(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 964 630 B9

(12) CORRECTED EUROPEAN PATENT SPECIFICATION

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Claims EN 1

(48) Corrigendum issued on:
09.08.2017 Bulletin 2017/32

(45) Date of publication and mention
of the grant of the patent:
10.05.2017 Bulletin 2017/19

(21) Application number: **14713667.5**

(22) Date of filing: **05.03.2014**

(51) Int Cl.:
C07D 401/14 $^{(2006.01)}$
C07D 413/14 $^{(2006.01)}$
C07D 401/12 $^{(2006.01)}$
C07D 417/14 $^{(2006.01)}$
A61K 31/506 $^{(2006.01)}$
A61P 31/12 $^{(2006.01)}$
A61K 45/06 $^{(2006.01)}$
A61K 31/5377 $^{(2006.01)}$

(86) International application number:
PCT/US2014/020661

(87) International publication number:
WO 2014/138199 (12.09.2014 Gazette 2014/37)

(54) PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

PYRIMIDIN- VERBINDUNGEN ZUR BEHANDLUNG VON HEPATITIS C

COMPOSÉS DE PYRIMIDINE POUR LE TRAITEMENT DE L'HÉPATITE C

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **07.03.2013 US 201361773980 P**

(43) Date of publication of application:
13.01.2016 Bulletin 2016/02

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(56) References cited:
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Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

[0001] The disclosure generally relates to the novel compounds of formula I including pharmaceutically acceptable salts, which have activity against hepatitis C virus (HCV) and are useful in treating those infected with HCV. The disclosure also relates to compositions and methods of using these compounds.

[0002] Hepatitis C virus (HCV) chronically infects an estimated 170 million people worldwide, with 3 to 4 million infected individuals in the United States alone (Boyer, N. and Marcellin, P. J. Hepatology. 2000, 32:98-112; Alter, M. J., et al. Engl. J. Med. 1999, 341:556-562). Prior to the mid 1990s, transfusion with infected blood products was the main route of HCV transmission. Following the introduction of blood screening methods, transmission via injection drug use became the primary risk factor. Chronic infection often leads to the development of severe liver complications, including fibrosis, cirrhosis, and hepatocellular carcinoma. HCV infection is also the leading cause of orthotopic liver transplantation in the United States. The degree to which disease progression is related to viral and cellular factors is not completely understood.

[0003] Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence of the HCV genome (Simmonds, P. J. Gen. Virology. 2004, 85:3173-3188). Based on this sequence diversity, six major genotypes and multiple associated subtypes have been described. The genotypes of HCV differ in their worldwide distribution, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

[0004] Medical treatment for HCV is limited by the lack of a vaccine or approved therapies that specifically target the virus. Currently, patients undergo treatment with a combination of parenterally administered pegylated alpha-interferon and oral ribavirin. Genotype 1 HCV is the most difficult to treat and elimination of the virus (sustained virologic response) is achieved for only approximately 50% of patients (Fried, M. W. et al. N. Engl. J. Med. 2002, 347:975-982; Zeumzem, S. Nature Clinical Practice. 2008, 5:610-622). This poor treatment response, combined with often severe side effects induced by therapy, highlight a need for improved antiviral drugs with better efficacy and safety profiles.

[0005] HCV is a member of the Flaviviridae family of viruses with a single-stranded positive-sense RNA genome. Following infection of host cells, the 9.6 Kb genome is translated into a polyprotein precursor of approximately 3,000 amino acids (reviewed in Lindenbach, B. D. and Rice, C. M. Nature. 2005, 436:933-938; Moradpour, D, Penin, F., and Rice, C. M. Nature Reviews. 2007, 5:453-463). Post-translational processing by both cellular and viral proteases results in the generation of at least 10 separate viral proteins. The structural proteins (which by definition are found in mature virions) include core, E1, E2, and possibly p7, and originate from the amino-terminal region of the polyprotein. The core protein assembles into the viral nucleocapsid. The E1 and E2 glycoproteins form heterodimers that are found within the lipid envelope surrounding the viral particles, and mediate host cell receptor binding and entry of the virus into cells. It is unclear if p7 is a structural protein, and its role in replication has yet to be defined. However p7 is believed to form an ion channel in cellular membranes, preventing acidification of intracellular compartments in which virions are assembled, and it has been shown to be essential for viral replication and assembly. The nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B are produced through maturational cleavages of the carboxy-terminal region of the polyprotein. NS2 along with the amino terminus of NS3 form the NS2-3 metalloprotease which cleaves at the NS2-NS3 junction. Additionally, NS2 is involved in assembly and egress of nascent virions. The NS3 protein contains both a serine protease in its amino-terminal region, and a nucleotide-dependent RNA helicase in its carboxy-terminal region. NS3 forms a heterodimer with the NS4A protein, constituting the active protease which mediates cleavages of the polyprotein downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. The NS4B protein has been shown to be important for localization of HCV proteins into replication complexes in altered membranous structures within the cell. NS5B encodes an RNA-dependent RNA polymerase that is involved in the replication of HCV.

[0006] Subgenomic HCV replicons, containing the untranslated regions 5' and 3' to the coding sequence fused to the nonstructural proteins or the full-length polyprotein, are competent for translation, viral protein expression, and replication within cultured cells (Lohmann, V. et al. Science. 1999, 285:110-113; Moradpour, D, Penin, F., and Rice, C. M. Nature Reviews. 2007, 5:453-463). The replicon system has proven valuable for the identification of inhibitors targeting the nonstructural proteins associated with these functions. However, only limited subsets of HCV genotypes have been used to generate functional replicons.

[0007] Other systems have been used to study the biology of the HCV structural proteins that mediate the entry into host cells. For example, virus-like-particles made in recombinant baculovirus-infected cells with the HCV core, E1 and E2 proteins have also been used to study the function of the HCV E1 and E2 proteins (Barth, H., et al. J. Biol. Chem. 2003, 278:41003-41012). In addition, pseudotyping systems where the E1 and E2 glycoproteins are used to functionally replace the glycoproteins of retroviruses have been developed (Bartosch, B., Dubuisson, J. and Cosset, F.-L. J. Exp.

Med. 2003,197:633-642; Hsu, M. et al. Proc. Natl. Acad. Sci. USA. 2003, 100:7271-7276). These systems yield HCV pseudoparticles that bind to and enter host cells in a manner which is believed to be analogous to the natural virus, thus making them a convenient tool to study the viral entry steps as well as to identify inhibitors block this process.

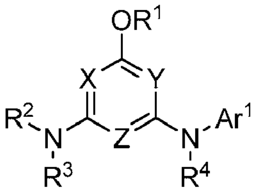
[0008] Recently, a full-length genotype 2a HCV clone, JFH1, was isolated and demonstrated the ability to replicate *in vitro.* Through repeated passage and adaptation in cell culture increased titers of infectious virus were produced (Lindenbach, B. D., et al. Science. 2005, 309:623-626; Wakita, T. et al. Nature Med. 2005, 11:791-796). In contrast to the HCV replicon or pseudotyping systems, the infectious virus is useful for studying the complete HCV replication cycle, including identifying inhibitors of not only the replication proteins, but those involved in early steps in virus infection (entry and uncoating) and production of progeny viruses (genome packaging, nucleocapsid assembly, virion envelopment and egress).

[0009] Triazines have been disclosed. See WO 2009/091388 and US 2009/0286778.

[0010] The invention provides technical advantages, for example, the compounds are novel and are effective against hepatitis C. Additionally, the compounds provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanism of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, or bioavailability.

DESCRIPTION OF THE INVENTION

[0011] One aspect of the invention is a compound of formula I



I

where

X and Y are N and Z is CH, Y and Z are N and X is CH; or X and Z are N and Y is CH;

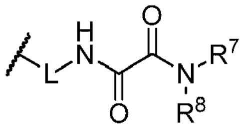
R^1 is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl, hydroxycycloalkyl, alkoxycycloalkyl, halocycloalkyl, cycloalkenyl, indanyl, alkylcarbonyl, or benzyl wherein the benzyl moiety is substituted with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;

R^2 is alkyl, (Ar^2)alkyl, (Ar^2)cycloalkyl, ((Ar^2)cycloalkyl)alkyl, ((Ar^2)alkyl)cycloalkyl, or (((Ar^2)alkyl)cycloalkyl)alkyl;

R^3 is hydrogen or alkyl;

R^4 is hydrogen or alkyl;

R^5 is



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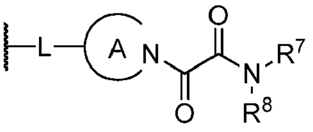


where ring A is a 4 to 7 membered alkylene ring substituted with L;

R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, (alkyl)cycloalkyl, ((alkyl))cycloalkyl)alkyl, a bridged bicycloalkyl, or Ar^3, and is substituted with 0-4 substituents selected from the group consisting of halo, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, benzyloxy, CO_2R^9 $N(R^{10})(R^{11})$, tetrahydrofuranyl, tetrahydropyranyl, and Ar^4;

R^8 is hydrogen or alkyl;

or R^7 and R^8 taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydroisoquinolinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;
R^9 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, ((hydroxyalkyl)alkoxy)alkoxy, or ((alkoxy)alkoxy)alkoxy;
R^{10} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl;
R^{11} is hydrogen or alkyl;
or R^{10} and R^{11} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;
R^{12} is hydrogen or alkyl;
R^{13} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl;
R^{14} is hydrogen or alkyl;
or R^{13} and R^{14} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;

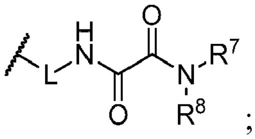
L is alkylene, cycloalkylene, (cycloalkyl)alkyl, (alkyl)cycloalkyl, or alkyl(cycloalkyl)alkyl, and is substituted with 0-2 substituents selected from alkoxy, hydroxy, CO_2R^{12} and $CONR^{13}R^{14}$;

Ar^1 is phenyl, pyridinyl or pyrimidinyl, and is substituted with 1 $CON(R^5)(R^6)$ and with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;
Ar^2 is phenyl substituted with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;
Ar^3 is phenyl, indanyl, fluorenyl, biphenyl, terphenyl, pyridinyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, benzoxazolyl, indolinyl, or dibenzofuranyl, and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkenyl, haloalkyl, cycloalkyl, (CO_2R^{12})alkyl, (CO_2R^{12})alkenyl $(CON(R^{13})(R^{14}))$alkyl, phenyl, hydroxyl, alkoxy, haloalkoxy, alkylcarbonyl, CO_2R^{12}, and $CON(R^{13})(R^{14})$;
or Ar^3 is phenyl substituted with 1 substituent selected from benzyl, tetrazolyloxy, thiazolyl, phenylpyrazolyl, methyloxadiazolyl, thiadiazolyl, triazolyl, methyltriazolyl, tetrazolyl, pyridinyl, and dimethoxypyrimdinyl; and
Ar^4 is phenyl, indanyl, tetrahydronaphthyl, isochromanyl, benzodioxolyl, pyridinyl, pyrazolyl, imidazolyl, or triazolyl and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkyenyl, haloalkyl, alkoxy, and haloalkoxy, $N(R^{13})(R^{14})$, and alkylCO;

or a pharmaceutically acceptable salt thereof.

[0012] Another aspect of the invention is a compound of formula I where

X and Y are N and Z is CH;
R^1 is haloalkyl;
R^2 is (Ar^2)alkyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 is



R^6 is hydrogen or alkyl;

R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3;
R^8 is hydrogen or alkyl;
or R^7 and R^8 taken together with the nitrogen to which they are attached is piperidinyl, morpholinyl, or tetrahydroisoquinolinyl;
L is alkylene;

Ar^1 is pyridinyl substituted with 1 CON(R^5)(R^6);
Ar^2 is phenyl substituted with 0-3 halo substituents; and
Ar^3 is phenyl, isoxazolyl, thiazolyl, or thiadiazolyl, and is substituted with 0-3 substituents selected from cyano, halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;

or a pharmaceutically acceptable salt thereof.

[0013] Another aspect of the invention is a compound of formula I where R^1 is haloalkyl; R^2 is (Ar^2)alkyl; R^3 is hydrogen; R^4 is hydrogen; R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3; L is

;

Ar^1 is phenyl substituted with 1 CON(R^5)(R^6); Ar^2 is phenyl substituted with 1 halo; and Ar^3 is phenyl, isoxazolyl, thiazolyl, or thiadiazolyl, and is substituted with 0-1 substituents selected from cyano, halo, and alkyl; or a pharmaceutically acceptable salt thereof.

[0014] Another aspect of the invention is a compound of formula I where R^1 is haloalkyl or a pharmaceutically acceptable salt thereof.

[0015] Another aspect of the invention is a compound of formula I where R^1 is trifluroethyl or a pharmaceutically acceptable salt thereof.

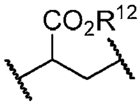
[0016] Another aspect of the invention is a compound of formula I where R^2 is (Ar^2)alkyl or (Ar^2)cycloalkyl, or a pharmaceutically acceptable salt thereof.

