

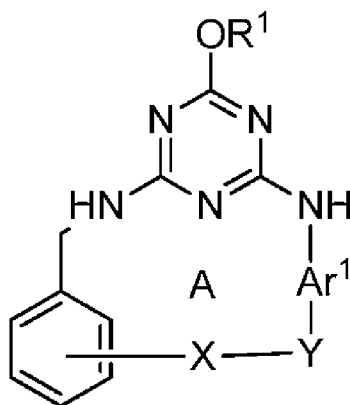


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(54) Title: MACROCYCLIC TRIAZINE COMPOUNDS FOR THE TREATMENT OF HEPATITIS C



I

(57) Abstract: The disclosure provides compounds of formula I, including pharmaceutically acceptable salts, as well as compositions and methods of using compounds for the treatment of hepatitis C the compounds. The compounds have activity against hepatitis C virus (HCV) and may be useful in treating those infected with HCV.



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MACROCYCLIC TRIAZINE COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 This patent application claims the benefit of U.S. provisional patent application no. 61/475,484 filed April 14, 2011.

BACKGROUND OF THE INVENTION

- 10 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.

- 15 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
20 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
25 is not completely understood.

- 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
30 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.

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.

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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

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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
5 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.

10 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
15 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.

Other systems have been used to study the biology of the HCV structural
20 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
25 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
30 inhibitors block this process.

Recently, a full-length genotype 2a HCV clone, JFH1, was isolated and demonstrated the ability to replicate *in vitro*. Through repeated passage and

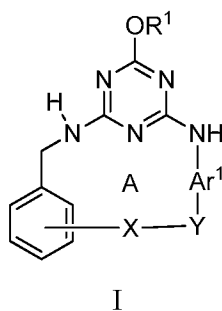
adaptation in cell culture increased titers of infectious virus were produced
 (Lindenbach, B. D., et al. *Science*. **2005**, 309:623-626; Wakita, T. et al. *Nature Med.*
2005, 11:791-796). In contrast to the HCV replicon or pseudotyping systems, the
 infectious virus is useful for studying the complete HCV replication cycle, including
 5 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).

Triazines have been disclosed. See WO 2009/091388 and US 2009/0286778.
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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
 15 profiles, or bioavailability.

DESCRIPTION OF THE INVENTION

One aspect of the invention is a compound of formula I
 20



where

25 R¹ is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl, hydroxycycloalkyl,
 alkoxycycloalkyl, halocycloalkyl, cycloalkenyl, benzyl, indanyl, or alkylcarbonyl;

R² is hydrogen, alkyl, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl,
 alkylaminocarbonyl, or dialkylaminocarbonyl;

R³ is hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, or dialkylaminocarbonyl;

R⁴ is hydrogen or alkyl;

5

Ar¹ is pyridindiyl, pyrimidindiyl, pyrazindiyl, pyridazindiyl, pyrazoldiyl, or imidazoldiyl;

X is O or NR²;

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Y is an alkylene or alkenylene chain containing 0-6 groups selected from the group consisting of O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, NR⁴C(NR¹²)NR⁴, and Z, provided that O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, and NR⁴C(NR¹²)NR⁴ do not directly bond to each other, such that ring

15 A is 14-36 membered; and where the alkylene or alkenylene chain is substituted with 0-6 alkyl substituents; and

Z is C₃₋₇cycloalkylene or phenylene;

20 or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where R¹ is haloalkyl; R² is hydrogen; R³ is hydrogen; R⁴ is hydrogen; Ar¹ is pyridindiyl, pyrimidindiyl, or pyrazoldiyl; X is O or NR²; Y is an alkylene or alkenylene chain
25 containing 0-6 groups selected from the group consisting of O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, NR⁴C(NR¹²)NR⁴, and Z, provided that O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, and NR⁴C(NR¹²)NR⁴ do not directly bond to each other, such that ring A is 14-36 membered; and where the alkylene or alkenylene chain is substituted with 0-6 alkyl substituents; and Z is
30 phenylene; or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is a compound of formula I where R¹ is haloalkyl.

Another aspect of the invention is a compound of formula I where R¹ is trifluoroethyl.

Another aspect of the invention is a compound of formula I where Ar¹ is
5 pyridindiyl, pyrimidindiyl, or pyrazoldiyl.

Another aspect of the invention is a compound of formula I where Ar¹ is pyridindiyl.

10 Another aspect of the invention is a compound of formula I where Ar¹ is pyrimidindiyl.

Another aspect of the invention is a compound of formula I where Ar¹ is pyrazoldiyl.

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Another aspect of the invention is a compound of formula I where X is O.

Another aspect of the invention is a compound of formula I where X is NR².

20 Another aspect of the invention is a compound of formula I where Y is an alkylene or alkenylene chain containing 0-6 groups selected from the group consisting of O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, NR⁴C(NR¹²)NR⁴, and Z, provided that O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, and NR⁴C(NR¹²)NR⁴ do not directly bond to each other, such that ring
25 A is 14-36 membered; and where the alkylene or alkenylene chain is substituted with 0-6 alkyl substituents.

Any scope of any variable, including R¹, R², R³, R⁴, Ar¹, X, Y, and Z, can be used independently with the scope of any other instance of a variable.

30

Unless specified otherwise, these terms have the following meanings.

