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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY
[US/US]; P.O. Box 4000, Route 206 and Province Line
Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors: WANG, Tao; c/o Bristol-Myers Squibb Com-
pany, 5 Research Parkway, Wallingford, Connecticut
06492 (US). ZHANG, Zhongxing; c/o Bristol-Myers
Squibb Company, 5 Research Parkway, Wallingford, Con-
necticut 06492 (US). KADOW, John F.; c/o Bristol-My-
ers Squibb Company, 5 Research Parkway, Wallingford,
Connecticut 06492 (US).

(74) Agents: LEVIS, John F. et al.; Bristol-Myers Squibb
Company, Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US).

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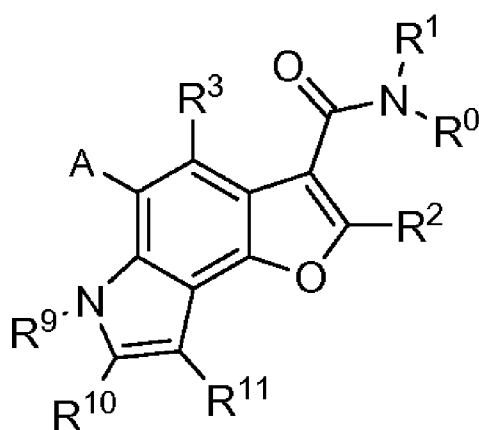
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[Continued on next page]

(54) Title: 6H-FURO[2,3-E]INDOLE COMPOUNDS FOR THE TREATMENT OF HEPATITIS C



I

(57) Abstract: Compounds of Formula I, including
their salts, as well as compositions and methods of
using the compounds are set forth. The compounds
have activity against hepatitis C virus (HCV) and
may be useful in treating those infected with HCV.



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6H-FURO[2,3-E]INDOLE COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No.
5 61/968,747 filed March 21, 2014, which is hereby incorporated by reference in its
entirety.

FIELD OF THE INVENTION

The invention relates to novel compounds, including their salts, which have
10 activity against hepatitis C virus (HCV) and which are useful in treating those infected
with HCV. The invention also relates to compositions containing these compounds, as
well as to methods of making and using these compounds.

BACKGROUND OF THE INVENTION

15 Hepatitis C virus (HCV) is a major human pathogen, infecting an estimated 170
million persons worldwide - roughly five times the number infected by human
immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals
develop serious progressive liver disease, including cirrhosis and hepatocellular
carcinoma (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* 2001, 345, 41-52).

20 HCV is a positive-stranded RNA virus. Based on a comparison of the deduced
amino acid sequence and the extensive similarity in the 5'-untranslated region, HCV has
been classified as a separate genus in the Flaviviridae family. All members of the
Flaviviridae family have enveloped virions that contain a positive stranded RNA genome
25 encoding all known virus-specific proteins via translation of a single, uninterrupted, open
reading frame.

Considerable heterogeneity is found within the nucleotide and encoded amino acid
sequence throughout the HCV genome. At least six major genotypes have been
30 characterized, and more than 50 subtypes have been described. The major genotypes of
HCV differ in their distribution worldwide, 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.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to as NS3 protease) and mediates all the subsequent cleavages 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 NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. 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. NS5B (also referred to as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV. The HCV NS5B protein is described in "Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides (Bressanelli; S. et al., *Journal of Virology* 2002, 3482-3492; and Defrancesco and Rice, *Clinics in Liver Disease* 2003, 7, 211-242).

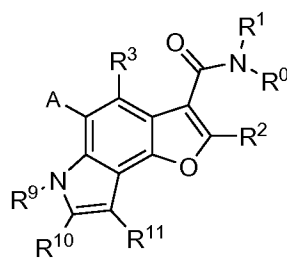
Currently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients (Poynard, T. et al. *Lancet* 1998, 352, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* 2000, 343, 1666-1672). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and important need to develop effective therapeutics for treatment of HCV infection.

HCV-796, an HCV NS5B inhibitor, has shown an ability to reduce HCV RNA levels in patients. The viral RNA levels decreased transiently and then rebounded during dosing when treatment was with the compound as a single agent but levels dropped more robustly when combined with the standard of care which is a form of interferon and ribavirin. The development of this compound was suspended due to hepatic toxicity observed during extended dosing of the combination regimens. US patent 7,265,152 and the corresponding PCT patent application WO2004/041201 describe compounds of the HCV-796 class. Other compounds have been disclosed; see for example, WO2009/101022, as well as WO 2012/058125.

What is therefore needed in the art are additional compounds which are novel and effective against hepatitis C. Additionally, these compounds should 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, and/or bioavailability. Also needed are new formulations and methods of treatment which utilize these compounds.

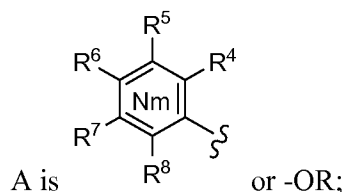
SUMMARY OF THE INVENTION

One aspect of the invention is a compound of Formula I, including pharmaceutically acceptable salts thereof:



I

wherein



R is alkyl, cycloalkyl, alkenyl, cyclokenyl or alkynyl;

5 m is 0 or 1;

R^0 , R^1 is each independently methyl or ethyl;

R^2 is phenyl that is independently substituted with 0-2 halo or methoxy, or is para
10 substituted with $W-Ar^1$;

W is -O- or -NH-;

Ar^1 is phenyl or para-halophenyl;

15

R^3 is hydrogen, halo, or alkyl;

R^4 , R^5 , R^6 , R^7 , R^8 are independently selected from the group of hydrogen, halo, alkyl,
cycloalkyl, haloalkyl, halocycloalkyl, hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl,
20 alkoxycycloalkyl, alkoxy, hydroxyalkyloxy, alkoxyalkyloxy, Ar^2 , $COOR^{101}$ and
 $CON(R^{102})(R^{103})$;

R^{101} is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl,
alkoxy, and haloalkoxy;

25

R^{102} , R^{103} are each independently selected from the group of hydrogen, alkyl, cycloalkyl,
alkenyl, cycloalkyl alkynyl, cyclic ether, cyclic amine, lactame, fused bicyclic alkyl,
bridged bicyclic alkyl, spiro bicyclic alkyl, fused bicyclic ether, bridged bicyclic ether,
spiro bicyclic ether, fused bicyclic amine, bridged bicyclic amine and spiro bicyclic
30 amine, with 0-3 substituents selected from the group of halo, OH, OR^{104} , NH_2 , $NR^{105}R^{106}$,