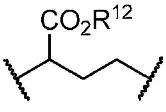
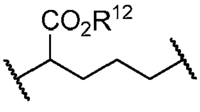
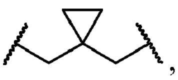
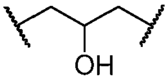
[0017] Another aspect of the invention is a compound of formula I where R^3 is hydrogen and R^4 is hydrogen, or a pharmaceutically acceptable salt thereof.

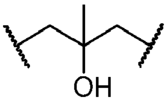
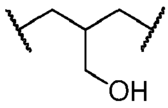
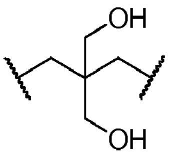
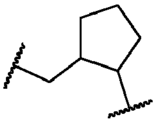
[0018] Another aspect of the invention is a compound of formula I where R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3; R^8 is hydrogen or alkyl; or R^7 and R^8 taken together with the nitrogen to which they are attached is piperidinyl, morpholinyl, or tetrahydroisoquinolinyl; or a pharmaceutically acceptable salt thereof.

[0019] Another aspect of the invention is a compound of formula I where R^7 is Ar^3 or a pharmaceutically acceptable salt thereof.

[0020] Another aspect of the invention is a compound of formula I where L is

,

, , , , ,

, ,  or ;

or a pharmaceutically acceptable salt thereof.

[0021] Another aspect of the invention is a compound of formula I where Ar^1 is pyridinyl substituted with 1 CON(R^5)(R^6), or a pharmaceutically acceptable salt thereof, Another aspect of the invention is a compound of formula I where R^1 is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl, hydroxycycloalkyl, alkoxycycloalkyl, halocycloalkyl, cycloalkenyl, benzyl, indanyl, or alkylcarbonyl.

[0022] Another aspect of the invention is a compound of formula I where R^2 is alkyl, (Ar^2)alkyl, (Ar^2)cycloalkyl, ((Ar^2)cycloalkyl)alkyl, ((Ar^2)alkyl)cycloalkyl, or (((Ar^2)alkyl)cycloalkyl)alkyl.

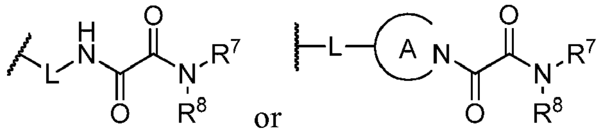
[0023] Another aspect of the invention is a compound of formula I where R^3 is hydrogen or alkyl.

[0024] Another aspect of the invention is a compound of formula I where R^3 is hydrogen.

[0025] Another aspect of the invention is a compound of formula I where R^4 is hydrogen or alkyl.

[0026] Another aspect of the invention is a compound of formula I where R^4 is hydrogen.

[0027] Another aspect of the invention is a compound of formula I where R^5 is



where ring A is a 4 to 7 membered alkylene ring substituted with L.

[0028] Another aspect of the invention is a compound of formula I where R^6 is hydrogen or alkyl.

[0029] Another aspect of the invention is a compound of formula I where R^7 is alkyl, cycloalkyl, (cycloalkyl)alkyl, (alkyl)cycloalkyl, ((alkyl))cycloalkyl)alkyl, or a bridged bicycloalkyl, and is substituted with 0-4 substituents selected from the group consisting of halo, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, benzyloxy, CO_2R^9 $N(R^{10})(R^{11})$, tetrahydrofuranyl, tetrahydropyranyl, and Ar^4.

[0030] Another aspect of the invention is a compound of formula I where R^7 is hydrogen, N-alkoxycarbonylpiperidinyl, piperidinonyl, or Ar^3.

[0031] Another aspect of the invention is a compound of formula I where R^8 is hydrogen or alkyl.

[0032] Another aspect of the invention is a compound of formula I where R^7 and R^8 taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl.

[0033] Another aspect of the invention is a compound of formula I where R^9 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, ((hydroxyalkyl)alkoxy)alkoxy, or ((alkoxy)alkoxy)alkoxy.

[0034] Another aspect of the invention is a compound of formula I where R^{10} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl.

[0035] Another aspect of the invention is a compound of formula I where R^{11} is hydrogen, alkyl.

[0036] Another aspect of the invention is a compound of formula I where R^{10} and R^{11} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl.

[0037] Another aspect of the invention is a compound of formula I where R^{12} is hydrogen or alkyl.

[0038] Another aspect of the invention is a compound of formula I where R^{13} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl.

[0039] Another aspect of the invention is a compound of formula I where R^{14} is hydrogen or alkyl;

[0040] Another aspect of the invention is a compound of formula I where R^{13} and R^{14} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl.

[0041] Another aspect of the invention is a compound of formula I where L is alkylene, cycloalkylene, (cycloalkyl)alkyl, (alkyl)cycloalkyl, or alkyl(cycloalkyl)alkyl, and is substituted with 0-1 CO_2R^{12} or $CONR^{13}R^{14}$.

[0042] Another aspect of the invention is a compound of formula I where Ar^1 is phenyl, pyridyl or pyrimidinyl substituted with 1 $CON(R^5)(R^6)$ or OR^5 or or $N(R^5)(R^6)$ and with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy.

[0043] Another aspect of the invention is a compound of formula I where Ar^2 is phenyl substituted with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy.

[0044] Another aspect of the invention is a compound of formula I where Ar^3 is phenyl, indanyl, fluorenyl, biphenyl, terphenyl, pyridinyl, pyrazolyl, isoxazolyl, imidazolyl, thiazolyl, triazolyl, thiadiazolyl, benzoxazolyl, indolinyl, or dibenzofuranyl, and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkenyl, haloalkyl, cycloalkyl, (CO_2R^{12})alkyl, (CO_2R^{12})alkenyl, $(CON(R^{13})(R^{14}))$alkyl, phenyl, hydroxyl, alkoxy, haloalkoxy, alkylcarbonyl, CO_2R^{12}, $CON(R^{13})(R^{14})$, or $PhCONHSO_2$.

[0045] Another aspect of the invention is a compound of formula I where Ar^3 is phenyl substituted with 1 substituents selected from benzyl, tetrazolyloxy, thiazolyl, phenylpyrazolyl, methyloxadiazolyl, thiadiazolyl, triazolyl, methyltriazolyl, tetrazolyl, pyridinyl, and dimethoxypyrimdinyl.

[0046] Another aspect of the invention is a compound of formula I where Ar^4 is phenyl, indanyl, tetrahydronaphthyl, isochromanyl, benzodioxolyl, pyridinyl, pyrazolyl, or imidazolyl, triazolyl and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkyenyl, haloalkyl, alkoxy, and haloalkoxy, $N(R^{13})(R^{14})$, and alkylCO.

[0047] Another aspect of the invention is a compound of formula I where R^1 is haloalkyl or a pharmaceutically acceptable salt thereof.

[0048] Another aspect of the invention is a compound of formula I where R^1 is trifluroethyl or a pharmaceutically acceptable salt thereof.

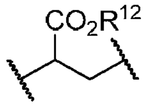
[0049] Another aspect of the invention is a compound of formula I where R^2 is (Ar^2)alkyl or (Ar^2)cycloalkyl, or a pharmaceutically acceptable salt thereof.

[0050] Another aspect of the invention is a compound of formula I where R^2 is (Ar^2)alkyl or (Ar^2)cycloalkyl, or a pharmaceutically acceptable salt thereof.

[0051] Another aspect of the invention is a compound of formula I where R^7 is alkyl, cycloalkyl, (cycloalkyl)alkyl, (alkyl)cycloalkyl, ((alkyl))cycloalkyl)alkyl, or a bridged bicycloalkyl, and is substituted with 0-4 substituents selected from the group consisting of halo, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, benzyloxy, CO_2R^9 $N(R^{10})(R^{11})$, tetrahydrofuranyl, tetrahydropyranyl, and Ar^4; or a pharmaceutically acceptable salt thereof.

[0052] Another aspect of the invention is a compound of formula I where R^7 is Ar^3 or a pharmaceutically acceptable salt thereof.

[0053] Another aspect of the invention is a compound of formula I where L is



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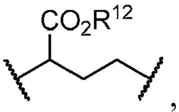

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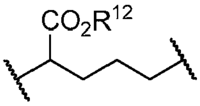

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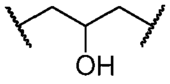

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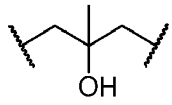

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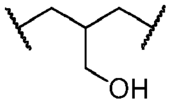

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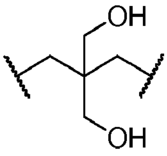

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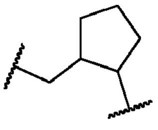

;

or a pharmaceutically acceptable salt thereof.

[0054] Any scope of any variable, including R^1, R^2, R^3, R^2, R^2, R^6, R^2, R^2, R^9, R^{10}, R^{11} R^{12}, R^{13}, R^{14}, L, Ar^1, Ar^2, Ar^3, and Ar^4, can be used independently with the scope of any other instance of a variable.

[0055] Unless specified otherwise, these terms have the following meanings. "Halo" means fluoro, chloro, bromo, or iodo. "Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons. "Alkenyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one double bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 8 carbons. "Alkylene" means a straight or branched divalent alkyl group. "Alkenylene" means a straight or branched divalent alkyl group with at least one double bond. "Cycloalkylene" means a divalent cycloalkane moiety composed of 3 to 7 carbons and includes gem-divalency (for example 1,1-cyclopropanediyl) as well as non-gem-divalency (for example, 1,4-cyclohexanediyl). "Alkylidinyl" means a divalent alkene substituent where the divalency occurs on the same carbon of the alkene. "Hydroxyalkyl," "alkoxy" and other terms with a substituted alkyl moiety include straight and branched isomers composed of 1 to 6 carbon atoms for the alkyl moiety. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic and heterocyclic aromatic substituents. Phenylene is a divalent benzene ring. "1,4-Phenylene" means 1,4-benzenediyl with respect to regiochemistry for the divalent moiety. Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

[0056] The substituents described above may be attached at any suitable point of attachment unless otherwise specified. However, it is understood that the compounds encompassed by the present invention are those that are chemically stable as understood by those skilled in the art. Additionally, the compounds encompassed by the present disclosure are those that are suitably stable for use as a pharmaceutical agent.

[0057] The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, camsylate, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

[0058] Some of the compounds of the invention possess asymmetric carbon atoms (see, for example, the structures below). The invention includes all stereoisomeric forms, including enantiomers and diastereomers as well as mixtures of stereoisomers such as racemates. Some stereoisomers can be made using methods known in the art. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods commonly known in the art. The use of wedges or hashes in the depictions of molecular structures in the following schemes and tables is intended only to indicate relative stereochemistry, and should not be interpreted as implying absolute stereochemical assignments.

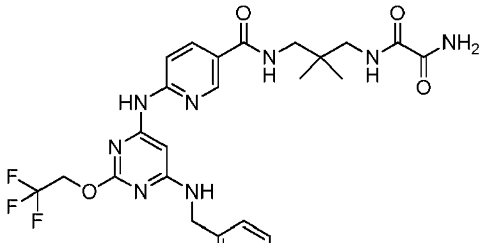
[0059] The invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

Biological Methods

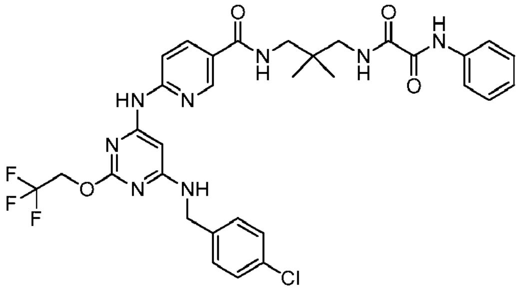
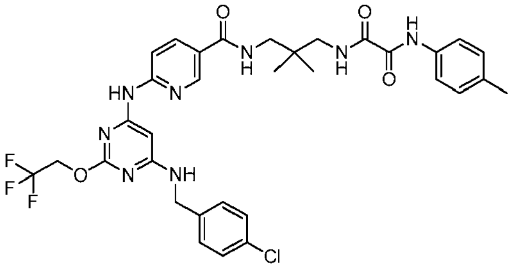
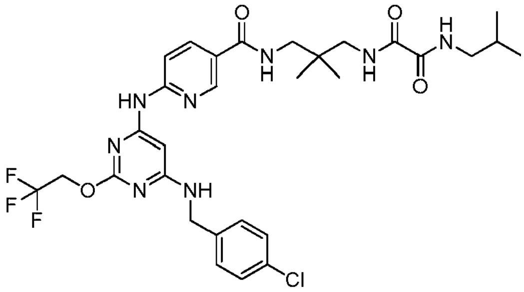
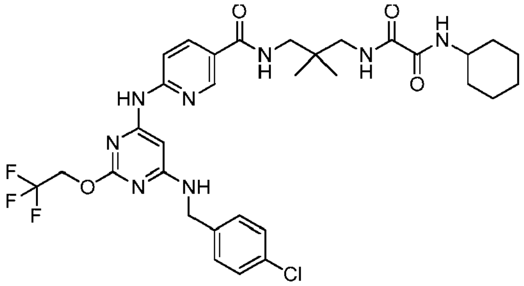
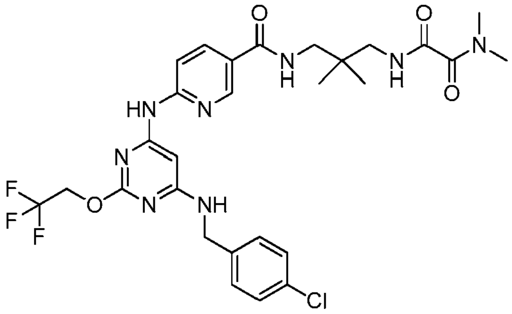
[0060] *Infection assays.* HCV pseudoparticles, produced using standardized methodology (Bartosch, B., Dubuisson, J. and Cosset, F.-L. J. Exp. Med. 2003, 197:633-642) were made via a liposome-based transfection procedure of 293T cells with plasmids expressing the murine leukemia virus capsid and polymerase proteins, an MLV genome encoding the luciferase reporter gene, and envelope glycoproteins from either HCV or vesicular stomatitis virus (VSV). The genotype 1a HCV E1 and E2 envelope coding sequences were derived from the H77C isolate (GenBank accession number AF009606). Media containing pseudoparticles was collected 3 days following transfection, filtered, and stored at -20°C as a viral stock. Infections were performed in 384-well plates by mixing pseudovirus with 1 x 10^4 Huh7 cells/well in the presence or absence of test inhibitors, followed by incubation at 37°C. Luciferase activity, reflecting the degree of entry of the pseudoparticles into host cells, was measured 2 days after infection. The specificity of the compounds for inhibiting HCV was determined by evaluating inhibition of VSV pseudoparticle infection.