“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 7 carbons. "Alkylene" means a straight or branched divalent alkyl group composed of 2 to 36 carbons. "Alkenylene" means a straight or branched divalent alkyl group composed of 2 to 36 carbons with at least one double bond. For ring A, Y
5 is an alkylene or alkenylene chain with sufficient carbons and optionally other defined groups to form a 13-36 membered ring. "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). "Alkylidiny" means a divalent alkene substituent where the
10 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. "Halo" means fluor, chloro, bromo, or iodo. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic
15 and heterocyclic aromatic substituents. Phenylene is a divalent benzene ring. Ar¹ is a divalent heteroaryl ring with respect to forming ring A as in formula I. Parenthetical and multiparenthetical 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.

20

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
25 the present disclosure are those that are suitably stable for use as a pharmaceutical agent.

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do
30 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, glucouurate, 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, 5 diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

Some of the compounds of the invention possess asymmetric carbon atoms (see, for example, the structures below). The invention includes all stereoisomeric 10 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 15 and tables is intended only to indicate relative stereochemistry, and should not be interpreted as implying absolute stereochemical assignments.

The invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number 20 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 25 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.

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Biological Methods

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 1×10^4 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.

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 μ M 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 EC₅₀ values (reflecting the concentration at which 50% inhibition of virus replication was achieved) were calculated. Compound EC₅₀ data is expressed as A: = 0.10-500 nM; B = 500-5000 nM; C = 5000-50000 nM). Representative data for compounds are reported in Table 1.

Table 1.

Ex.	Activity Range	EC ₅₀ (nM)
1002	B	2090.00
1004	C	
1006	C	
1008	B	
1009	C	8178.00
1012	C	
1013		
1014	B	
1016	B	
1017		
1018		
1019	C	
1021	A	
1022	C	
1023	C	
1024	B	
1025	B	
1027	C	
1028	A	205.10
1030	C	
1031	C	
1032	A	
1033	C	
1035	C	
1036	B	
1037	B	
1038	B	
1039	C	
1040	B	

Ex.	Activity Range	EC ₅₀ (nM)
2001		
2002	A	
2003		
2005		
2006	A	
2007	A	105.40
3001	A	
3002	A	134.00

Pharmaceutical Compositions and Methods of Treatment

The compounds demonstrate activity against HCV NS5B and can be useful in
 5 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.

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

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

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.

20 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, Imiquimod, ribavirin, an inosine 5'-
 25 monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

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
5 a nucleoside analog for the treatment of an HCV infection.

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.

10

Another aspect of the invention 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.

15

Another aspect of the invention 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.

Another aspect of the invention is a method of treating an HCV infection in a
20 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.

25

Another aspect of the invention 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.

30

Another aspect of the invention is the method where the other compound having anti-HCV activity is an interferon.

Another aspect of the invention is the method where the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

5 Another aspect of the invention is the method where the other compound having anti-HCV activity is a cyclosporin.

Another aspect of the invention is the method where the cyclosporin is cyclosporin A.

10

Another aspect of the invention 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, Imiquimod, ribavirin, an inosine 5'-monophosphate

15

Another aspect of the invention 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.

20

Another aspect of the invention is the method where the other compound

25 having anti-HCV activity is effective to inhibit the function of target in the HCV life cycle other than the HCV NS5B protein.

25

“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.

30

“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.

“Treatment,” “therapy,” “regimen,” “HCV infection,” and related terms are used as understood by practitioners in the field of hepatitis and HCV infection.

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, lozenges, 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.

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.

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.

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.

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.

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

Table 2.

Brand Name	Type of Inhibitor or Target	Source Company
Omega IFN	IFN- ω	Intarcia Therapeutics
BILN-2061	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
Summetrel	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
Roferon A	IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys	PEGylated IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ribavirin	PEGylated IFN- α 2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
CellCept	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Wellferon	lymphoblastoid IFN- α n1	GlaxoSmithKline plc, Uxbridge, UK

Brand Name	Type of Inhibitor or Target	Source Company
Albuferon - α	albumin IFN- α 2b	Human Genome Sciences Inc., Rockville, MD
Levovirin	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
IDN-6556	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
IP-501	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
Actimmune	INF- γ	InterMune Inc., Brisbane, CA
Infergen A	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
ISIS 14803	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
JTK-003	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Pegasys and Ceplene	PEGylated IFN- α 2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Ceplene	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Civacir	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

Brand Name	Type of Inhibitor or Target	Source Company
Intron A and Zadaxin	IFN- α 2b/ α 1-thymosin	RegeneRx Biopharmaceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Levovirin	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Viramidine	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
Intron A	IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron	PEGylated IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
Rebetron	IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Ribavirin	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	PEGylated IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	Type of Inhibitor or Target	Source Company
Zadazim	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Rebif	IFN- β 1a	Serono, Geneva, Switzerland
IFN- β and EMZ701	IFN- β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Batabulin (T67)	β -tubulin inhibitor	Tularik Inc., South San Francisco, CA
Merimepodib (VX-497)	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
Telaprevir (VX-950, LY-570310)	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
Omniferon	natural IFN- α	Viragen Inc., Plantation, FL
XTL-6865 (XTL-002)	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
HCV-796	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	NS5B Replicase Inhibitor	Gilead

Brand Name	Type of Inhibitor or Target	Source Company
PSI 6130	NS5B Replicase Inhibitor	Roche
R1626	NS5B Replicase Inhibitor	Roche
SCH 503034	serine protease inhibitor	Schering Plough
NIM811	Cyclophilin Inhibitor	Novartis
Suvus	Methylene blue	Bioenvision
Multiferon	Long lasting IFN	Viragen/Valentis
Actilon (CPG10101)	TLR9 agonist	Coley
Interferon- β	Interferon- β -1a	Serono
Zadaxin	Immunomodulator	Sciclone
Pyrazolopyrimidine compounds and salts From WO- 2005047288 26 May 2005	HCV Inhibitors	Arrow Therapeutics Ltd.
2'C Methyl adenosine	NS5B Replicase Inhibitor	Merck
GS-9132 (ACH-806)	HCV Inhibitor	Achillion / Gilead

Synthetic Methods

The compounds may be made by methods known in the art including those
 5 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
 10 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.