COOR¹⁰⁴, CONR¹⁰⁵R¹⁰⁶, S(O)₂R¹⁰⁴, S(O)₂NR¹⁰⁵R¹⁰⁶, NR¹⁰⁴CONR¹⁰⁵R¹⁰⁶,
 OR¹⁰⁴CONR¹⁰⁵R¹⁰⁶, C(=NR¹⁰⁷)NR¹⁰⁵R¹⁰⁶, NR¹⁰⁸C(=NR¹⁰⁷)NR¹⁰⁵R¹⁰⁶, haloalkoxy, Ar²,
 O-Ar², and NR¹⁰⁵-Ar²;

5 or R¹⁰² and R¹⁰³ can form a ring by joining two atoms, one from each of R¹⁰² and R¹⁰³;

or R¹⁰² and R¹⁰³ can form a bicyclic or tricyclic ring by joining multiple atoms from each
 of R¹⁰² and R¹⁰³;

10

Ar² is phenyl, 5-membered heterocyclic or 6-membered heterocyclic (aromatic or
 nonaromatic) ring, and is substituted with 0-3 substituents selected from the group of
 cyano, halo, alkyl, cycloalkyl, haloalkyl, OH, OR¹⁰⁴, haloalkoxy, NH₂, NR¹⁰⁵R¹⁰⁶,
 COOR¹⁰⁴, CONR¹⁰⁵R¹⁰⁶, S(O)₂R¹⁰⁴, S(O)₂NR¹⁰⁵R¹⁰⁶, and NR¹⁰⁴CONR¹⁰⁵R¹⁰⁶;

15

R¹⁰⁴ is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl,
 alkoxy, and haloalkoxy;

R¹⁰⁵, R¹⁰⁶ are each independently hydrogen, alkyl or cycloalkyl with 0-3 substituents
 20 selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R¹⁰⁵ and R¹⁰⁶ can form a ring by joining two atoms, one from each of R¹⁰⁵ and R¹⁰⁶;

R¹⁰⁷, R¹⁰⁸ are each independently hydrogen, alkyl or cycloalkyl with 0-3 substituents
 25 selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R¹⁰⁷ and R¹⁰⁸ can form a ring by joining two atoms, one from each of R¹⁰⁷ and R¹⁰⁸;

R⁹ is hydrogen, R²⁰¹, COR²⁰¹ or SO₂R²⁰¹;
 30

R²⁰¹ is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from the group of
 halo, hydroxyl, alkoxy, haloalkoxy, phenyl and heterocyclic;

R¹⁰, R¹¹ are each independently selected from the group of hydrogen, alkyl, cycloalkyl, ester, amide, 2-keto acid, 2-keto ester, 2-keto amide, phenyl and heterocyclic, with 0-3 substituents selected from the group of halo, hydroxyl, alkoxy, haloalkoxy, ester, amide, oxalate, oxalamide, phenyl and heterocyclic.

5

The invention also relates to pharmaceutical compositions comprising a compound of Formula 1, including a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient and/or diluent.

10

In addition, the invention provides one or more methods of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of Formula I to a patient.

15

Also provided as part of the invention are one or more methods for making the compounds of Formula I.

The present invention is directed to these, as well as other important ends, hereinafter described.

20

DETAILED DESCRIPTION OF THE EMBODIMENTS

The singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

Unless otherwise specifically set forth elsewhere in the application, the following terms may be used herein and shall have the following meanings: “Hydrogen” or “H” refers to hydrogen, including its isotopes, such as deuterium, which may be labeled herein as “D”. “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 7 carbons.

“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” includes all halogenated isomers from monohalo substituted to perhalo substituted in substituents defined with halo, for example, “Haloalkyl” and “haloalkoxy”, “halophenyl”,

“halophenoxy.” “Aryl” means a monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. Representative
5 examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. “Heteroaryl” means a 5 to 7 membered monocyclic or 8 to 11 membered bicyclic aromatic ring system with 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Parenthetical and multiparenthetical terms are intended to clarify bonding relationships to those skilled in the art. For example, a term
10 such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R. Substituents which are illustrated by chemical drawing to bond at variable positions on a multiple ring system (for example a bicyclic ring system) are intended to bond to the ring where they are drawn to append.

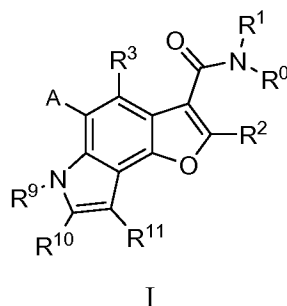
The invention includes all pharmaceutically acceptable salt forms of the
15 compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. 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,
20 fumarate, glucuronate, 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.

25 Some of the compounds of the invention possess asymmetric carbon atoms. 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
30 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.

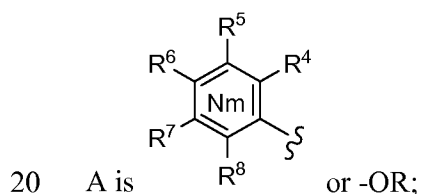
The invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon 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.

The invention is also intended to encompass prodrugs of the compounds herein.

As set forth above, the invention is directed to one or more compounds of Formula I, including pharmaceutically acceptable salts thereof:



wherein



R is alkyl, cycloalkyl, alkenyl, cyclokenyl or alkynyl;

m is 0 or 1;

R^0, R^1 is each independently methyl or ethyl;

R^2 is phenyl that is independently substituted with 0-2 halo or methoxy or is para substituted with $W-Ar^1$;

5

W is -O- or -NH-;

Ar^1 is phenyl or para-halophenyl;

10 R^3 is hydrogen, halo, or alkyl;

R^4, R^5, R^6, R^7, R^8 are independently selected from the group of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, halocycloalkyl, hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, alkoxy, hydroxyalkyloxy, alkoxyalkyloxy, Ar^2 , $COOR^{101}$ and

15 $CON(R^{102})(R^{103})$;

R^{101} is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

20 R^{102}, R^{103} are each independently selected from the group of hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkyl alkynyl, cyclic ether, cyclic amine, lactame, fused bicyclic alkyl, bridged bicyclic alkyl, spiro bicyclic alkyl, fused bicyclic ether, bridged bicyclic ether, spiro bicyclic ether, fused bicyclic amine, bridged bicyclic amine and spiro bicyclic amine, with 0-3 substituents selected from the group of halo, OH, OR^{104} , NH_2 , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, $S(O)_2R^{104}$, $S(O)_2NR^{105}R^{106}$, $NR^{104}CONR^{105}R^{106}$, $OR^{104}CONR^{105}R^{106}$, $C(=NR^{107})NR^{105}R^{106}$, $NR^{108}C(=NR^{107})NR^{105}R^{106}$, haloalkoxy, Ar^2 , $O-Ar^2$, and $NR^{105}-Ar^2$; or