[0061] *Compounds and data analysis.* Test compounds were serially diluted 3-fold in dimethyl sulfoxide (DMSO) to give a final concentration range in the assay of 50.0 μM to 0.04 pM. Maximum activity (100% of control) and background were derived from control wells containing DMSO but no inhibitor or from uninfected wells, respectively. The individual signals in each of the compound test wells were then divided by the averaged control values after background subtraction and multiplied by 100% to determine percent activity. Assays were performed in duplicate and average EC_{50} values (reflecting the concentration at which 50% inhibition of virus replication was achieved) were calculated. Compound EC_{50} data is expressed as A = 0.01≤10 nM; B = 10-1000 nM. Representative data for compounds are reported in Table 1.

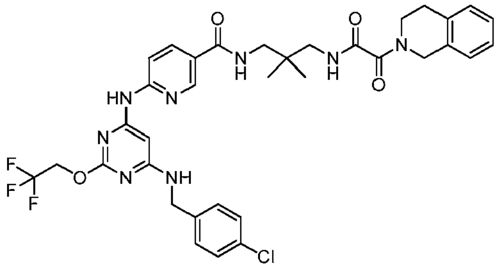
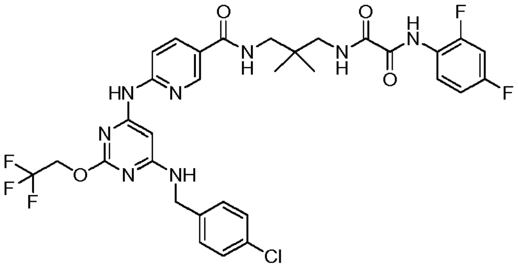
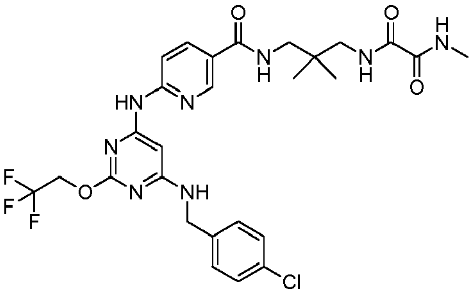
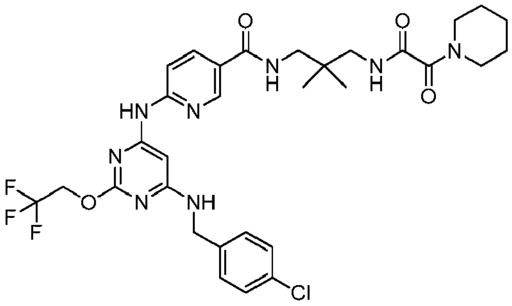
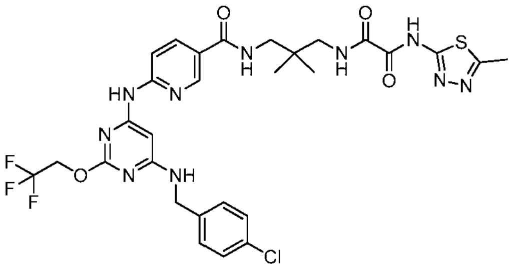
Table 1.

Example	Structure	EC_{50} (nM) 1a (H77C)	EC_{50} (nM) 1a (H77C)
1001		1.465	A

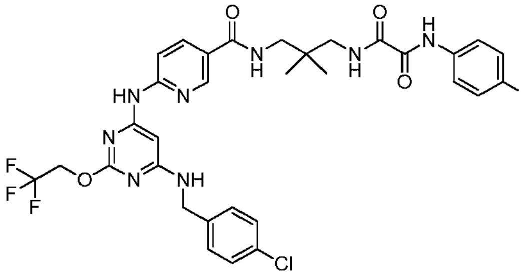
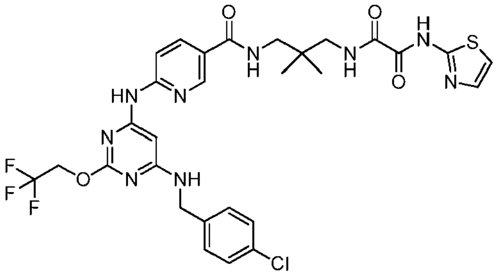
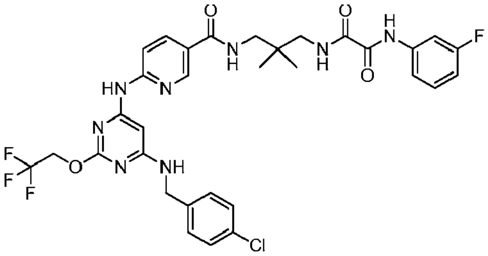
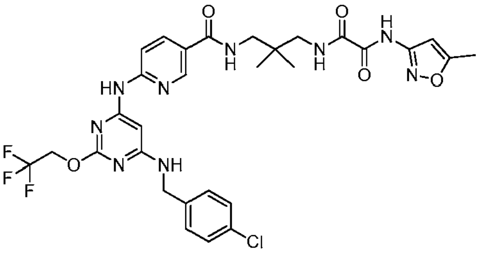
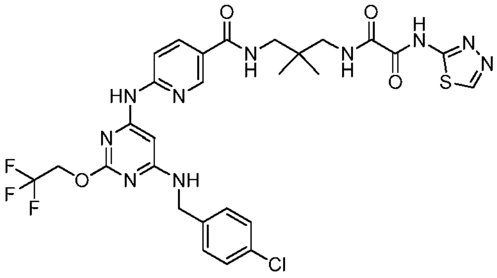
(continued)

Example	Structure	EC_{50} (nM) 1a (H77C)	EC_{50} (nM) 1a (H77C)
1002			A
1003		0.214	A
1004			A
1005			A
1006			B

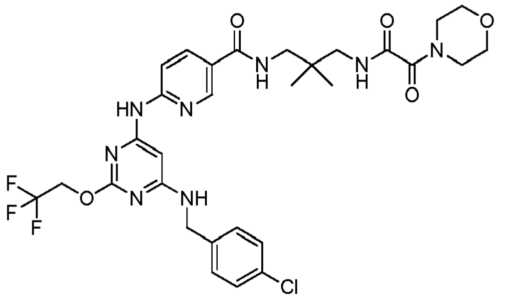
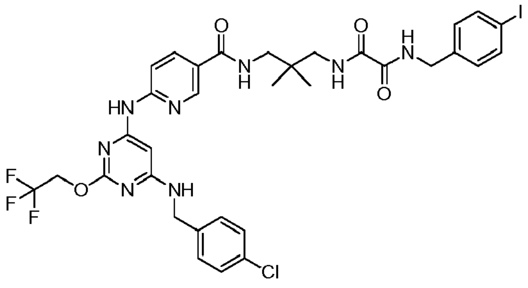
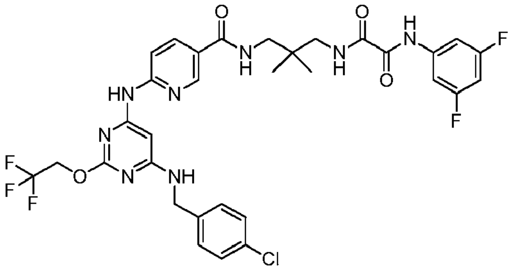
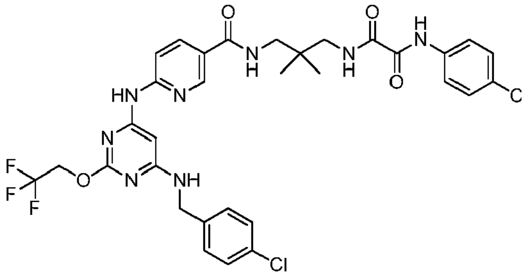
(continued)

Example	Structure	EC_{50} (nM) 1a (H77C)	EC_{50} (nM) 1a (H77C)
1007			A
1008			A
1009			A
1010			B
1011			B

(continued)

Example	Structure	EC_{50} (nM) 1a (H77C)	EC_{50} (nM) 1a (H77C)
1012		0.482	A
1013			A
1014			A
1015		1.309	A
1016		56.840	B

(continued)

Example	Structure	EC$_{50}$ (nM) 1a (H77C)	EC$_{50}$ (nM) 1a (H77C)
1017		26.780	B
1018			A
1019			B
1020			A

Pharmaceutical Compositions and Methods of Treatment

[0062] The compounds demonstrate activity against HCV NS5B and can be useful in treating HCV and HCV infection. Therefore, another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0063] Another aspect of the invention is a composition further comprising a compound having anti-HCV activity.

[0064] Another aspect of the invention is a composition where the compound having anti-HCV activity is an interferon or a ribavirin. Another aspect of the invention is where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, interferon lambda, and lymphoblastoid interferon tau.

[0065] Another aspect of the invention is a composition where the compound having anti-HCV activity is a cyclosporin. Another aspect of the invention is where the cyclosporin is cyclosporin A.

[0066] Another aspect of the invention is a composition where the compound having anti-HCV activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type

1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0067] Another aspect of the invention is a composition where the compound having anti-HCV activity is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

[0068] Another aspect of the invention is a composition comprising a compound, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, an interferon and ribavirin.

[0069] Another aspect of the disclosure is a method of inhibiting the function of the HCV replicon comprising contacting the HCV replicon with a compound or a pharmaceutically acceptable salt thereof.

[0070] Another aspect of the disclosure is a method of inhibiting the function of the HCV NS5B protein comprising contacting the HCV NS5B protein with a compound or a pharmaceutically acceptable salt thereof.

[0071] Another aspect of the disclosure is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof. In another embodiment the compound is effective to inhibit the function of the HCV replicon. In another embodiment the compound is effective to inhibit the function of the HCV NS5B protein.

[0072] Another aspect of the disclosure is a method of treating an HCV infection in a patient comprising administering to the patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, in conjunction with (prior to, after, or concurrently) another compound having anti-HCV activity.

[0073] Another aspect of the disclosure is the method where the other compound having anti-HCV activity is an interferon or a ribavirin.

[0074] Another aspect of the disclosure is the method where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, interferon lambda, and lymphoblastoid interferon tau.

[0075] Another aspect of the disclosure is the method where the other compound having anti-HCV activity is a cyclosporin.

[0076] Another aspect of the disclosure is the method where the cyclosporin is cyclosporin A.

[0077] Another aspect of the disclosure is the method where the other compound having anti-HCV activity is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0078] Another aspect of the disclosure is the method where the other compound having anti-HCV activity is effective to inhibit the function of a target selected from the group consisting of HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

[0079] Another aspect of the disclosure is the method where the other compound having anti-HCV activity is effective to inhibit the function of target in the HCV life cycle other than the HCV NS5B protein.

[0080] "Therapeutically effective" means the amount of agent required to provide a meaningful patient benefit as understood by practitioners in the field of hepatitis and HCV infection.

[0081] "Patient" means a person infected with the HCV virus and suitable for therapy as understood by practitioners in the field of hepatitis and HCV infection.

[0082] "Treatment," "therapy," "regimen," "HCV infection," and related terms are used as understood by practitioners in the field of hepatitis and HCV infection.

[0083] The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier and may contain conventional excipients. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including for example capsules, tablets, losenges, and powders as well as liquid suspensions, syrups, elixers, and solutions. Compositions are made using common formulation techniques, and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols) are generally used for compositions. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 17th edition, 1985.

[0084] Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg. Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 0.25-1000 mg/unit.

[0085] Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of 1-100 mg/mL. Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL. Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is

1-100 mg/mL.