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; "Et₂O" 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 CF₃(CF₂)₃SO₂-; and "TMOF" for trimethylorthoformate.

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.

Chemistry Experimental (1000 series)

5

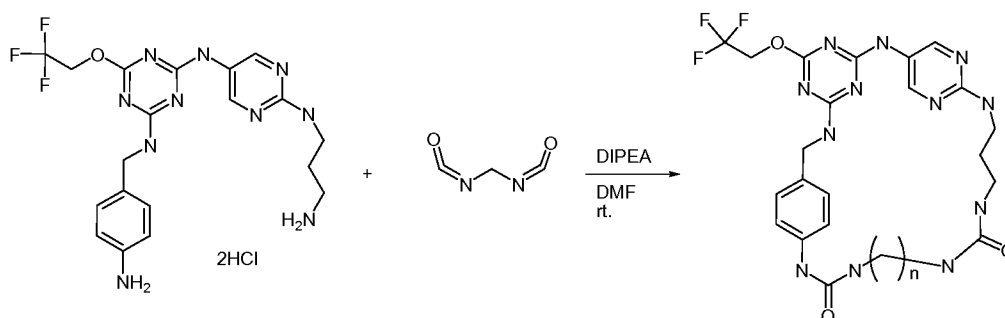
LC/MS Method (i.e., compound identification)

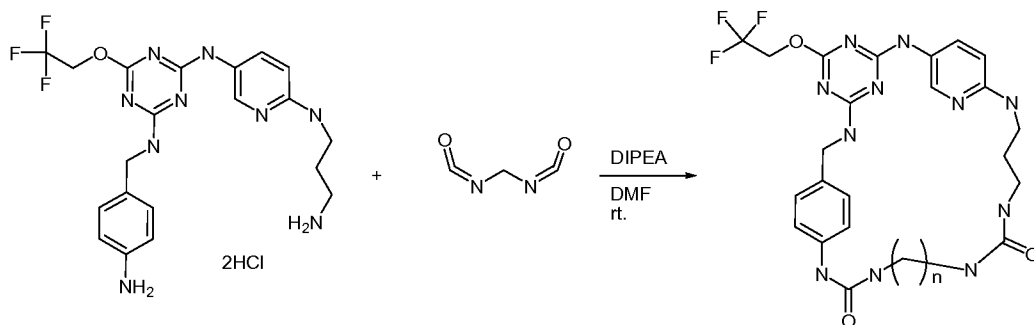
All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS or LC-20AS liquid chromatograph using a SPD-10AV or SPD-20A UV-Vis
10 detector and Mass Spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode.

HPLC Method (i.e., compound isolation)

15 Compounds purified by preparative HPLC were diluted in methanol (1.2 mL) and purified using a Shimadzu LC-8A or LC-10A automated preparative HPLC system.

*The general procedures below pertain to the experimental procedure for library
20 compounds: Compounds 1002 - 1012*





To the diamine core (50 mg, 1 eq.) was added pyridine (10 mL) and diisocyanates (1 eq.) and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was monitored by LCMS analysis. The crude product was purified by reverse phase preparative HPLC.

Prep. HPLC method:

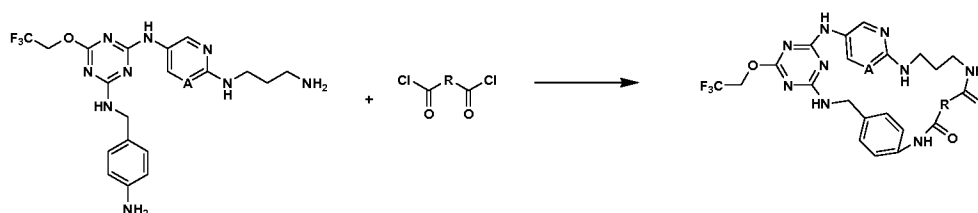
Column: Phenomenex Axia Luna C18, (250x 21.2) mm; 10 μ m
 10 Mobile Phase: 0.05% TFA in water / Acetonitrile
 Flow Rate: 15 mL/min.
 Gradient: 0-10 min; %B: 10-50

Analytical LCMS Method 1: Ascentis Express C18 4.6 x 50 mm, 2.7 μ m column; 4 min gradient from 0%B to 100%B; flow rate 4 mL/min; A = 5% AcN- 95% H₂O 10mM NH₄OAc, B = 95% AcN - 5% H₂O 10 mM NH₄OAc; UV detection at 220 nm; and a column heater set at 45° C.

