviso that (i) when o is 1 and R^1 is hydrogen, methyl, ethyl, or isopropyl, the compound is a single enantiomer at the carbon bearing Ar^1 and Ar^2,

or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, and

(b) an anti-hepatitis C compound other than a compound of formula (I).

16. Use of a compound of claim 9 or pharmaceutically acceptable salts, stereoisomers, and mixtures comprising stereoisomers thereof, in the manufacture of a medicament for treating or preventing cancer in a mammal in need thereof.