[0086] The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred. Generally, the dosing regimen will be similar to other agents used clinically. Typically, the daily dose will be 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

[0087] The invention also encompasses methods where the compound is given in combination therapy. That is, the compound can be used in conjunction with, but separately from, other agents useful in treating hepatitis and HCV infection. In these combination methods, the compound will generally be given in a daily dose of 1-100 mg/kg body weight daily in conjunction with other agents. The other agents generally will be given in the amounts used therapeutically. The specific dosing regime, however, will be determined by a physician using sound medical judgement.

[0088] Some examples of compounds suitable for compositions and methods are listed in Table 2.

Table 2.

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immuno-modulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead

(continued)

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharma. Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

(continued)

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/ Valentis
Wellferon	Interferon	Lympho-blastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	serine protease inhibitor	Schering Plough
TMS-435	Antiviral	serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium
BI-201335	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	serine protease inhibitor	Merck
PF-00868554	Antiviral	replicase inhibitor	Pfizer
ANA598	Antiviral	Non-Nucleoside NS5B Polymerase Inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Non-Nucleoside Replicase Inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	NS5B Polymerase Inhibitor	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI-7851	Antiviral	Nucleoside Polymerase Inhibitor	Pharmasset, Princeton, NJ, USA

(continued)

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
PSI-7977	Antiviral	Nucleotide NS5B Polymerase Inhibitor	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	NS5B Polymerase Inhibitor	ViroChem Pharma
VCH-916	Antiviral	NS5B Polymerase Inhibitor	ViroChem Pharma
GS-9190	Antiviral	NS5B Polymerase Inhibitor	Gilead
Peg-interferon lamda	Antiviral	Interferon	ZymoGenetics/Brist ol-Myers Squibb

Synthetic Methods

[0089] The compounds may be made by methods known in the art including those described below and including variations within the skill of the art. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (e.g. numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make the compounds and are not to be confused with variables used in the claims or in other sections of the specification. The following methods are for illustrative purposes and are not intended to limit the scope of the invention.

[0090] Abbreviations used in the schemes generally follow conventions used in the art. Chemical abbreviations used in the specification and examples are defined as follows: "NaHMDS" for sodium bis(trimethylsilyl)amide; "DMF" for N,N-dimethylformamide; "MeOH" for methanol; "NBS" for N-bromosuccinimide; "Ar" for aryl; "TFA" for trifluoroacetic acid; "LAH" for lithium aluminum hydride; "BOC", "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "EDTA" for ethylenediaminetetraacetic acid; "Et_2O" for diethyl ether; "DMAP" for 4-dimethylaminopyridine; "DCE" for 1,2-dichloroethane; "ACN" for acetonitrile; "DME" for 1,2-dimethoxyethane; "HOBt" for 1-hydroxybenzotriazole hydrate; "DIEA" for diisopropylethylamine, "Nf" for $CF_3(CF_2)_3SO_2$-; and "TMOF" for trimethylorthoformate.

[0091] Abbreviations are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "^1H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

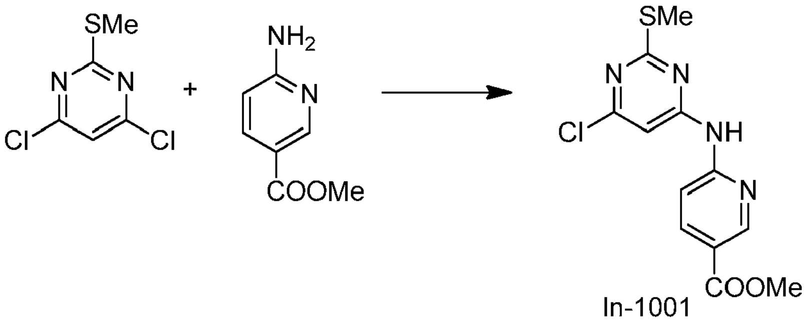
[0092] *LC/MS Method (i.e., compound identification).* All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS or LC-20AS liquid chromotograph using a SPD-10AV or SPD-20A UV-Vis detector and Mass Spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode.

[0093] *HPLC Method (i.e., compound isolation).* Compounds purified by preparative HPLC were diluted in methanol (1.2 mL) and purified using a Shimadzu LC-8A or LC-10A or Dionex APS-3000 or Waters Acquity™ automated preparative HPLC system.

Syntheses of Intermediates:

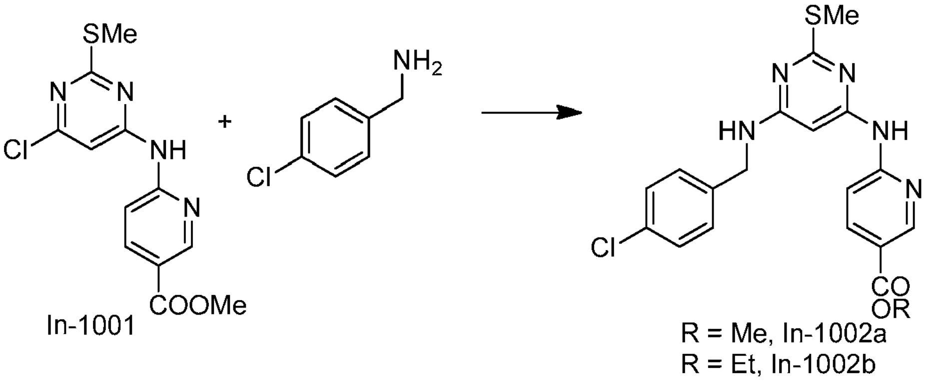
Preparation of Intermediates:

[0094]



[0095] NaHMDS (65.7 mL, 1M in THF) was added into the solution of 4,6-dichloro-2-(methylthio)pyrimidine (6.4 g) and methyl 4-aminobenzoate (5 g) in THF (200 mL). The reaction was stirred at room temperature for 16 hours, before being quenched by water. The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give the crude **In-1001**, methyl 6-((6-chloro-2-(methylthio)pyrimidin-4-yl)amino)nicotinate, which was used in the next step without purification.

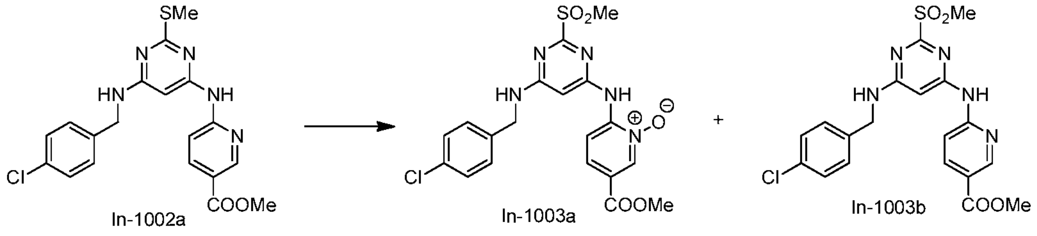
Methyl 6-(6-chloro-2-(methylthio)pyrimidin-4-ylamino)nicotinate Methyl 6-((6-chloro-2-(methylthio)pyrimidin-4-yl)amino)nicotinate	
MS $(M+H)^+$ Calcd.	311.0
MS $(M+H)^+$ Observ.	311.1
Retention Time	1.83 minutes
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u



[0096] The mixture of ethyl 6-(6-chloro-2-(methylthio)pyrimidin-4-ylamino)nicotinate (500 mg) and (4-chlorophenyl)methanamine (1139 mg) in EtOH (20 mL) was heated to 115°C for 4 hours, showing formation of ethyl 6-(6-(4-chlorobenzylamino)-2-(methylthio)pyrimidin-4-ylamino)nicotinate. After removal of solvents, the residue was purified by silica gele chromatography to give a mixture of methyl 6-((6-((4-chlorobenzyl)amino)-2-(methylthio)pyrimidin-4-yl)amino)nicotinate **(In-1002a)** and ethyl 6-((6-((4-chlorobenzyl)amino)-2-(methylthio)pyrimidin-4-yl)amino)nicotinate (**In-1002b**).

methyl 6-((6-((4-chlorobenzyl)amino)-2-(methylthio)pyrimidin-4-yl)amino)nicotinate	
MS $(M+H)^+$ Calcd.	416.1
MS $(M+H)^+$ Observ.	416.5
Retention Time	1.84 minutes
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u

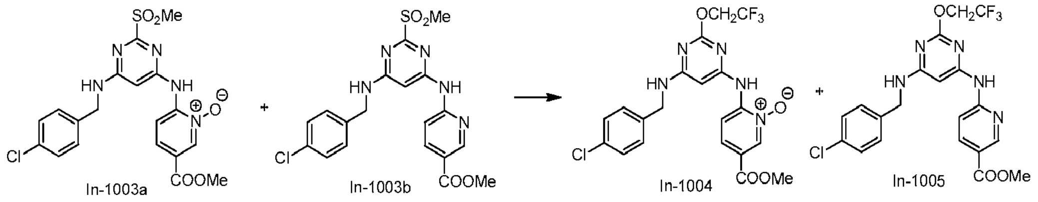
ethyl 6-((6-((4-chlorobenzyl)amino)-2-(methylthio)pyrimidin-4-yl)amino)nicotinate	
MS $(M+H)^+$ Calcd.	430.1
MS $(M+H)^+$ Observ.	430.4
Retention Time	2.06 minutes
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u



[0097] mCPBA (2.91 g, 77%) was added into the solution of crude methyl 6-((6-((4-hydroxybenzyl)amino)-2-(methylthio)pyrimidin-4-yl)amino)nicotinate (1.8 g) in CH_2Cl_2 (100 mL). The reaction was stirred at room temperature for 48 hours to give 2-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)-5-(methoxycarbonyl)pyridine 1-oxide (**In-1003a**) and methyl 6-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)nicotinate (**In-1003b**), before being quenched by water. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give the crude product whichwas used as was.

2-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)-5-(methoxycarbonyl)pyridine 1-oxide	
MS $(M+H)^+$ Calcd.	464.1
MS $(M+H)^+$ Observ.	464.4
Retention Time	1.46 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u

methyl 6-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)nicotinate	
MS $(M+H)^+$ Calcd.	448.1
MS $(M+H)^+$ Observ.	448.4
Retention Time	1.62 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u



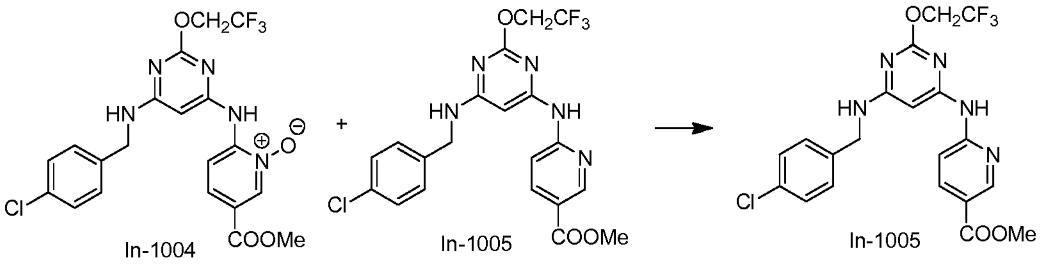
[0098] 2,2,2-trifluoroethanol (3.88 g) and NaH (1.552 g, 60%) were added into the solution of the mixture of 2-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)-5-(methoxycarbonyl)pyridine 1-oxide (**In-1003a**) and methyl 6-((6-((4-chlorobenzyl)amino)-2-(methylsulfonyl)pyrimidin-4-yl)amino)nicotinate (**In-1003b**) (1.8 g) in THF (100 mL). The reaction was stirred at room temperature for 72 hours before being quenched by water. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give a mixture of products, 2-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)-5-(methoxycarbonyl)pyridine 1-oxide (**In-1004**) and methyl 6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinate (**In-1005**), which was used without purification.

2-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)-5-(methoxycarbonyl)pyridine 1-oxide	
MS $(M+H)^+$ Calcd.	484.1
MS $(M+H)^+$ Observ.	484.5
Retention Time	1.77 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u

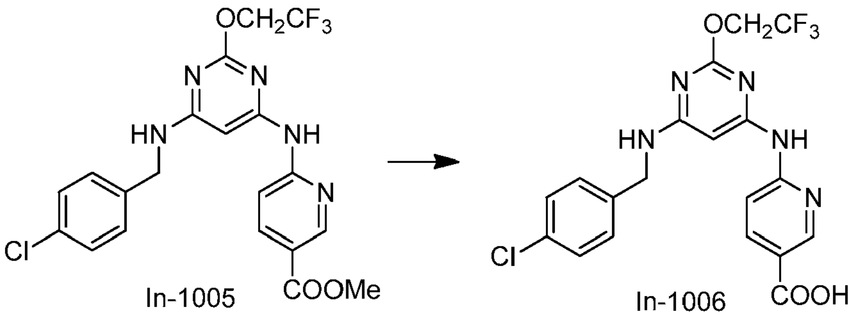
methyl 6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinate	
MS $(M+H)^+$ Calcd.	468.1
MS $(M+H)^+$ Observ.	468.5
Retention Time	1.92 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220

(continued)

LC Condition	
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30x2, 3u



PCl_3 (483 mg) was added into the solution of the crude mixture of **In-1004** and In-1005 (1.7 g) in EtOAc (10 mL). The reaction was stirred for 24 hours, before being quenched by $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give a residue was used without purification.