Example	ass ⁺	RT(min)	Method
1002	33.2	1.790	Method 1
1004	61.4	1.993	Method 1

Example	ass ⁺	RT(min)	Method
1006	05.2	1.552	Method 1
1008	32.4	1.848	Method 1
1009	04.2	1.656	Method 1
1012	60.4	2.073	Method 1

General procedure for the following compounds:



- 5 A stock suspensions of the N2-(4-aminobenzyl)-N4-(2-(3-aminopropylamino)pyrimidin-5-yl)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine HCl salt (1.05 g) and the N2-(4-aminobenzyl)-N4-(6-(3-aminopropylamino)pyridin-3-yl)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine HCl salt (1.05 g) in DMF(21 mL) was prepared. iPr₂NEt (1.83 mL) was added to
- 10 each of these suspensions. To each of the bis acid chlorides weighed into 16x100 threaded Wheaton vials was added 6 mL of dichloroethane. To each of the acid

chlorides was added 1 mL of the appropriate diamine / iPr₂NEt suspension. Vials were capped and allowed to shake at 350 rpm on an Innova platform shaker at room temperature for 18 hours. Samples were blown down in the Zymark tabletop dryer at 40°C for 3 hours. 1 mL of DMF was added to each vial. Suspend contents were

5 vortexed well. Suspensions were applied to 6-ml silica SPE cartridges, eluting w/ 4 mls MeOH each, collecting into 16x100 mm culture tubes. Samples were blown down in the Zymark tabletop dryer at 40° C for 3 hours. 1 mL DMF was added to each vial. Contents were transferred to 96 well 25 µm filter plate collecting into a 96 well deep-well plate. Vials was rinsed and transferred to the appropriate wells of the

10 filter plate. 30 µL of contents was removed from each well and diluted to 1000 µLs for LC/MS analysis. The mixtures were purified by preparative HPLC.

Initial Analysis:

15 WFD-446-UPLC4:

MassLynx 4.1

Waters 2777 Sample Manager (CTC MXY01-01B)

Waters Acquity Binary UPLC pump

Waters Acquity TUV detector (220 nm)

20 Waters SD mass spectrometer with ESI probe

Column-Waters Xbridge 2.1x50mm 1.7 µm C18 (BEH-C18 for UPLC)

Mobile Phase- A = 5:95 SS:Water; B = 95:5 SS:Water; Modifier = 10 mM NH₄OAc

25 *Methods*

WFD-UPLC-001 MeOH (2x50mm, 1.7µm, 5min):

	Time	B%	Flow		Time	B%	Flow
	_0.00'	_0	_0.5		_5.50'	_0	_0.5
30	_4.00'	100	_0.5				
	_5.00'	100	_0.5				
	_5.10'	_0	_0.5				

WFD-UPLC-002 ACN (2x50mm, 1.7um, 5min):

	Time	B%	Flow		Time	B%	Flow
	_0.00'	__0	_0.83		_5.50'	__0	_0.83
	_4.00'	100	_0.83				
5	_5.00'	100	_0.83				
	_5.10'	__0	_0.83				

Prep

10 *Method*

WFD-LCMS-003 MeOH (4.6x50mm, 5um, 9min):

	Time	B%	Flow		Time	B%	Flow
	_0.00'	__0	_2.0		10.00'	__0	_2.0
15	_8.00'	100	_2.0				
	_9.00'	100	_2.0				
	_9.10'	__0	_2.0				

Prep

20

WFD-445-PMS1 (Waters):

Masslynx 4.0 SP2

Waters 2767 Sample Manager (autosampler / fraction collector)

Waters Column Fluidics Organizer

25

Waters 2525 binary pump

Waters 515 pumps for Makeup, At-Column-Dilution, and Dial-A-Mix flows
(resp.)

Waters 2787 UV detector

Waters ZQ with ESCi mass spectrometer

30

Column-Waters Xbridge 19x200mm 5 um C18

Guard Column-Waters Xbridge 19x10mm 5 um C18

Mobile Phase- A = Water; B = 95:5 Acetonitrile; Water; Modifier = 20 mM
NH₄OAc

Method

WFD-PMS1-Nwx14aA (19x200mm): for B = ACN
 25 mL/min, 0' = 20% B, 0.5' (12.5 mL/min) = 20% B, 2' (12.5 mL/min) =
 5 20% B, 2.5' = 20% B, 23' = 95% B, 30' = 95% B

Sample Drying- GeneVac Program HT-24 - ACN-H₂O-Buffer in 16x100 TT
 & AL blocks: Temp = 45 C, 0.3 h @ 175 to 40 bar, 1.7 h @ 40 bar, defrost, 6
 h @ 8 bar, 6 h @ Full Vac, defrost.

10

Final Analysis

WFD-446-MUX1:
 Masslynx 4.0 SP4
 15 CTC-Leap HTS-PAL autosampler with Harney 4-port injection module
 Waters 1525 binary pump Waters 2488 UV detector Polymer Lab 1000
 ELS detector (Evap. Temp. = 90°C, Neb. Temp. = 80°C) Waters LCT mass
 spectrometer with 4 way MUX source
 Column- Supelco Ascentis Express 4.6x50mm 2.7 um C18
 20 Mobile Phase- A = 5:95 ACN:Water; B = 95:5 ACN:Water; Modifier = 10
 mM NH₄OAc

Method

25 WFD-MUX-004 (4.6x50mm):

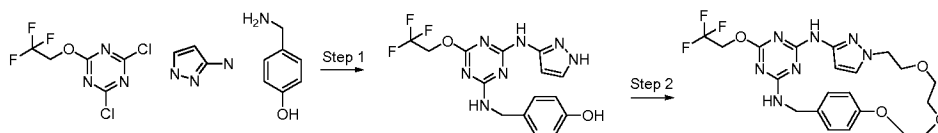
Time	B%	Flow		Time	B%	Flow
_0.00'	_0	_2.0		10.00'	_0	_2.0
_8.00'	100	_2.0				
_9.00'	100	_2.0				
30 _9.10'	100	_2.0				