30 R^{102} and R^{103} can form a ring by joining two atoms, one from each of R^{102} and R^{103} ;

R^{102} and R^{103} can form a bicyclic or tricyclic ring by joining multiple atoms from each of R^{102} and R^{103} ;

Ar² is phenyl, 5-membered heterocyclic or 6-membered heterocyclic (aromatic or nonaromatic) ring, and is substituted with 0-3 substituents selected from the group of cyano, halo, alkyl, cycloalkyl, haloalkyl, OH, OR¹⁰⁴, haloalkoxy, NH₂, NR¹⁰⁵R¹⁰⁶, COOR¹⁰⁴, CONR¹⁰⁵R¹⁰⁶, S(O)₂R¹⁰⁴, S(O)₂NR¹⁰⁵R¹⁰⁶, and NR¹⁰⁴CONR¹⁰⁵R¹⁰⁶;

5

R¹⁰⁴ is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R¹⁰⁵, R¹⁰⁶ are each independently hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

10

R¹⁰⁵ and R¹⁰⁶ can form a ring by joining two atoms, one from each of R¹⁰⁵ and R¹⁰⁶;

R¹⁰⁷, R¹⁰⁸ are each independently selected from the group of hydrogen, alkyl and cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

15

R¹⁰⁷ and R¹⁰⁸ can form a ring by joining two atoms, one from each of R¹⁰⁷ and R¹⁰⁸;

R⁹ is hydrogen, R²⁰¹, COR²⁰¹ or SO₂R²⁰¹;

20

R²⁰¹ is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from the group of halo, hydroxyl, alkoxy, haloalkoxy, phenyl and heterocyclic;

R¹⁰, R¹¹ are each independently selected from the group of hydrogen, alkyl, cycloalkyl, ester, amide, 2-keto acid, 2-keto ester, 2-keto amide, phenyl and heterocyclic, with 0-3 substituents selected from the group of halo, hydroxyl, alkoxy, haloalkoxy, ester, amide, oxalate, oxalamide, phenyl and heterocyclic

25

In a preferred embodiment of the invention, m is 0.

30

Also preferred is the embodiment wherein R² is phenyl which is substituted with one halo group, more preferably a fluoro group.

It is also preferred that R^4 , R^5 , R^6 , R^7 , R^8 are each independently selected from the group of COOR^{101} and $\text{CON}(\text{R}^{102})(\text{R}^{103})$. More preferably, R^7 is selected from the group of COOR^{101} and $\text{CON}(\text{R}^{102})(\text{R}^{103})$.

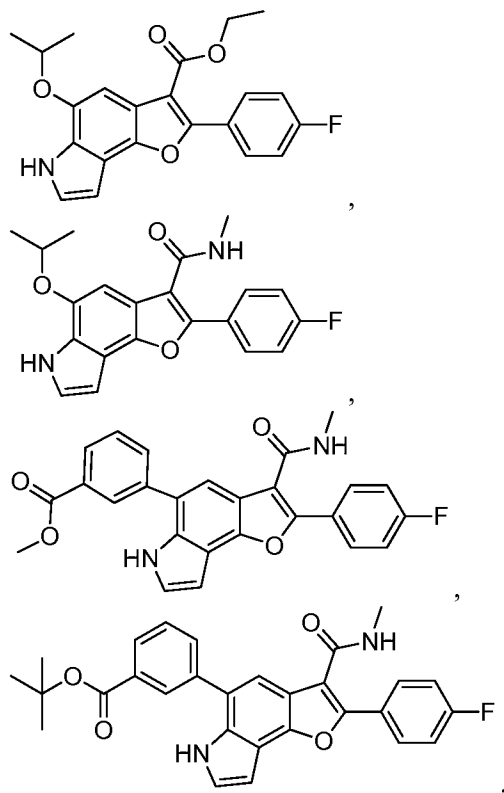
- 5 Additionally, it is preferred that R^{102} , R^{103} are each independently selected from the group of hydrogen, alkyl, and haloalkyl.

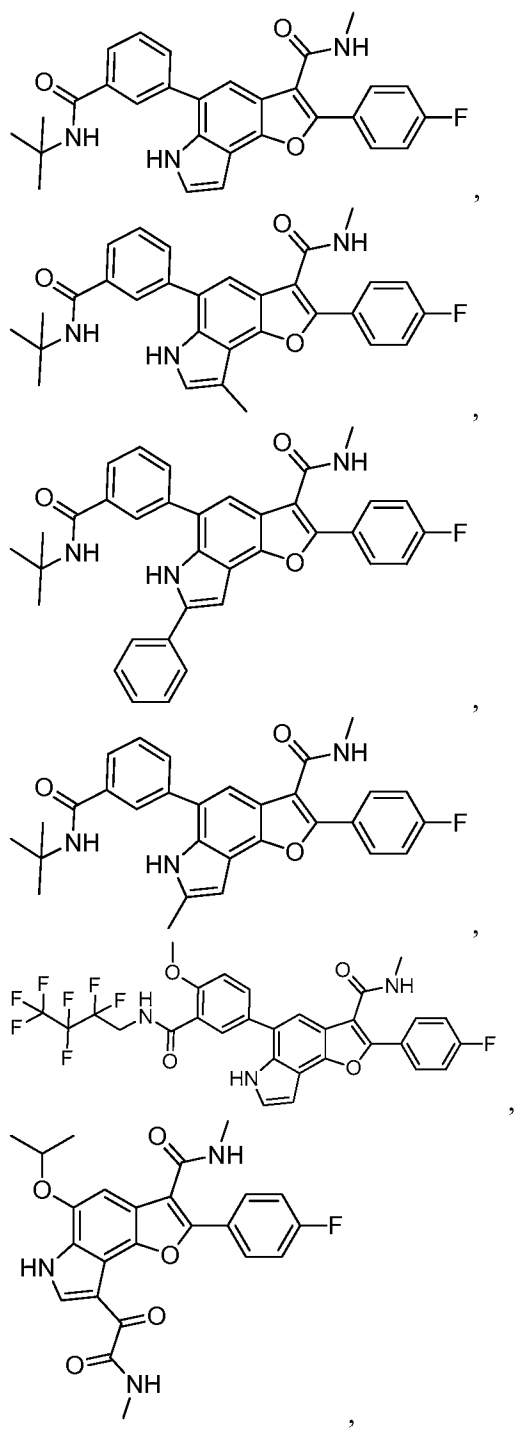
In certain embodiments it is also preferred that R^9 is $\text{SO}_2\text{R}^{201}$.