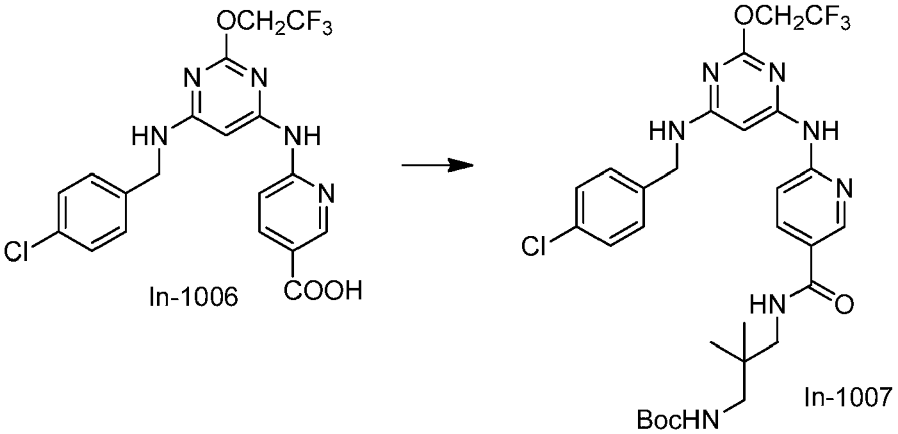


[0099] K_2CO_3 (112 mg) was added into the solution of the crude **In-1005a** in acetone (25 mL) and water (5 mL). The reaction was run at 85°C for 72 hours, before acetone was removed under vacumm. The aqueous layer's pH was adjusted to pH5 using 1NHCl solution and was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give the crude 6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinic acid (**In-1006**) which was used without purification.

6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinic acid	
MS $(M+H)^+$ Calcd.	454.1
MS $(M+H)^+$ Observ.	454.0
Retention Time	2.11 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min

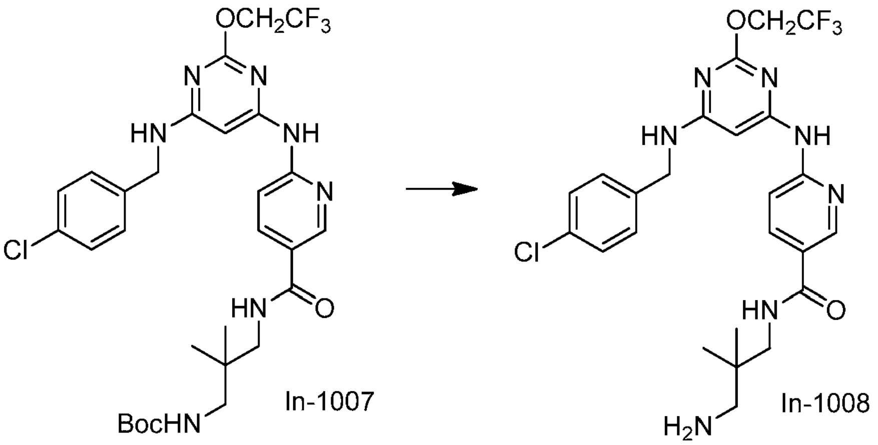
(continued)

LC Condition	
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um



[0100] iPr_2NEt (0.5 mL), HCTU (593 mg) were added into the solution of 6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinic acid **(In-1006)** (500 mg) and tert-butyl (3-amino-2,2-dimethylpropyl)carbamate (267 mg) in DMF (20 mL). The reaction was stirred at room temperature for 24 hours before being quenched by $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum to give tert-butyl (3-(6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamido)-2,2-dimethylpropyl)carbamate (**In-1007**) was used without purification.

tert-butyl (3-(6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamido)-2,2-dimethylpropyl)carbamate	
MS $(M+H)^+$ Calcd.	638.2
MS $(M+H)^+$ Observ.	638.2
Retention Time	2.29 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

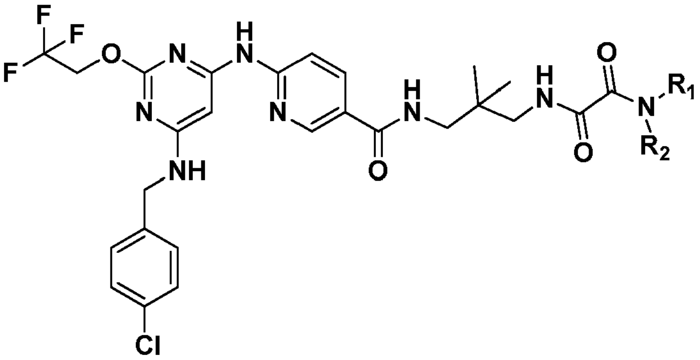


[0101] TFA (5 mL) was added into a solution of crude tert-butyl (3-(6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamido)-2,2-dimethylpropyl)carbamate (In-1007) (1g) in CH_2CL_2 (50 mL). The reaction was carried out at room temperature for 24 hours. After removal of the solvents, the residue was purified by silica gel chromatography to give N-(3-amino-2,2-dimethylpropyl)-6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamide (**In-1008**).

N-(3-amino-2,2-dimethylpropyl)-6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamide	
MS $(M+H)^+$ Calcd.	538.2
MS $(M+H)^+$ Observ.	538.2
Retention Time	1.91 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

General Procedure for the Preparation of Compounds 1001 - 1019, from In-1008:

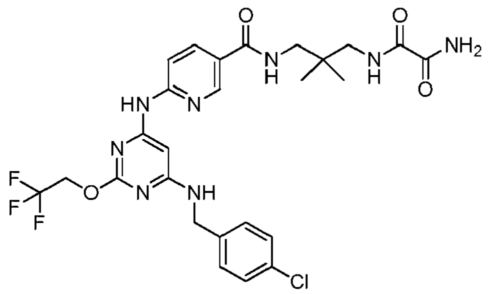
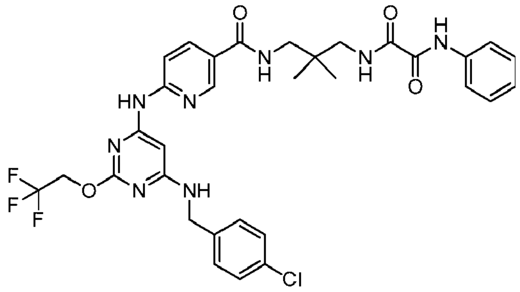
[0102]



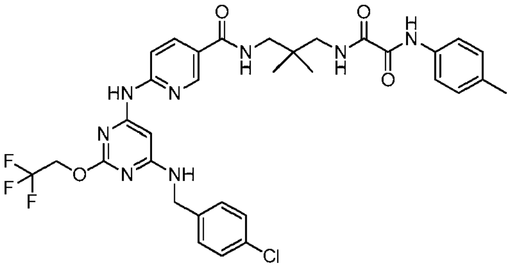
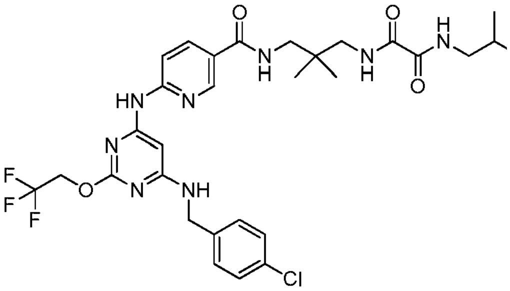
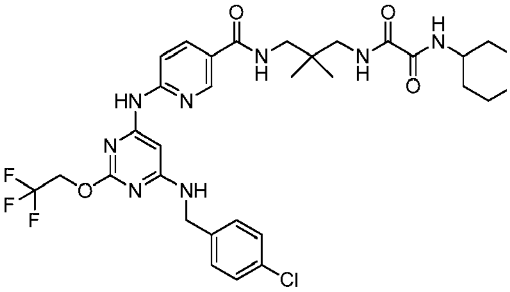
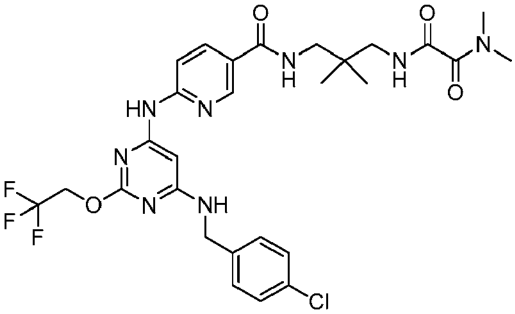
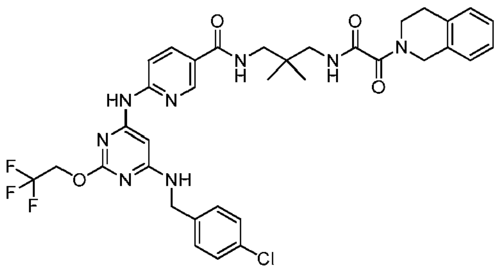
[0103] A solution of HATU (201 mg, 532 μmol) in DMF (9.5 mL) was prepared. To each of the carboxylic acids (1 eq.) weighed into 16x48 mm threaded vials was added 500 μL of the HATU solution. The mixtures were allowed to shake at room temperature for 10 minutes. A solution of N-(3-amino-2,2-dimethylpropyl)-6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamide **(In-1008)** (190 mg, 1eq.)) and DIPEA (247 μL) in DMF (9.5 mL) was also prepared. To each of the reaction vials was added 500 μL of the N-(3-amino-2,2-dimethylpropyl)-6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinamide/ DIPEA solution. Vials were capped and allowed to shake at room temperature for 18 hours before the mixtures were purified by preparative HPLC systems.

[0104] Method M=Column: Waters BEH C18, 2.0 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 methanol:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 methanol:water with 10 mM ammonium acetate; Temperature: 40 °C; Gradient: 0.5 min hold at 0%B, 0-100% B over 4 minutes, then a 0.5-minute hold at 100% B; Flow: 0.5 mL/min.

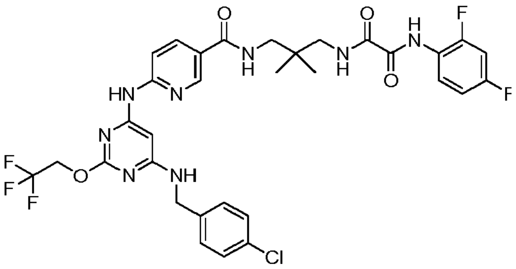
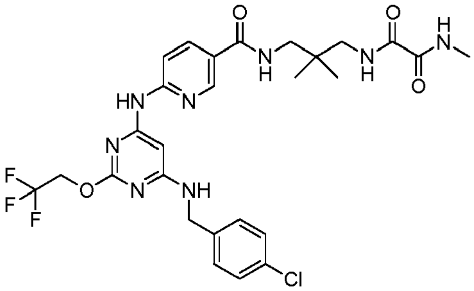
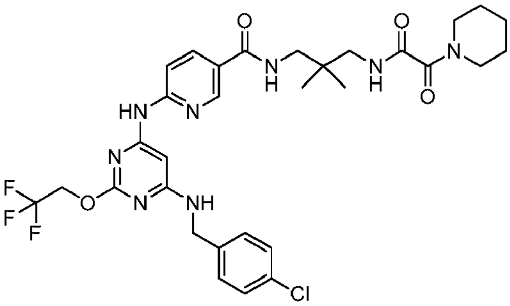
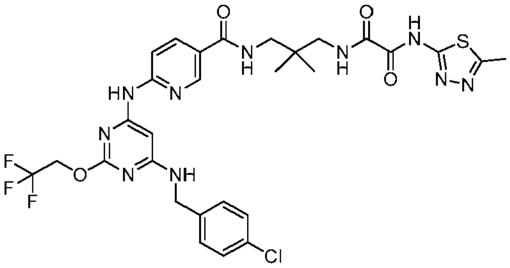
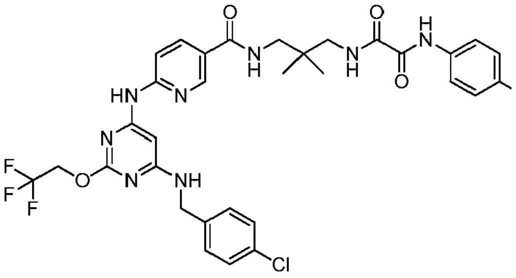
[0105] Method A= Column: Waters BEH C18, 2.0 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 40 °C; Gradient: 0.5 min hold at 0%B, 0-100% B over 4 minutes, then a 0.5-minute hold at 100% B; Flow: 1 mL/min.