Compd#	HPLC Rt	Obs. MS Ion
1013	3.9	588.3
1014	3.98	622.24
1016	3.8	574.27
1017	3.88	578.2
1018	4.85	658.47
1019	4.24	616.33
1021	4.05	594.26
1022	3.83	594.2
1023	4.03	602.3
1024	4.43	630.38
1025	4.12	666.3
1027	3.86	560.23
1028	3.43	623.41
1030	2.99	575.41
1031	2.91	545.36
1032	3.31	579.36
1033	3.58	617.46
1035	3.17	595.39
1036	3.35	603.44
1037	3.86	631.48
1038	3.56	667.44
1039	3.02	563.38
1040	3.26	561.37

Chemistry Experimental (2000) series

Example 2001: Preparation of Compound 2001

5

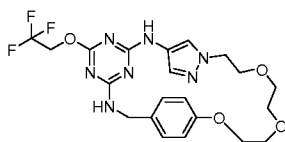


Step 1: To a solution of 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine (0.496 g, 2 mmol) and Hunig'sBase (0.699 mL, 4.00 mmol) in THF (8 mL) was added 1H-pyrazol-3-amine (0.174 g, 2.100 mmol) and stirred for 16 h. The solution will be used in the next step as it is. To the above solution was added Hunig'sBase (699 μ l, 4.00 mmol) followed by 4-(aminomethyl)phenol (246 mg, 2.000 mmol) and stirred for 16 h. Concentration and purification by Biotage eluting with 2.5%-5% MeOH in CH_2Cl_2 gave 600 mg of the desired product as a solid. MS m/z (M+H)⁺ 382.08.

Step 2: To a solution of 4-((4-(1H-pyrazol-3-ylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)methyl)phenol (66 mg, 0.173 mmol) and 1,2-bis(2-iodoethoxy)ethane (64.0 mg, 0.173 mmol) in DMF (10 mL) was added Cs_2CO_3 (226 mg, 0.692 mmol). The resulting mixture was stirred at rt for 16 hrs. DMF was removed under vacuum. The residue was purified by prep HPLC to give 5 mg of the desired product compound 2001 as a solid. MS m/z (M+H)⁺ 496.01.

15

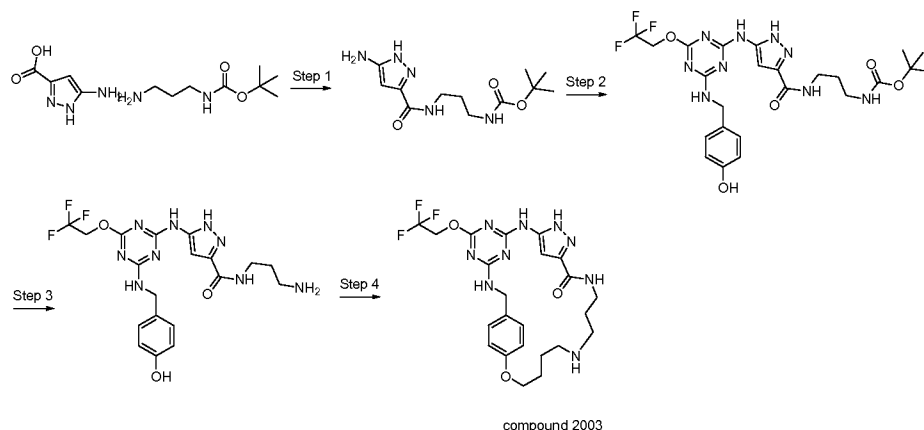
Example 2002: Preparation of Compound 2002



20 The Compound 2002 was synthesized following the procedure reported in Example 2001. 1H-pyrazol-4-amine HCl salt was used as starting material instead of 1H-pyrazol-3-amine in step 1. MS m/z (M+H)⁺ 496.01.

25

30

Example 2003: Preparation of Compound 2003

- 5 Step 1: To slurry of 5-amino-1H-pyrazole-3-carboxylic acid (0.318 g, 2.5 mmol),
tert-butyl 3-aminopropylcarbamate (0.479 g, 2.75 mmol) and Hunig'sBase (2.183
mL, 12.50 mmol) in CH₂Cl₂ (8 mL) was added PyBOP (1.561 g, 3.00 mmol) and the
resulting solution was stirred for 16 h. After concentration, the residue was purified
by Biotage eluting with 5%-20% MeOH in CH₂Cl₂ to give 700 mg of a crude product
10 that will be used as it is in the next step. MS m/z (M+H)⁺ 284.10.

- Step 2: To a solution of 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine (0.620
g, 2.5 mmol) and Hunig'sBase (1.747 mL, 10.00 mmol) in THF (8 mL) was added
tert-butyl 3-(5-amino-1H-pyrazole-3-carboxamido)propylcarbamate (0.708 g, 2.500
15 mmol) and stirred for 16 h. To the above solution was added Hunig'sBase (873 μ L,
5.00 mmol) followed by 4-(aminomethyl)phenol (308 mg, 2.500 mmol) and stirred
for 16 h. Concentration and purification by Biotage eluting with 2.5%-5% MeOH in
CH₂Cl₂ gave 700 mg of the desired product as a solid. MS m/z (M+H)⁺ 582.12.

- 20 Step 3: A solution of tert-butyl 3-(5-(4-(4-hydroxybenzylamino)-6-(2,2,2-
trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazole-3-
carboxamido)propylcarbamate (116 mg, 0.2 mmol) in TFA (1 mL, 12.98 mmol) was
stirred for 4 h. TFA was removed under vacuum. The residue will be used in the
next step as it is. MS m/z (M+H)⁺ 481.99.