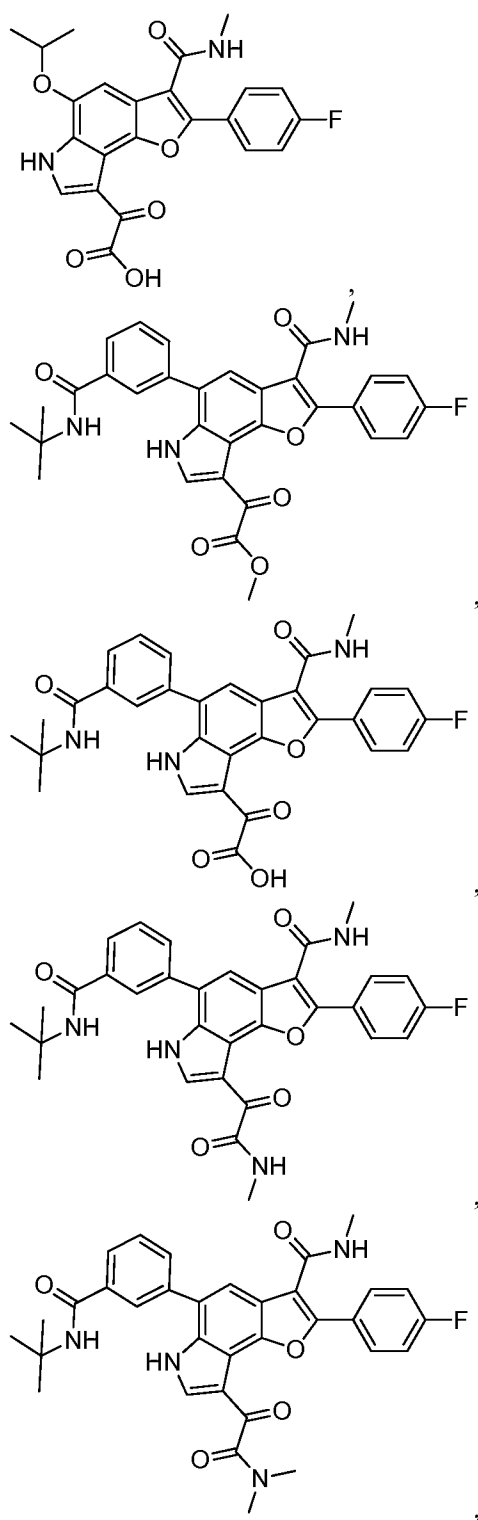
- 10 In another embodiment, it is preferred that m is 0, R^2 is phenyl which is substituted with one fluoro group, and R^7 is $\text{CON}(\text{R}^{102})(\text{R}^{103})$.

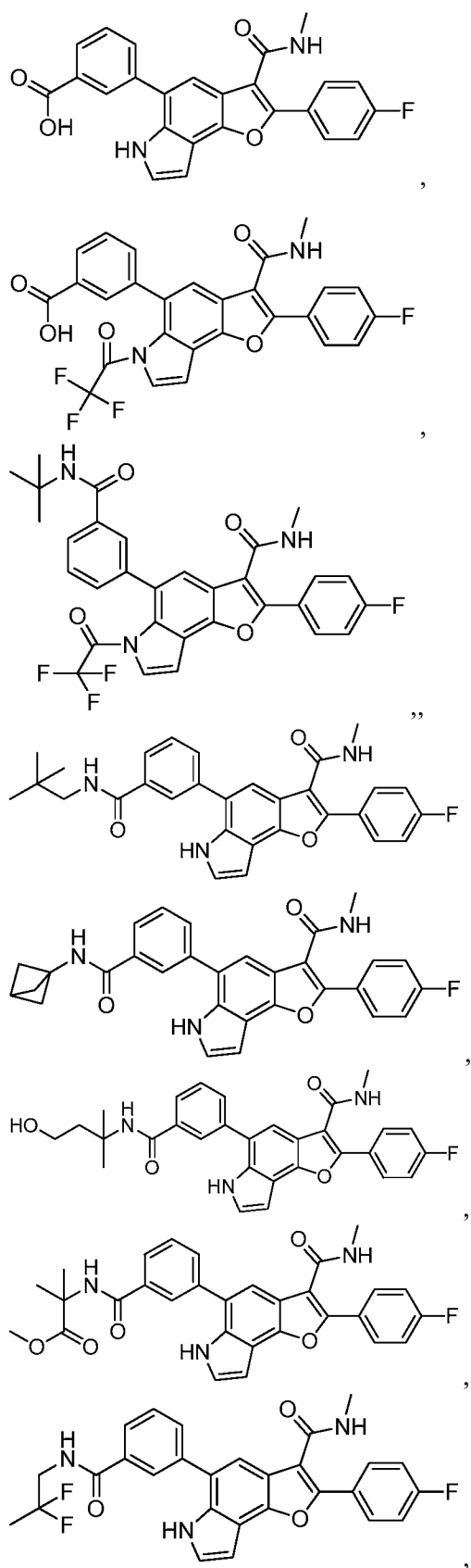
Also preferred are compounds, including pharmaceutically acceptable salts thereof, which are selected from the group of:

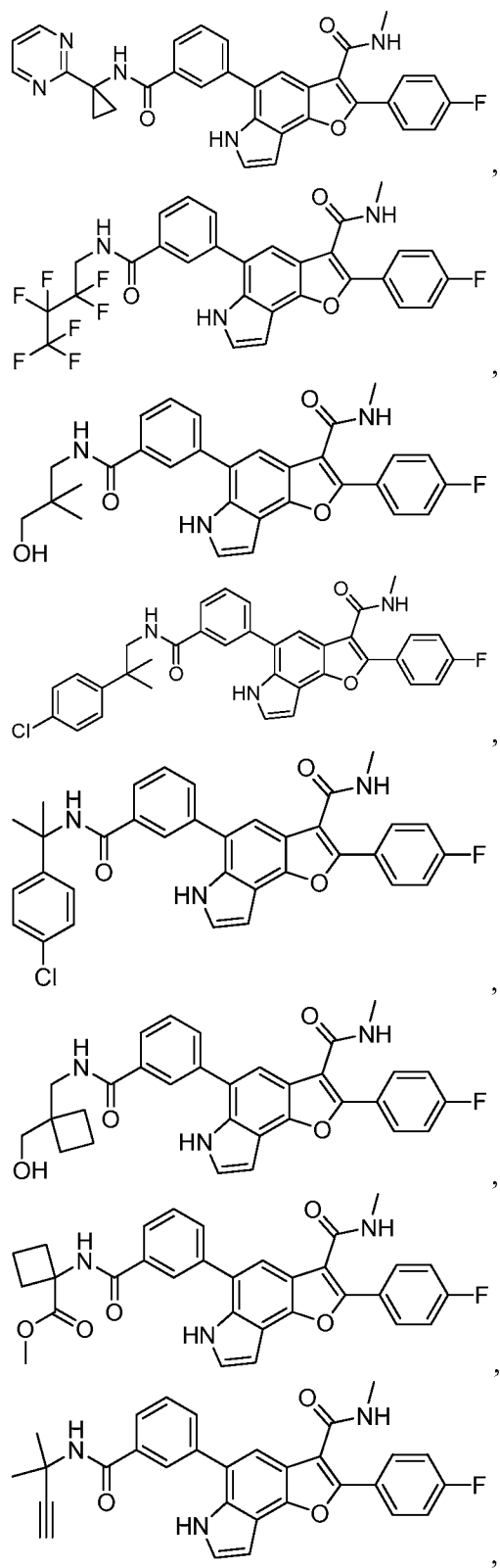
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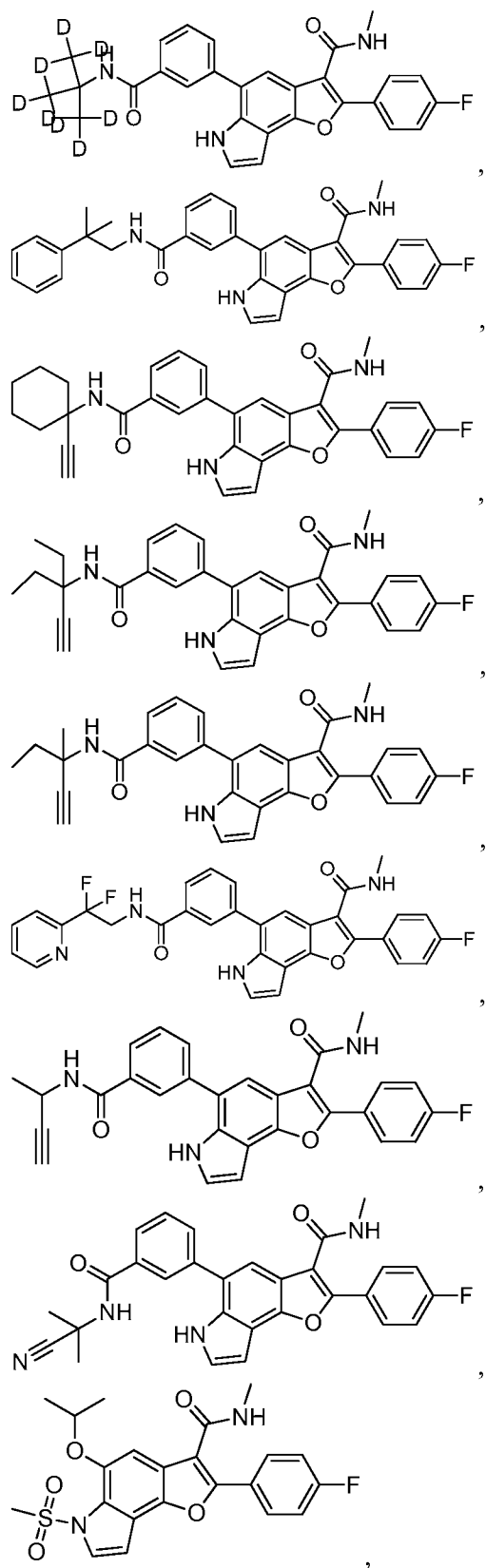