Compd	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Obs.	HPLC Rt (min)	Method
1001		609.2	609.5	4.07	M
1002		685.2	685.6	3.36	A

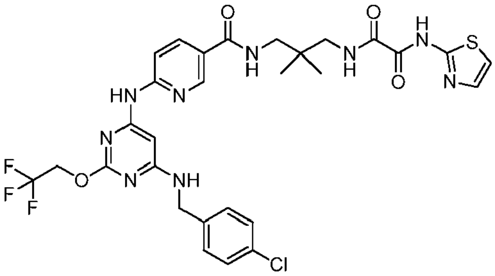
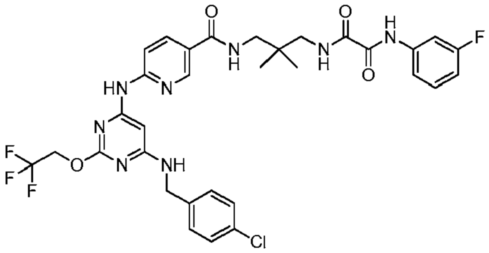
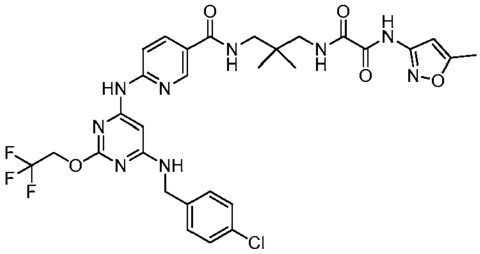
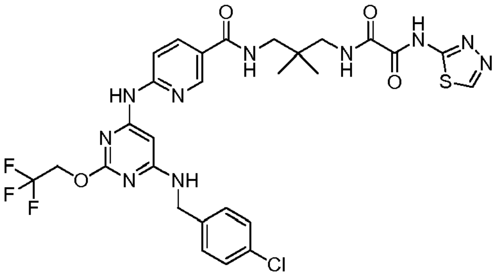
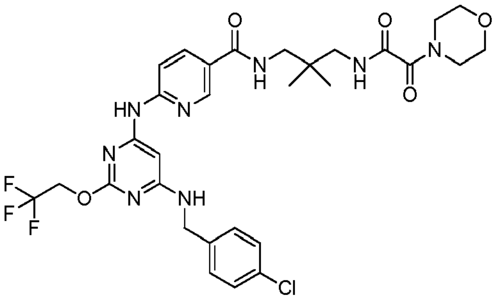
(continued)

Compd	Structure	MS (M+H)⁺ Calcd.	MS (M+H) ⁺ Obs.	HPLC Rt (min)	Method
1003		699.2	699.6	4.53	M
1004		665.3	665.7	3.24	A
1005		691.3	691.8	3.39	A
1006		637.2	637.7	4.05	M
1007		725.3	725.8	3.27	A

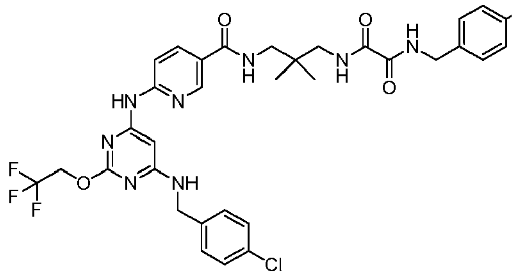
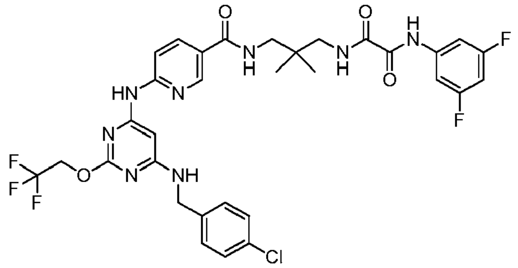
(continued)

Compd	Structure	MS (M+H)+ Calcd.	MS (M+H) + Obs.	HPLC Rt (min)	Method
1008		721.2	721.6	4.49	M
1009		623.2	623.5	4.14	M
1010		677.3	677.8	3.07	A
1011		707.2	707.5	4.18	M
1012		703.2	703.5	3.37	A

(continued)

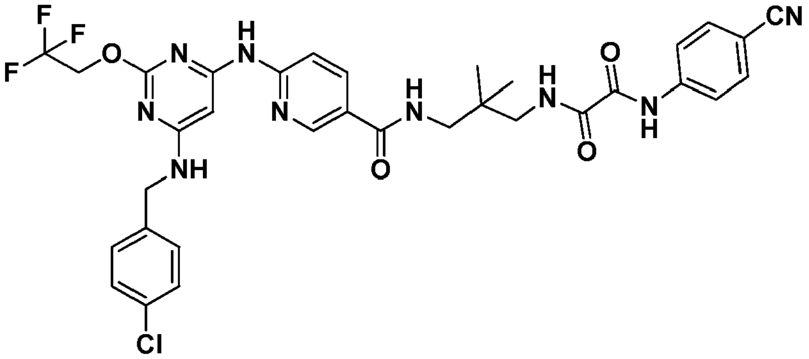
Compd	Structure	MS (M+H)+ Calcd.	MS (M+H) + Obs.	HPLC Rt (min)	Method
1013		692.2	692.5	4.31	M
1014		703.2	703.6	4.47	M
1015		690.2	690.7	4.22	M
1016		693.2	693.7	4.01	M
1017		679.2	678.8	4.05	M

(continued)

Compd	Structure	MS (M+H)$^+$ Calcd.	MS (M+H)$^+$ Obs.	HPLC Rt (min)	Method
1018		717.2	717.6	4.33	M
1019		721.2	721.7	4.48	M

Preparation of Compounds 1020:

[0106]



[0107] iPr_2NEt (0.5 mL), HATU (182 mg) were added into the solution of 6-((6-((4-chlorobenzyl)amino)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)amino)nicotinic acid (200 mg) and N_1-(3-amino-2,2-dimethylpropyl)-N_2-(4-cyanophenyl)oxalamide hydrochloride (137 mg) in THF (20 mL). The reaction was stirred at room temperature for 24 hours. The solvents were removed under vaccum and the residue was purified by preparative HPLC system.

Compound **1020**	
MS (M+H)$^+$ Calcd.	710.2
MS (M+H)$^+$ Observ.	710.2
Retention Time	2.24 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0

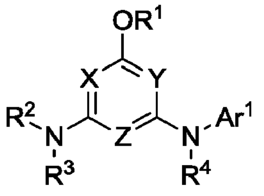
(continued)

LC Condition	
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

[0108] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning of the claims are therefore intended to be embraced therein.

Claims

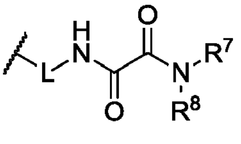
1. A compound of formula I



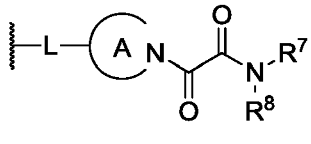
I

where

X and Y are N and Z is CH, Y and Z are N and X is CH; or X and Z are N and Y is CH;
R^1 is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl, hydroxycycloalkyl, alkoxycycloalkyl, halocycloalkyl, cycloalkenyl, indanyl, alkylcarbonyl, or benzyl wherein the benzyl moiety is substituted with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;
R^2 is alkyl, (Ar^2)alkyl, (Ar^2)cycloalkyl, ((Ar^2)cycloalkyl)alkyl, ((Ar^2)alkyl)cycloalkyl, or (((Ar^2)alkyl)cycloalkyl)alkyl;
R^3 is hydrogen or alkyl;
R^4 is hydrogen or alkyl;
R^5 is



or



where ring A is a 4 to 7 membered alkylene ring substituted with L;
R^6 is hydrogen or alkyl;
R^7 is hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, (alkyl)cycloalkyl, ((alkyl))cycloalkyl)alkyl, a bridged bicycloalkyl, or Ar^3, and is substituted with 0-4 substituents selected from the group consisting of halo, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, hydroxy, alkoxy, benzyloxy, CO$_2$R^9, N(R^{10})(R^{11}), tetrahydrofuranyl, tetrahydropyranyl, and Ar^4;
R^8 is hydrogen or alkyl;
or R^7 and R^8 taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl,

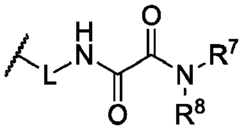
piperazinyl, morpholinyl, or tetrahydroisoquinolinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;
R^9 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, ((hydroxyalkyl)alkoxy)alkoxy, or ((alkoxy)alkoxy)alkoxy;
R^{10} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl;
R^{11} is hydrogen or alkyl;
or R^{10} and R^{11} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;
R^{12} is hydrogen or alkyl;
R^{13} is hydrogen, alkyl, cycloalkyl, alkylcarbonyl, or alkoxycarbonyl;
R^{14} is hydrogen or alkyl;
or R^{13} and R^{14} taken together with the nitrogen to which they are attached is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, and is substituted with 0-2 substituents selected from alkyl, alkylcarbonyl, and alkoxycarbonyl;
L is alkylene, cycloalkylene, (cycloalkyl)alkyl, (alkyl)cycloalkyl, or alkyl(cycloalkyl)alkyl, and is substituted with 0-2 substituents selected from alkoxy, hydroxy, CO_2R^{12} and $CONR^{13}R^{14}$;

Ar^1 is phenyl, pyridinyl or pyrimidinyl, and is substituted with 1 $CON(R^5)(R^6)$ and with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;
Ar^2 is phenyl substituted with 0-3 substituents selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;
Ar^3 is phenyl, indanyl, fluorenyl, biphenyl, terphenyl, pyridinyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, benzoxazolyl, indolinyl, or dibenzofuranyl, and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkenyl, haloalkyl, cycloalkyl, (CO_2R^{12})alkyl, (CO_2R^{12})alkenyl, $(CON(R^{13})(R^{14}))$alkyl, phenyl, hydroxyl, alkoxy, haloalkoxy, alkylcarbonyl, CO_2R^{12}, and $CON(R^{13})(R^{14})$;
or Ar^3 is phenyl substituted with 1 substituent selected from benzyl, tetrazolyloxy, thiazolyl, phenylpyrazolyl, methyloxadiazolyl, thiadiazolyl, triazolyl, methyltriazolyl, tetrazolyl, pyridinyl, and dimethoxypyrimdinyl; and
Ar^4 is phenyl, indanyl, tetrahydronaphthyl, isochromanyl, benzodioxolyl, pyridinyl, pyrazolyl, imidazolyl, or triazolyl and is substituted with 0-3 substituents selected from cyano, halo, alkyl, alkyenyl, haloalkyl, alkoxy, and haloalkoxy, $N(R^{13})(R^{14})$, and alkylCO;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where

X and Y are N and Z is CH;
R^1 is haloalkyl;
R^2 is (Ar^2)alkyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 is



;

R^6 is hydrogen or alkyl;

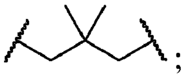
R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3;
R^8 is hydrogen or alkyl;
or R^7 and R^8 taken together with the nitrogen to which they are attached is piperidinyl, morpholinyl, or tetrahydroisoquinolinyl;
L is alkylene;

Ar^1 is pyridinyl substituted with 1 $CON(R^5)(R^6)$;
Ar^2 is phenyl substituted with 0-3 halo substituents; and

Ar^3 is phenyl, isoxazolyl, thiazolyl, or thiadiazolyl, and is substituted with 0-3 substituents selected from cyano, halo, alkyl, haloalkyl, alkoxy, and haloalkoxy;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 where R^1 is haloalkyl; R^2 is (Ar^2)alkyl; R^3 is hydrogen; R^4 is hydrogen; R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3; L is



Ar^1 is phenyl substituted with 1 $CON(R^5)(R^6)$; Ar^2 is phenyl substituted with 1 halo; and Ar^3 is phenyl, isoxazolyl, thiazolyl, or thiadiazolyl, and is substituted with 0-1 substituents selected from cyano, halo, and alkyl; or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 where R^1 is haloalkyl or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 where R^1 is trifluroethyl or a pharmaceutically acceptable salt thereof.

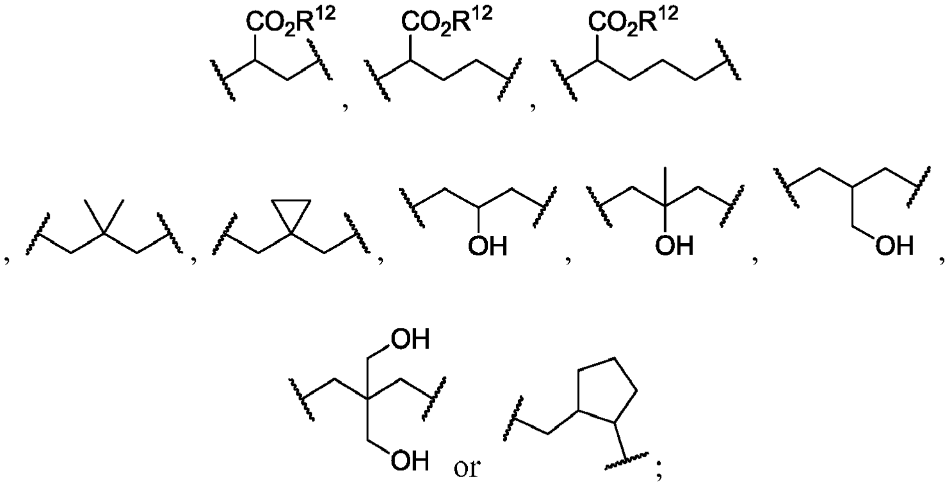
6. A compound of claim 1 where R^2 is (Ar^2)alkyl or (Ar^2)cycloalkyl, or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1 where R^3 is hydrogen and R^4 is hydrogen, or a pharmaceutically acceptable salt thereof.