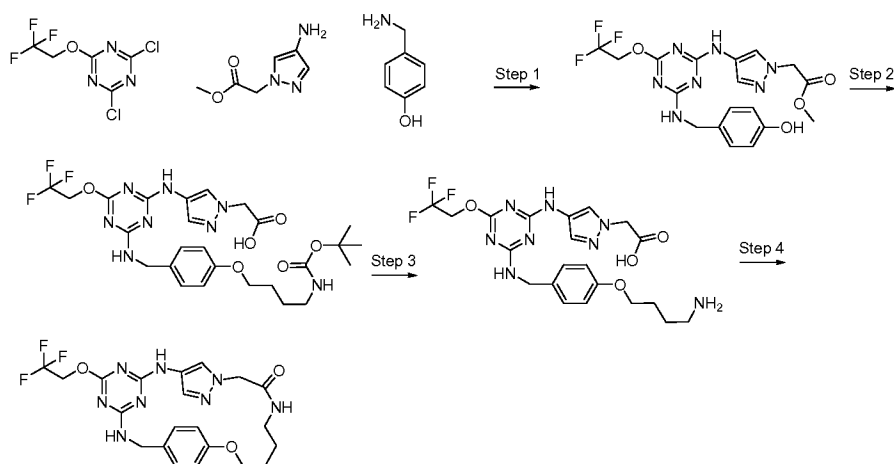
25

Step 4: To a solution of N-(3-aminopropyl)-5-(4-(4-hydroxybenzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazole-3-carboxamide, 2 HCl (111 mg, 0.2 mmol) and 1,4-diiodobutane (62.0 mg, 0.200 mmol) in DMF (20 mL) was added Cs₂CO₃ (261 mg, 0.800 mmol). The resulting mixture was stirred at rt for 16 hrs. DMF was removed under vacuum. The residue was purified by prep HPLC to give 50 mg starting material, 2 mg of compound 2003

Compound 2003: MS m/z (M+H)⁺ 536.06;

Examples 2005: Preparation of Compound 2005

10



Step 1: To a solution of 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine (0.496 g, 2 mmol) and Hunig'sBase (0.699 mL, 4.00 mmol) in THF (8 mL) was added methyl 2-(4-amino-1H-pyrazol-1-yl)acetate (0.326 g, 2.100 mmol) and stirred for 16 h. The solution will be used in the next step as it is. To the above solution was added Hunig'sBase (699 µl, 4.00 mmol) followed by 4-(aminomethyl)phenol (246 mg, 2.000 mmol) and stirred for 16 h. After concentration, the solid was collected washing with CH₂Cl₂ to give 700 mg of the desired product as a solid. MS m/z (M+H)⁺ 453.97.

Step 2: To a solution of methyl 2-(4-(4-(4-hydroxybenzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazol-1-yl)acetate (91 mg, 0.2 mmol) and tert-butyl 4-bromobutylcarbamate (50.4 mg, 0.200 mmol) in DMF (1 mL) was added Cs₂CO₃ (261 mg, 0.800 mmol). The resulting mixture was stirred at 60°C for

0.5h in microwave. DMF was removed under vacuum. The residue was purified by prep HPLC to give 22 mg of the desired product. MS m/z (M+H)⁺ 611.03.

Step 3: A solution of 2-(4-(4-(4-(4-(tert-

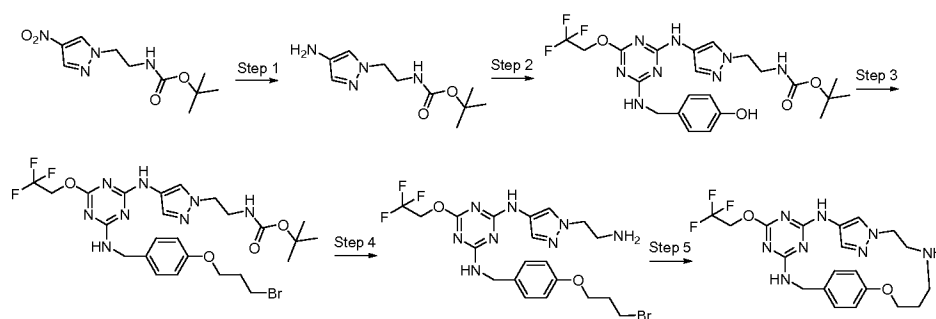
5 butoxycarbonylamino)butoxy)benzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazol-1-yl)acetic acid (45 mg, 0.074 mmol) and 4 M hydrogen chloride in dioxane (1 ml, 4.00 mmol) was stirred for 4h. The solvent was removed under vacuum. The residue will be used in the next step as it is. MS m/z (M+H)⁺ 510.96.

10

Step 4: To slurry of 2-(4-(4-(4-(4-aminobutoxy)benzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazol-1-yl)acetic acid, 2 HCl (21.00 mg, 0.036 mmol) and Hunig'sBase (0.031 mL, 0.180 mmol) in CH₂Cl₂ (Volume: 8 mL) was added PyBOP (28.1 mg, 0.054 mmol) and the resulting solution was stirred for 16 h. After concentration, the residue was purified by prep HPLC to give 5 mg of the desired product as a solid. MS m/z (M+H)⁺ 492.96.