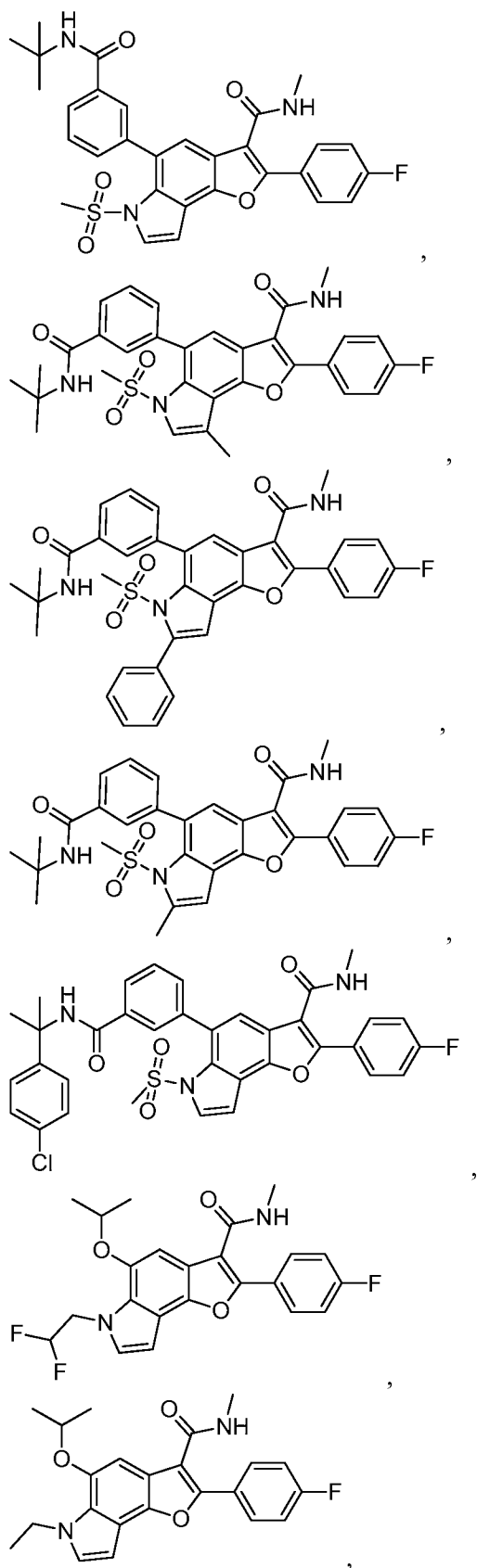


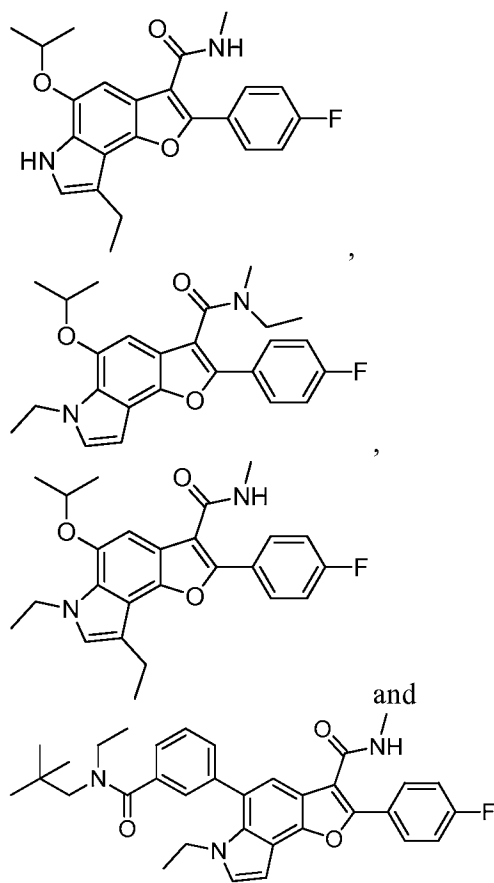




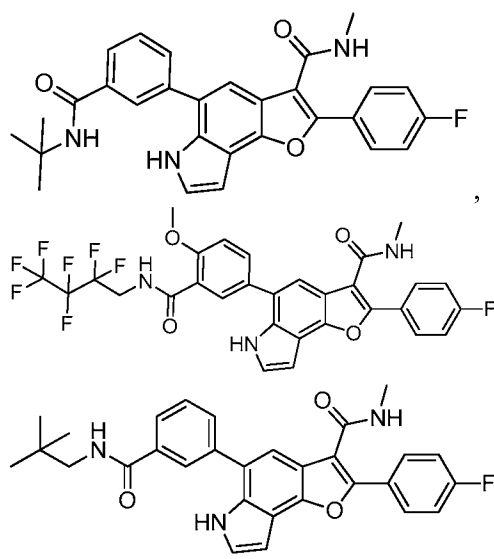


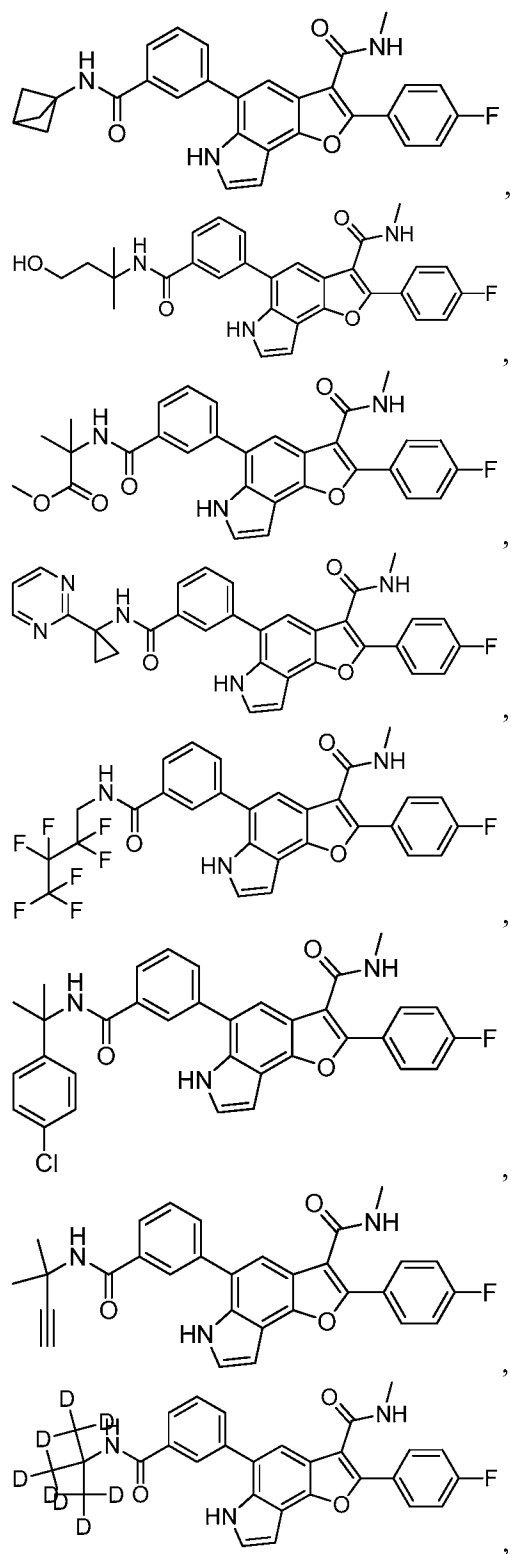


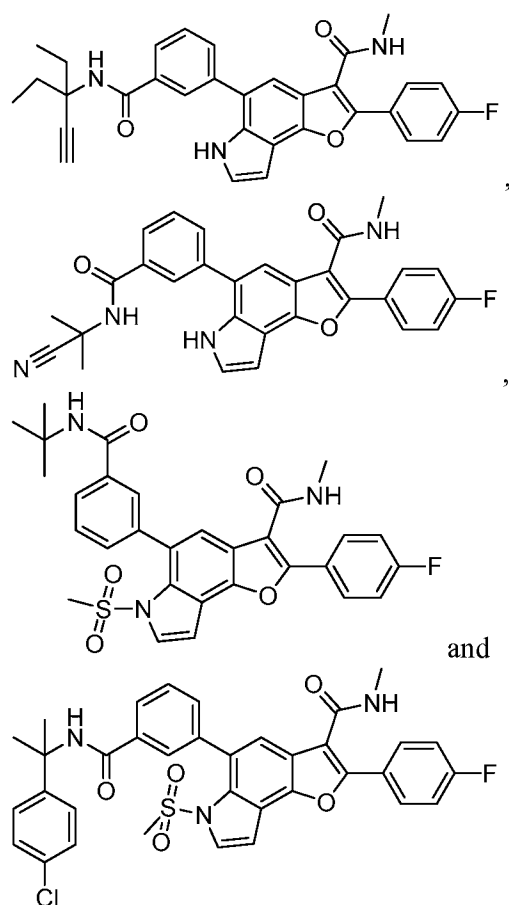




Additionally preferred are compounds, including pharmaceutically acceptable salts thereof, which are selected from the group of:







Pharmaceutical Compositions and Methods of Treatment

The compounds according to the various embodiments herein set forth
 5 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 of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient and/or diluent.

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

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 wherein
 15 the interferon is selected from the group of interferon alpha 2B, pegylated interferon

alpha, consensus interferon, interferon alpha 2A, interferon lambda, 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.

Another aspect of the invention is a composition where the compound having anti-HCV activity is selected from the group 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'-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 the group 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.

Another aspect of the invention is a composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, excipient and/or diluent, an interferon and ribavirin.

Another aspect of the invention is a method of inhibiting the function of the HCV replicon comprising contacting the HCV replicon with a compound of Formula I or a pharmaceutically acceptable salt thereof.