8. A compound of claim 1 where R^7 is hydrogen, alkyl, cycloalkyl, or Ar^3; R^8 is hydrogen or alkyl; or R^7 and R^8 taken together with the nitrogen to which they are attached is piperidinyl, morpholinyl, or tetrahydroisoquinolinyl; or a pharmaceutically acceptable salt thereof.

9. A compound of claim 1 where R^7 is Ar^3 or a pharmaceutically acceptable salt thereof.

10. A compound of claim 1 where L is



or a pharmaceutically acceptable salt thereof.

11. A compound of claim 1 where Ar^1 is pyridinyl substituted with 1 $CON(R^5)(R^6)$, or a pharmaceutically acceptable salt thereof.

12. A composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. The composition of claim 12 further comprising at least one additional compound having therapeutic benefits for

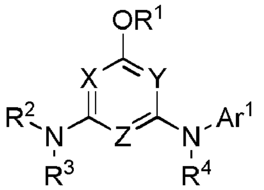
HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

14. A compound of any one of claims 1 to 11 for use in a method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.

15. The compound for the use in the method of claim 14 further comprising administering at least one additional compound having therapeutic benefits for HCV wherein the compound is selected from the group consisting of interferons, cyclosporins, interleukins, HCV metalloprotease inhibitors, HCV serine protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, HCV NS4B protein inhibitors, HCV entry inhibitors, HCV assembly inhibitors, HCV egress inhibitors, HCV NS5A protein inhibitors, HCV NS5B protein inhibitors, and HCV replicon inhibitors.

Patentansprüche

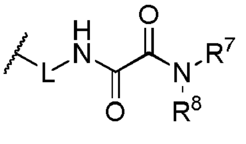
1. Verbindung der Formel I



I

worin:

X und Y N sind und Z CH ist, Y und Z N sind und X CH ist; oder X und Z N sind und Y CH ist;
R^1 Alkyl, Hydroxyalkyl, Alkoxyalkyl, Halogenalkyl, Cycloalkyl, Hydroxycycloalkyl, Alkoxycycloalkyl, Halogencycloalkyl, Cycloalkenyl, Indanyl, Alkylcarbonyl oder Benzyl ist, worin der Benzyl-Teil substituiert ist mit 0 bis 3 Substituenten, ausgewählt aus Halogen, Alkyl, Halogenalkyl, Alkoxy, und Halogenalkoxy;
R^2 Alkyl, (Ar^2)Alkyl, (Ar^2)Cycloalkyl, ((Ar^2)Cycloalkyl)alkyl, ((Ar^2)Alkyl)cycloalkyl oder (((Ar^2)Alkyl)cycloalkyl)alkyl ist;
R^3 Wasserstoff oder Alkyl ist;
R^4 Wasserstoff oder Alkyl ist;
R^5



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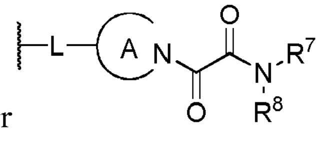


ist, worin Ring A ein 4- bis 7-gliedriger Alkylenring ist, der substituiert ist mit L;
R^6 Wasserstoff oder Alkyl ist;
R^7 Wasserstoff, Alkyl, Cycloalkyl, (Cycloalkyl)alkyl, (Alkyl)cycloalkyl, ((Alkyl)cycloalkyl)alkyl, ein verbrücktes Bicycloalkyl oder Ar^3 ist und substituiert ist mit 0 bis 4 Substituenten, ausgewählt aus Halogen, Alkyl, Cycloalkyl, Hydroxyalkyl, Alkoxyalkyl, Hydroxy, Alkoxy, Benzyloxy, CO_2R^9, $N(R^{10})(R^{11})$, Tetrahydrofuranyl, Tetrahydropyranyl und Ar^4;
R^8 Wasserstoff oder Alkyl ist;
oder R^7 und R^8, zusammengenommen mit dem Stickstoff, an den sie gebunden sind, Azetidinyl, Pyrrolidinyl, Piperidinyl, Piperazinyl, Morpholinyl oder Tetrahydroisochinolinyl sind und substituiert sind mit 0 bis 2 Substituenten, ausgewählt aus Alkyl, Alkylcarbonyl und Alkoxycarbonyl;
R^9 Wasserstoff, Alkyl, Hydroxyalkyl, Alkoxyalkyl, ((Hydroxyalkyl)alkoxy)alkoxy oder ((Alkoxy)alkoxy)alkoxy ist;

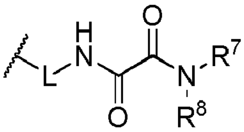
R^{10} Wasserstoff, Alkyl, Cycloalkyl, Alkylcarbonyl oder Alkoxycarbonyl ist;
R^{11} Wasserstoff oder Alkyl ist;
oder R^{10} und R^{11}, zusammengenommen mit dem Stickstoff, an den sie gebunden sind, Azetidinyl, Pyrrolidinyl, Piperidinyl, Piperazinyl, oder Morpholinyl sind und substituiert sind mit 0 bis 2 Substituenten, ausgewählt aus Alkyl, Alkylcarbonyl, und Alkoxycarbonyl;
R^{12} Wasserstoff oder Alkyl ist;
R^{13} Wasserstoff, Alkyl, Cycloalkyl, Alkylcarbonyl oder Alkoxycarbonyl ist;
R^{14} Wasserstoff oder Alkyl ist;
oder R^{13} und R^{14}, zusammengenommen mit dem Stickstoff, an den sie gebunden sind, Azetidinyl, Pyrrolidinyl, Piperidinyl, Piperazinyl oder Morpholinyl sind und substituiert sind mit 0 bis 2 Substituenten, ausgewählt aus Alkyl, Alkylcarbonyl und Alkoxycarbonyl;
L Alkylen, Cycloalkylen, (Cycloalkyl)alkyl, (Alkyl)cycloalkyl oder Alkyl(cycloalkyl)alkyl ist und substituiert ist mit 0 bis 2 Substituenten, ausgewählt aus Alkoxy, Hydroxy, CO_2R^{12} und $CONR^{13}R^{14}$;

Ar^1 Phenyl, Pyridinyl oder Pyrimidinyl ist und substituiert ist mit 1 $CON(R^5)(R^6)$ und mit 0 bis 3 Substituenten, ausgewählt aus Halogen, Alkyl, Halogenalkyl, Alkoxy und Halogenalkoxy;
Ar^2 Phenyl ist, substituiert mit 0 bis 3 Substituenten, ausgewählt aus Halogen, Alkyl, Halogenalkyl, Alkoxy und Halogenalkoxy;
Ar^3 Phenyl, Indanyl, Fluorenyl, Biphenyl, Terphenyl, Pyridinyl, Pyrazolyl, Isoxazolyl, Isothiazolyl, Imidazolyl, Oxazolyl, Thiazolyl, Triazolyl, Oxadiazolyl, Thiadiazolyl, Benzoxazolyl, Indolinyl oder Dibenzofuranyl ist und substituiert ist mit 0 bis 3 Substituenten, ausgewählt aus Cyano, Halogen, Alkyl, Alkenyl, Halogenalkyl, Cycloalkyl, (CO_2R^{12})Alkyl, (CO_2R^{12})Alkenyl, $(CON(R^{13})(R^{14}))$Alkyl, Phenyl, Hydroxyl, Alkoxy, Halogenalkoxy, Alkylcarbonyl, CO_2R^{12} und $CON(R^{13})(R^{14})$;
oder Ar^3 Phenyl ist, substituiert mit 1 Substituenten, ausgewählt aus Benzyl, Tetrazolyloxy, Thiazolyl, Phenylpyrazolyl, Methyloxadiazolyl, Thiadiazolyl, Triazolyl, Methyltriazolyl, Tetrazolyl, Pyridinyl und Dimethoxypyrimdinyl; und
Ar^4 Phenyl, Indanyl, Tetrahydronaphthyl, Isochromanyl, Benzodioxolyl, Pyridinyl, Pyrazolyl, Imidazolyl oder Triazolyl ist und substituiert ist mit 0 bis 3 Substituenten, ausgewählt aus Cyano, Halogen, Alkyl, Alkyenyl, Halogenalkyl, Alkoxy und Halogenalkoxy, $N(R^{13})(R^{14})$ und AlkylCO;

oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, worin:

X und Y N sind und Z CH ist;
R^1 Halogenalkyl ist;
R^2 (Ar^2)alkyl ist;
R^3 Wasserstoff ist;
R^4 Wasserstoff ist;
R^5



ist;
R^6 Wasserstoff oder Alkyl ist;

R^7 Wasserstoff, Alkyl, Cycloalkyl oder Ar^3 ist;
R^8 Wasserstoff oder Alkyl ist;
oder R^7 und R^8, zusammengenommen mit dem Stickstoff, an den sie gebunden sind, Piperidinyl, Morpholinyl, oder Tetrahydroisochinolinyl sind;
L Alkylen ist;

Ar^1 Pyridinyl ist, substituiert mit 1 $CON(R^5)(R^6)$;
Ar^2 Phenyl ist, substituiert mit 0 bis 3 Halogen-Substituenten; und

Ar^3 Phenyl, Isoxazolyl, Thiazolyl oder Thiadiazolyl ist und substituiert ist mit 0 bis 3 Substituenten, ausgewählt aus Cyano, Halogen, Alkyl, Halogenalkyl, Alkoxy und Halogenalkoxy;

oder ein pharmazeutisch verträgliches Salz davon.

3. Verbindung nach Anspruch 1, wobei R^1 Halogenalkyl ist; R^2 (Ar^2)Alkyl ist; R^3 Wasserstoff ist; R^4 Wasserstoff ist; R^7 Wasserstoff, Alkyl, Cycloalkyl oder Ar^3 ist; L

ist; Ar^1 Phenyl ist, substituiert mit 1 CON(R^5)(R^6); Ar^2 Phenyl ist, substituiert mit 1 Halogen; und Ar^3 Phenyl, Isoxazolyl, Thiazolyl oder Thiadiazolyl ist und substituiert ist mit 0 bis 1 Substituenten, ausgewählt aus Cyano, Halogen und Alkyl; oder ein pharmazeutisch verträgliches Salz davon.

4. Verbindung nach Anspruch 1, wobei R^1 Halogenalkyl ist oder ein pharmazeutisch verträgliches Salz davon.

5. Verbindung nach Anspruch 1, wobei R^1 Trifluorethyl ist oder ein pharmazeutisch verträgliches Salz davon.

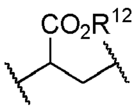
6. Verbindung nach Anspruch 1, wobei R^2 (Ar^2)Alkyl oder (Ar^2)Cycloalkyl ist oder ein pharmazeutisch verträgliches Salz davon.

7. Verbindung nach Anspruch 1, wobei R^3 Wasserstoff ist und R^4 Wasserstoff ist oder ein pharmazeutisch verträgliches Salz davon.

8. Verbindung nach Anspruch 1, wobei R^7 Wasserstoff, Alkyl, Cycloalkyl, oder Ar^3 ist; R^8 Wasserstoff oder Alkyl ist oder R^7 und R^8, zusammengenommen mit dem Stickstoff, an den sie gebunden sind, Piperidinyl, Morpholinyl oder Tetrahydroisochinolinyl sind; oder ein pharmazeutisch verträgliches Salz davon.

9. Verbindung nach Anspruch 1, wobei R^7 Ar^3 ist oder ein pharmazeutisch verträgliches Salz davon.

10. Verbindung nach Anspruch 1, wobei L



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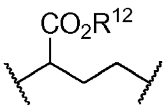

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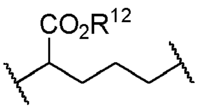

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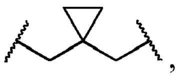
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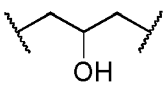

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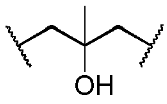

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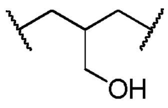

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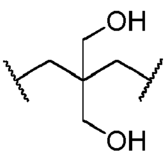

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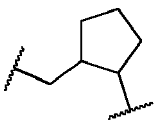


ist oder ein pharmazeutisch verträgliches Salz davon.

11. Verbindung nach Anspruch 1, wobei Ar^1 Pyridinyl ist, substituiert mit 1 CON(R^5)(R^6), oder ein pharmazeutisch verträgliches Salz davon.

12. Zusammensetzung, aufweisend eine Verbindung nach einem der Ansprüche 1 bis 11, oder ein pharmazeutisch verträgliches Salz davon und ein pharmazeutisch verträglicher Träger.

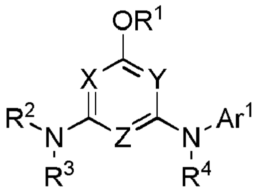
13. Zusammensetzung nach Anspruch 12, ferner aufweisend mindestens eine zusätzliche Verbindung mit therapeutischem Nutzen für HCV, wobei die Verbindung ausgewählt ist aus Interferonen, Cyclosporinen, Interleukinen, HCV-Metalloprotease-Inhibitoren, HCV-Serin-Protease-Inhibitoren, HCV-Polymerase-Inhibitoren, HCV-Helicase-Inhibitoren, HCV-NS4B-Protein-Inhibitoren, HCV-Entry-Inhibitoren, HCV-Assembly-Inhibitoren, HCV-Egress-Inhibitoren, HCV-NS5A-Protein-Inhibitoren, HCV-NS5B-Protein-Inhibitoren und HCV-Replikon-Inhibitoren.