15

Examples 2006: Preparation of Compound 2006



20

Step 1: To a solution of tert-butyl 2-(4-nitro-1H-pyrazol-1-yl)ethylcarbamate (1.7 g, 6.63 mmol) in EtOH (Volume: 30 mL) was added 5% Pt(S) on carbon (340 mg, 0.087 mmol) and the suspension was hydrogenated at 50 PSI for 16 h. After filtration through a celite plug washing with ethyl acetate, filtrate was concentrated, purified by Biotage eluting with 5% MeOH in CH₂Cl₂ to give 580 mg of desired product. MS m/z (M+Na)⁺ 249.09.

25

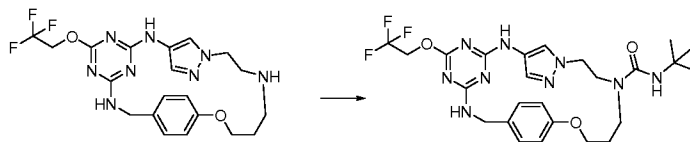
Step 2: To a solution of tert-butyl 2-(4-amino-1H-pyrazol-1-yl)ethylcarbamate (0.566 g, 2.500 mmol) and Hunig'sBase (0.873 mL, 5.00 mmol) in THF (8 mL) was added tert-butyl 2-(4-amino-1H-pyrazol-1-yl)ethylcarbamate (0.566 g, 2.500 mmol) and stirred for 16 h. The solution will be used in the next step as it is. To the above
5 solution was added Hunig'sBase (873 μ L, 5.00 mmol) followed by 4-(aminomethyl)phenol (308 mg, 2.500 mmol) and stirred for 16 h. After concentration, the solid was collected washing with CH₂Cl₂ to give 700 mg of the desired product as a solid. MS m/z (M+H)⁺ 524.94.

10 Step 3: To a solution of tert-butyl 2-(4-(4-(4-hydroxybenzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazol-1-yl)ethylcarbamate (105 mg, 0.2 mmol), 3-bromopropan-1-ol (38.9 mg, 0.280 mmol), and PPh₃ (84 mg, 0.320 mmol) in THF (2 mL) at 0°C was added DEAD (0.062 mL, 0.320 mmol). The resulting solution was stirred for 16h at
15 rt. After concentration, purification by Biotage eluting with 50% ethyl acetate in hexane to give 25 mg of the desired product as an oil. MS m/z (M+H)⁺ 646.91.

Step 4: To a solution of tert-butyl 2-(4-(4-(4-(3-bromopropoxy)benzylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)-1H-pyrazol-1-yl)ethylcarbamate (10
20 mg, 0.015 mmol) in CH₂Cl₂ (1 mL) was added TFA (0.2 μ L, 2.60 μ mol). The resulting solution was stirred for 1 h. The solvents were removed and the residue was used as it was without any further purification. MS m/z (M+H)⁺ 546.86.

Step 5: To a solution of N2-(1-(2-aminoethyl)-1H-pyrazol-4-yl)-N4-(4-(3-bromopropoxy)benzyl)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine (5 mg,
25 9.17 μ mol) in 7 mL microwave vial in MeCN (2 mL) was added K₂CO₃ (1.267 mg, 9.17 μ mol). The resulting mixture was stirred in microwave at 120°C for 1 h. The solvents were removed and the residue was purified by prep HPLC to give 3.4 mg of the product as TFA salt. MS m/z (M+H)⁺ 645.00.

30

Examples 2007: Preparation of Compound 2007

- 5 To a solution of (3E)-6-(2,2,2-trifluoroethoxy)-20-oxa-3,5,7,9,12,13,16,27-octaazatetracyclo[19.2.2.1~4,8~.1~10,13~]heptacos-1(23),3,5,8(27),10(26),11,21,24-octaene (10 mg, 0.022 mmol) in MeCN (1 mL) was added 2-isocyanato-2-methylpropane (10.67 mg, 0.108 mmol). The resulting mixture was stirred at rt for 16 h. The solvents were removed and the residue was
- 10 was purified by prep HPLC to give 5 mg of the product as TFA salt. MS m/z ($M+Na$)⁺ 564.21. ¹H NMR (400MHz, METHANOL- d_4) δ 7.34 (d, $J=0.5$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 7.09 (d, $J=8.8$ Hz, 2H), 6.54 (s, 1H), 4.94-4.90 (m, 2H), 4.58 (s, 2H), 4.26 - 4.19 (m, 2H), 3.81 - 3.73 (m, 2H), 3.68 - 3.60 (m, 2H), 3.29 - 3.21 (m, 2H), 1.81 (d, $J=5.3$ Hz, 2H), 1.25 (s, 9H).

15 Chemistry Experimental (3000) series

LC/MS Method (i.e., compound identification)

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS or LC-20AS liquid chromatograph using a SPD-10AV or SPD-20A UV-Vis

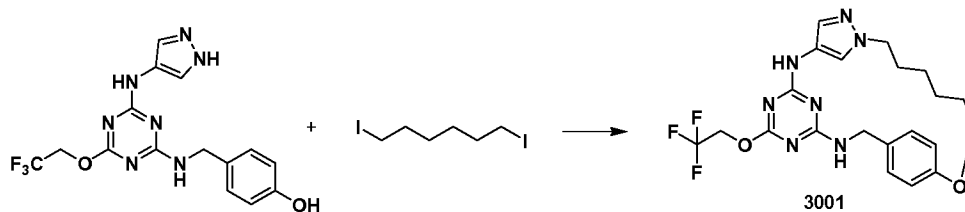
20 detector and Mass Spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode.

HPLC Method (i.e., compound isolation)

25

Compounds purified by preparative HPLC were diluted in methanol (1.2 mL) and purified using a Shimadzu LC-8A or LC-10A automated preparative HPLC system.