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 of Formula I or a pharmaceutically acceptable salt thereof.

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 of Formula I 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.

5 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 of Formula I, or a pharmaceutically acceptable salt thereof, in conjunction with (prior to, after, or concurrently) another compound having anti-HCV activity.

10 Another aspect of the invention is the method wherein the other compound having anti-HCV activity is an interferon or a ribavirin.

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

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

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

 Another aspect of the invention is the method where the other compound having anti-HCV activity is selected from the group of interleukin 2, interleukin 6, interleukin
25 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'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

 Another aspect of the invention is the method wherein the other compound having
30 anti-HCV activity is effective to inhibit the function of a target selected from the group 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.

Another aspect of the invention is the method wherein 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.

5 “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.

 “Patient” means a person infected with the HCV virus and suitable for therapy as
10 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.

15 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
20 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*
25 *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.
30 Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is about 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 about 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 about 1-100 mg/mL.

5 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 about 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. The specific dosing regimen, however, will be determined by a physician using sound medical
10 judgment.

 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 about 1-
15 100 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 regimen, however, will be determined by a physician using sound medical judgment.

 Some non-limiting examples of compounds suitable for compositions and
20 methods according to the invention are listed in Table 1.

Table 1

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
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 Pharmaceuticals Inc., New York, NY

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
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, Israel
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
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

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
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 immuno-suppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immuno-suppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN- α 2b	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- β 1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN- α 2b/ α 1-thymosin	RegeneRx Biopharma. Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
Rebetron	Interferon	IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
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- α 1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN- α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN- α 2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN- α 2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN- α 2b/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

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
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
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 lambda	Antiviral	Interferon	ZymoGenetics/Bristol-Myers Squibb

Synthesis Methods

5 The compounds may be made by methods available in the art, as well as those described below. Some reagents and intermediates are available in the art. Other reagents and intermediates can be made by methods available in the art using commercially 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 and
10 are not to be confused with variables used in the claims or in other sections of the specification. Abbreviations used within the schemes generally follow conventions used in the art.

Abbreviations used in the schemes generally follow conventions used in the art.
15 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

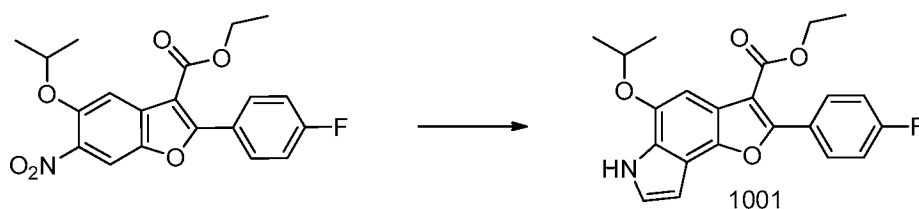
trifluoroacetic acid; "LAH" for lithium aluminum hydride; "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "EDTA" for ethylenediaminetetraacetic acid; "Et₂O" for diethyl 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.

For the section of compounds in the 0000 series 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 detector and Mass Spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode.

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 AcquityTM automated preparative HPLC system.

Examples:

Preparation of Compounds 1001, 1003 - 1008:

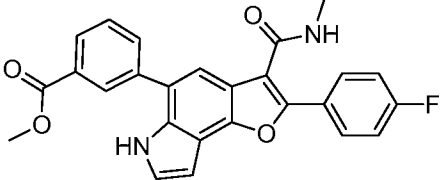


To a solution of ethyl 2-(4-fluorophenyl)-5-isopropoxy-6-nitrobenzofuran-3-carboxylate (30 mg) in THF (5 mL) was added vinylmagnesium bromide (71.2 mg) slowly at -78 °C. The mixture was stirred at -78 °C for 30 minutes then at -40 °C for 4 hours. The reaction was quenched with saturated NH₄Cl aqueous solution and extracted with EtOAc (2 x 25 mL). The organic was combined, washed with brine, dried over MgSO₄ and concentrated

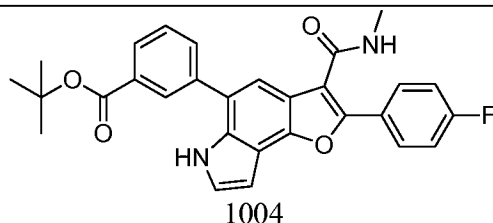
to give a residue which was purified by preparative HPLC system to afford compound 1001.

1001	
MS (M+H) ⁺ Calcd.	382.1
MS (M+H) ⁺ Observ.	382.1
Retention Time	1.69 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Actetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Actetate
Start % B	40
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

- 5 Compound 1003 was prepared via the same procedure toward compound 1001, using methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl)benzoate as the starting material.

 1003	
MS (M+H) ⁺ Calcd.	443.1
MS (M+H) ⁺ Observ.	443.0
Retention Time	1.90 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	30
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

Compound 1004 was prepared via the same procedure toward compound 1001, using tert-butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-nitrobenzofuran-5-yl)benzoate as the starting material.



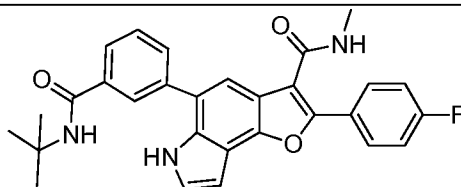
MS (M+H) ⁺ Calcd.	485.2
MS (M+H) ⁺ Observ.	485.2
Retention Time	1.89 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	50
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

5

Compounds 1005, 1006, 1007 and 1008 were prepared via the same procedure toward compound 1001, using 5-(3-(tert-butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide as one of the starting materials. The other starting materials were the corresponding Grinard agents.

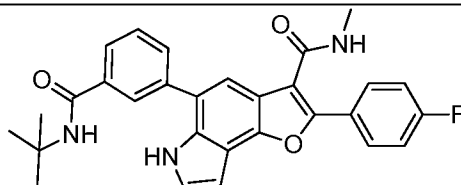
10

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	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um