14. Verbindung nach einem der Ansprüche 1 bis 11 zur Verwendung in einem Verfahren zur Behandlung von Hepatitis C-Infektion, umfassend Verabreichen einer therapeutisch wirksamen Menge einer Verbindung nach Anspruch 1 an einen Patienten.

15. Verbindung zur Verwendung in dem Verfahren nach Anspruch 14, ferner umfassend Verabreichen von mindestens einer zusätzlichen Verbindung mit therapeutischem Nutzen für HCV, wobei die Verbindung ausgewählt ist aus Interferonen, Cyclosporinen, Interleukinen, HCV-Metalloprotease-Inhibitoren, HCV-Serinprotease-Inhibitoren, HCV-Polymerase-Inhibitoren, HCV-Helicase-Inhibitoren, HCV-NS4B-Protein-Inhibitoren, HCV-Entry-Inhibitoren, HCV-Assembly-Inhibitoren, HCV-Egress-Inhibitoren, HCV-NS5A-Protein-Inhibitoren, HCV-NS5B-Protein-Inhibitoren und HCV-Replikon-Inhibitoren.

Revendications

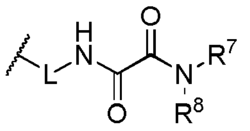
1. Composé de formule 1



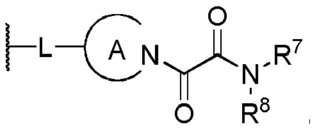
I

où

X et Y sont N et Z est CH, Y et Z sont N et X est CH; ou X et Z sont N et Y est CH;
R^1 est alkyle, hydroxyalkyle, alcoxyalkyle, halogénoalkyle, cycloalkyle, hydroxycycloalkyle, alcoxycycloalkyle, halogénocycloalkyle, cycloalcényle, indanyle, alkylcarbonyle, ou benzyle où le groupement benzyle est substitué par 0-3 substituants choisis parmi halogéno, alkyle, halogénoalkyle, alcoxy, et halogénoalcoxy;
R^2 est alkyle, (Ar^2)alkyle, (Ar^2)cycloalkyle, $((Ar^2)$cycloalkyl)alkyle, $((Ar^2)$alkyl)cycloalkyle, ou $(((Ar^2)$alkyl)cycloalkyl)alkyle;
R^3 est hydrogène ou alkyle;
R^4 est hydrogène ou alkyle;
R^5 est



ou



où le cycle A est un cycle alkylène à 4 à 7 chaînons substitué par L;
R^6 est hydrogène ou alkyle;
R^7 est hydrogène, alkyle, cycloalkyle, (cycloalkyl)alkyle, (alkyl)cycloalkyle, ((alkyl))cycloalkyl)alkyle, un bicycloalkyle ponté, ou Ar^3, et est substitué par 0-4 substituants choisis dans le groupe constitué par halogéno, alkyle, cycloalkyle, hydroxyalkyle, alcoxyalkyle, hydroxy, alcoxy, benzyloxy, CO_2R^9, $N(R^{10})(R^{11})$, tétrahydrofuranyle, tétrahydropyranyle, et Ar^4;
R^8 est hydrogène ou alkyle;
ou R^7 et R^8, pris ensemble avec l'azote auquel ils sont attachés, sont azétidinyle, pyrrolidinyle, pipéridinyle, pipérazinyle, morpholinyle, ou tétrahydroisoquinolinyle, et sont substitués par 0-2 substituants choisis parmi

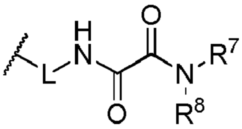
alkyle, alkylcarbonyle, et alcoxycarbonyle;
R^9 est hydrogène, alkyle, hydroxyalkyle, alcoxyalkyle, ((hydroxyalkyl)alcoxy)alcoxy, ou ((alcoxy)alcoxy)alcoxy;
R^{10} est hydrogène, alkyle, cycloalkyle, alkylcarbonyle, ou alcoxycarbonyle;
R^{11} est hydrogène ou alkyle;
ou R^{10} et R^{11}, pris ensemble avec l'azote auquel ils sont attachés, sont azétidinyle, pyrrolidinyle, pipéridinyle, pipérazinyle, ou morpholinyle, et sont substitués par 0-2 substituants choisis parmi alkyle, alkylcarbonyle, et alcoxycarbonyle;
R^{12} est hydrogène ou alkyle;
R^{13} est hydrogène, alkyle, cycloalkyle, alkylcarbonyle, ou alcoxycarbonyle;
R^{14} est hydrogène ou alkyle;
ou R^{13} et R^{14}, pris ensemble avec l'azote auquel ils sont attachés, sont azétidinyle, pyrrolidinyle, pipéridinyle, pipérazinyle, ou morpholinyle, et sont substitués par 0-2 substituants choisis parmi alkyle, alkylcarbonyle, et alcoxycarbonyle;
L est alkylène, cycloalkylène, (cycloalkyl)alkyle, (alkyl)cyclo alkyle, ou alkyl(cycloalkyl)alkyle, et est substitué par 0-2 substituants choisis parmi alcoxy, hydroxy, CO_2R^{12} et $CONR^{13}R^{14}$;

Ar^1 est phényle, pyridinyle ou pyrimidinyle, et est substitué par 1 $CON(R^5)(R^6)$ et par 0-3 substituants choisis parmi halogéno, alkyle, halogénoalkyle, alcoxy, et halogénoalcoxy;
Ar^2 est phényle substitué par 0-3 substituants choisis parmi halogéno, alkyle, halogénoalkyle, alcoxy, et halogénoalcoxy;
Ar^3 est phényle, indanyle, fluorényle, biphényle, terphényle, pyridinyle, pyrazolyle, isoxazolyle, isothiazolyle, imidazolyle, oxazolyle, thiazolyle, triazolyle, oxadiazolyle, thiadiazolyle, benzoxazolyle, indolinyle, ou dibenzofuranyle, et est substitué par 0-3 substituants choisis parmi cyano, halogéno, alkyle, alcényle, halogénoalkyle, cycloalkyle, (CO_2R^{12})alkyle, (CO_2R^{12})alcényle, $(CON(R^{13})(R^{14}))$alkyle, phényle, hydroxyle, alcoxy, halogénoalcoxy, alkylcarbonyle, CO_2R^{12}, et $CON(R^{13})(R^{14})$;
ou Ar^3 est phényle substitué par 1 substituant choisi parmi benzyle, tétrazolyloxy, thiazolyle, phénylpyrazolyle, méthyloxadiazolyle, thiadiazolyle, triazolyle, méthyltriazolyle, tétrazolyle, pyridinyle, et diméthoxypyrimdinyle; et
Ar^4 est phényle, indanyle, tétrahydronaphtyle, isochromanyle, benzodioxolyle, pyridinyle, pyrazolyle, imidazolyle, ou triazolyle et est substitué par 0-3 substituants choisis parmi cyano, halogéno, alkyle, alkyényle, halogénoalkyle, alcoxy, et halogénoalcoxy, $N(R^{13})(R^{14})$, et alkylCO;

ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, dans lequel

X et Y sont N et Z est CH;
R^1 est halogénoalkyle;
R^2 est (Ar^2)alkyle;
R^3 est hydrogène;
R^4 est hydrogène;
R^5 est



;

R^6 est hydrogène ou alkyle;

R^7 est hydrogène, alkyle, cycloalkyle, ou Ar^3;
R^8 est hydrogène ou alkyle;
ou R^7 et R^8, pris ensemble avec l'azote auquel ils sont attachés, sont pipéridinyle, morpholinyle, ou tétrahydroisoquinolinyle;
L est alkylène;

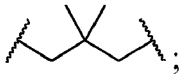
Ar^1 est pyridinyle substitué par 1 $CON(R^5)(R^6)$;

Ar^2 est phényle substitué par 0-3 substituants halogéno; et

Ar^3 est phényle, isoxazolyle, thiazolyle, ou thiadiazolyle, et est substitué par 0-3 substituants choisis parmi cyano, halogéno, alkyle, halogénoalkyle, alcoxy, et halogénoalcoxy;

ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 1, dans lequel R^1 est halogénoalkyle; R^2 est (Ar^2)alkyle; R^3 est hydrogène; R^4 est hydrogène; R^7 est hydrogène, alkyle, cycloalkyle, ou Ar^3; L est



;

Ar^1 est phényle substitué par 1 CON(R^5)(R^6); Ar^2 est phényle substitué par 1 halogéno; et Ar^3 est phényle, isoxazolyle, thiazolyle, ou thiadiazolyle, et est substitué par 0-1 substituant choisi parmi cyano, halogéno, et alkyle; ou un sel pharmaceutiquement acceptable de celui-ci.

4. Composé selon la revendication 1, dans lequel R^1 est halogénoalkyle, ou un sel pharmaceutiquement acceptable de celui-ci.

5. Composé selon la revendication 1, dans lequel R^1 est trifluroéthyle, ou un sel pharmaceutiquement acceptable de celui-ci.

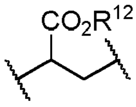
6. Composé selon la revendication 1, dans lequel R^2 est (Ar^2)alkyle ou (Ar^2)cycloalkyle, ou sel pharmaceutiquement acceptable de celui-ci.

7. Composé selon la revendication 1, dans lequel R^3 est hydrogène et R^4 est hydrogène, ou un sel pharmaceutiquement acceptable de celui-ci.

8. Composé selon la revendication 1, dans lequel R^7 est hydrogène, alkyle, cycloalkyle, ou Ar^3; R^8 est hydrogène ou alkyle; ou R^7 et R^8, pris ensemble avec l'azote auquel ils sont attachés, sont pipéridinyle, morpholinyle, ou tétrahydroisoquinolinyle; ou un sel pharmaceutiquement acceptable de celui-ci.

9. Composé selon la revendication 1, dans lequel R^7 est Ar^3, ou sel pharmaceutiquement acceptable de celui-ci.

10. Composé selon la revendication 1, dans lequel L est



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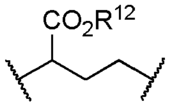

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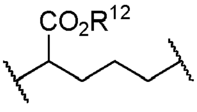

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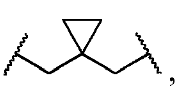

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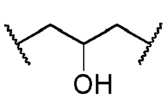

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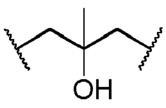

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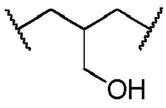

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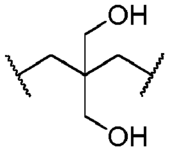

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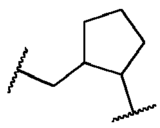

;

ou sel pharmaceutiquement acceptable de celui-ci.

11. Composé selon la revendication 1, dans lequel Ar^1 est pyridinyle substitué par 1 CON(R^5)(R^6), ou un sel pharmaceutiquement acceptable de celui-ci.

12. Composition comprenant un composé selon l'une quelconque des revendications 1 à 11, ou un sel pharmaceutiquement acceptable de celui-ci, et un véhicule pharmaceutiquement acceptable.

13. Composition selon la revendication 12, comprenant en outre au moins un composé supplémentaire ayant des bénéfices thérapeutiques contre le VHC, lequel composé est choisi dans le groupe constitué par les interférons, les cyclosporines, les interleukines, les inhibiteurs de métalloprotéase du VHC, les inhibiteurs de sérine protéase du VHC, les inhibiteurs de polymérase du VHC, les inhibiteurs d'hélicase du VHC, les inhibiteurs de la protéine NS4B du VHC, les inhibiteurs d'entrée du VHC, les inhibiteurs d'assemblage du VHC, les inhibiteurs de sortie du VHC, les inhibiteurs de la protéine NS5A du VHC, les inhibiteurs de la protéine NS5B du VHC et les inhibiteurs des réplicons du VHC.

14. Composé selon l'une quelconque des revendications 1 à 11, pour l'utilisation dans un procédé de traitement d'une infection par hépatite C comprenant l'administration d'une quantité thérapeutiquement efficace d'un composé selon la revendication 1 à un patient.

15. Composé pour l'utilisation dans le procédé selon la revendication 14, comprenant en outre l'administration d'au moins un composé supplémentaire ayant des bénéfices thérapeutiques contre le VHC, lequel composé est choisi dans le groupe constitué par les interférons, les cyclosporines, les interleukines, les inhibiteurs de métalloprotéase du VHC, les inhibiteurs de sérine protéase du VHC, les inhibiteurs de polymérase du VHC, les inhibiteurs d'hélicase du VHC, les inhibiteurs de la protéine NS4B du VHC, les inhibiteurs d'entrée du VHC, les inhibiteurs d'assemblage du VHC, les inhibiteurs de sortie du VHC, les inhibiteurs de la protéine NS5A du VHC, les inhibiteurs de la protéine NS5B du VHC et les inhibiteurs des réplicons du VHC.

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