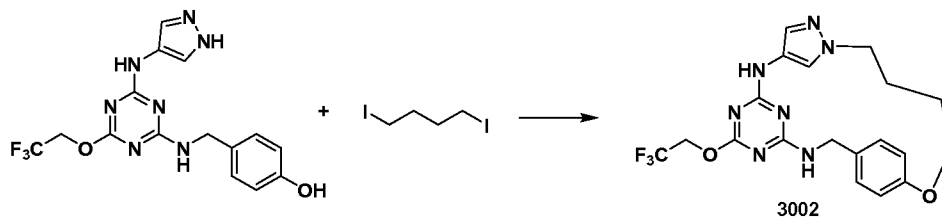
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Synthesis of Compound 3001:

- 5 To a solution of 4-((4-(1H-pyrazol-4-ylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)methyl)phenol (50 mg) and 1,6-diiodohexane (44.3 mg) in DMF (10 mL) was added Cs₂CO₃ (171 mg). The mixture was stirred at room temperature for 16 hours. DMF was removed under vacuum. The residue was purified by preparative HPLC to give Compound 3001 (1.5 mg).

10

Compound 3001	
MS (M+H) ⁺	464.2
Calcd.	
MS (M+H) ⁺	464.1
Observ.	
Retention Time	2.93 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	50
Final % B	100
Gradient Time	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 50mm 3um

Synthesis of Compound 3002:

- 5 To a solution of 4-((4-(1H-pyrazol-4-ylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)methyl)phenol (50 mg) and 1,4-diiodobutane (40.6 mg) in DMF (10 mL) was added Cs₂CO₃ (171 mg). The mixture was stirred at room temperature for 16 hours. DMF was removed under vacuum. The residue was purified by preparative HPLC to give Compound 3002 (1.2 mg).

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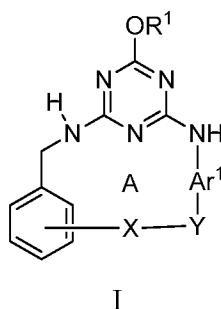
Compound 3002	
MS (M+H) ⁺ Calcd.	436.2
MS (M+H) ⁺ Observ.	436.0
Retention Time	2.17 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	50
Final % B	100
Gradient Time	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 50mm 3um

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
5 restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

We claim:

1. A compound of formula I



where

- R¹ is alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl, hydroxycycloalkyl, alkoxycycloalkyl, halocycloalkyl, cycloalkenyl, benzyl, indanyl, or alkylcarbonyl;

R² is hydrogen, alkyl, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, or dialkylaminocarbonyl;

- R³ is hydrogen, alkyl, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, or dialkylaminocarbonyl;

R⁴ is hydrogen or alkyl;

- Ar¹ is pyridindiyl, pyrimidindiyl, pyrazindiyl, pyridazindiyl, pyrazoldiyl, or imidazoldiyl;

X is O or NR²;

- Y is an alkylene or alkenylene chain containing 0-6 groups selected from the group consisting of O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, NR⁴C(NR¹²)NR⁴, and Z, provided that O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, and NR⁴C(NR¹²)NR⁴ do not directly bond to each other, such that ring

A is 14-36 membered; and where the alkylene or alkenylene chain is substituted with 0-6 alkyl substituents; and

Z is C₃₋₇cycloalkylene or phenylene;

5

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R¹ is haloalkyl; R² is hydrogen; R³ is hydrogen; R⁴ is hydrogen; Ar¹ is pyridindiyl, pyrimidindiyl, or pyrazoldiyl; X is O or
10 NR²; Y is an alkylene or alkenylene chain containing 0-6 groups selected from the group consisting of O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, NR⁴C(NR¹²)NR⁴, and Z, provided that O, NR³, C(O), C(O)O, C(O)NR⁴, OC(O)NR⁴, NR⁴C(O)NR⁴, and NR⁴C(NR¹²)NR⁴ do not directly bond to each other, such that ring
15 A is 14-36 membered; and where the alkylene or alkenylene chain is substituted with 0-6 alkyl substituents; and Z is phenylene; or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2 where R¹ is trifluoroethyl or a pharmaceutically acceptable salt thereof.

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4. A compound of claim 2 where Ar¹ is pyridindiyl or a pharmaceutically acceptable salt thereof.

5. A compound of claim 2 where Ar¹ is pyrimidindiyl or a pharmaceutically acceptable salt thereof.

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6. A compound of claim 2 where Ar¹ is pyrazoldiyl or a pharmaceutically acceptable salt thereof.

7. A compound of claim 2 where X is O or a pharmaceutically acceptable salt thereof.

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8. A compound of claim 2 where X is NR^2 or a pharmaceutically acceptable salt thereof.
9. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
10. The composition of claim 9 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.
11. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.
12. The method of claim 11 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.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/032674

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/06 A61K31/53 A61P31/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/132202 A2 (INCYTE CORP [US]; COMBS ANDREW PAUL [US]; SPARKS RICHARD B [US]; YUE E) 29 October 2009 (2009-10-29) cited in the application claims 1, 76	1-12
Y	WO 2004/026881 A1 (SCHERING AG [DE]) 1 April 2004 (2004-04-01) claims 1, 13, 16	1-12
Y	WO 02/079187 A1 (DONG WHA PHARM IND CO LTD [KR]; CHUNG YONG-HO [KR]; LEE CHI-WOO [KR];) 10 October 2002 (2002-10-10) claims 1,6	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 June 2012

Date of mailing of the international search report

13/06/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/032674

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