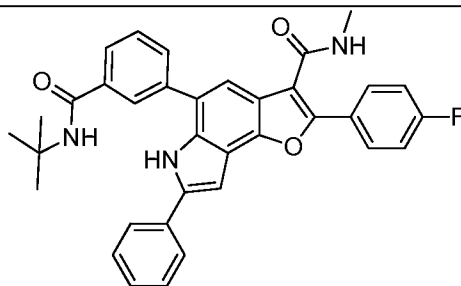
1005

MS (M+H) ⁺ Calcd.	484.2
MS (M+H) ⁺ Observ.	484.1
Retention Time	1.72 min



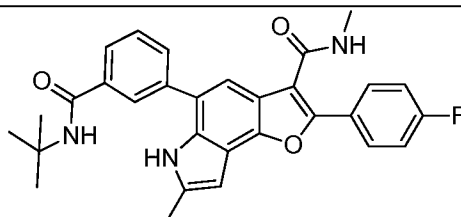
1006

MS (M+H) ⁺ Calcd.	498.2
MS (M+H) ⁺ Observ.	498.1
Retention Time	1.80 min



1007

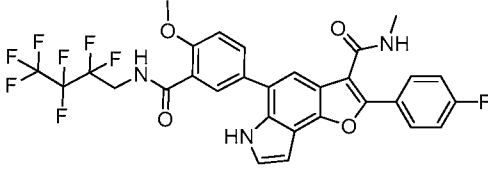
MS (M+H) ⁺ Calcd.	560.2
MS (M+H) ⁺ Observ.	560.2
Retention Time	2.16 min



1008

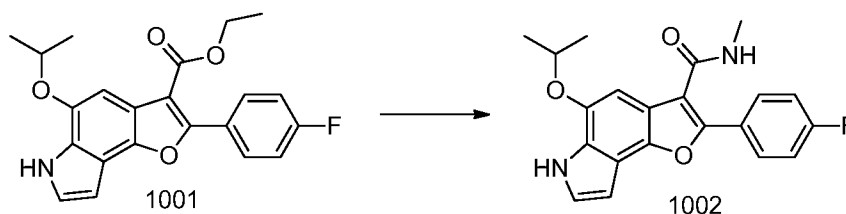
MS (M+H) ⁺ Calcd.	498.2
MS (M+H) ⁺ Observ.	498.1
Retention Time	1.84 min

Compound 1009 was prepared via the same procedure toward compound 1001, using 2-(4-fluorophenyl)-5-(3-((2,2,3,3,4,4,4-heptafluorobutyl)carbamoyl)-4-methoxyphenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide as one of the starting material.

 1009	
MS (M-H) ⁺ Calcd.	638.1
MS (M-H) ⁺ Observ.	638.4
Retention Time	1.96 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

5

Preparation of Compound 1002:

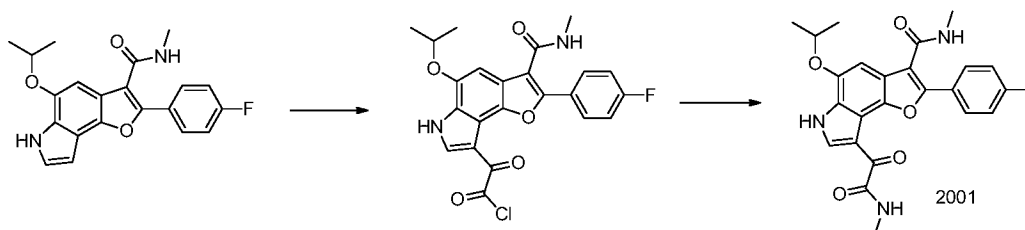


To a solution of ethyl 2-(4-fluorophenyl)-5-isopropoxy-6H-furo[2,3-e]indole-3-carboxylate (30 mg) in ethanol (1.5 mL) was added methanamine (3 mL, 40% in water). The mixture was heated at 80°C for 16 hours. All the solvents were removed under vacuum to give a residue which was purified by preparative HPLC system.

1002	
MS (M+H) ⁺ Calcd.	367.1
MS (M+H) ⁺ Observ.	367.1
Retention Time	1.27 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	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

Preparation of Compound 2001:



5

Step 1: To a suspension of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (60 mg) in ether (5 mL) was added oxalyl dichloride (0.246 mL). The mixture was stirred at room temperature for 4 hours. All the solvents were removed under vacuum. The residue was used as was.

10

Step 2: To a solution of 2-(2-(4-fluorophenyl)-5-isopropoxy-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-8-yl)-2-oxoacetyl chloride (20 mg) in THF (2 mL) was added methanamine hydrochloride (59.1 mg). The mixture was stirred at room temperature for 16 hours. All the solvents were removed under vacuum to give a residue which was

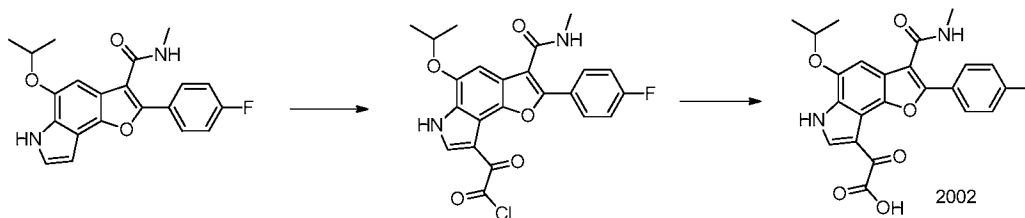
15

purified by preparative HPLC system.

2001	
MS (M+H) ⁺ Calcd.	452.2
MS (M+H) ⁺ Observ.	452.2
Retention Time	1.64 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	30

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

Preparation of Compound 2002:



5

Step 1: To a suspension of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (60 mg) in ether (5 mL) was added oxalyl dichloride (0.246 mL). The mixture was stirred at room temperature for 4 hours. All the solvents were removed under vacuum. The residue was used as was.

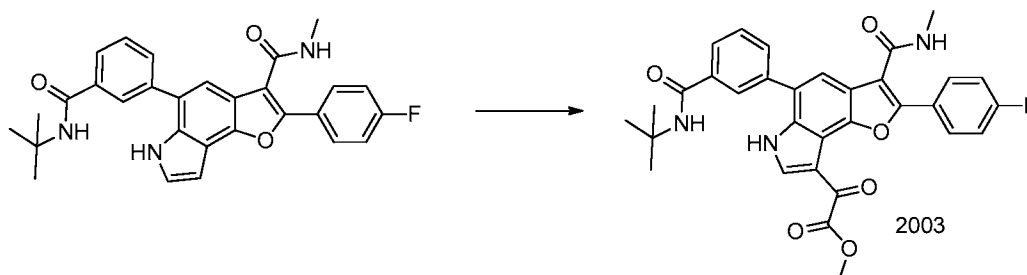
10

Step 2: To a solution of 2-(2-(4-fluorophenyl)-5-isopropoxy-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-8-yl)-2-oxoacetyl chloride (20 mg) in THF (2 mL) was added water (15.77 mg). The mixture was stirred at room temperature for 16 hours. All the solvents were removed under vacuum to give a residue which was purified by preparative HPLC

15 system.

2002	
MS (M+H) ⁺ Calcd.	439.1
MS (M+H) ⁺ Observ.	439.1
Retention Time	1.44 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	30
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

Preparation of Compound 2003:



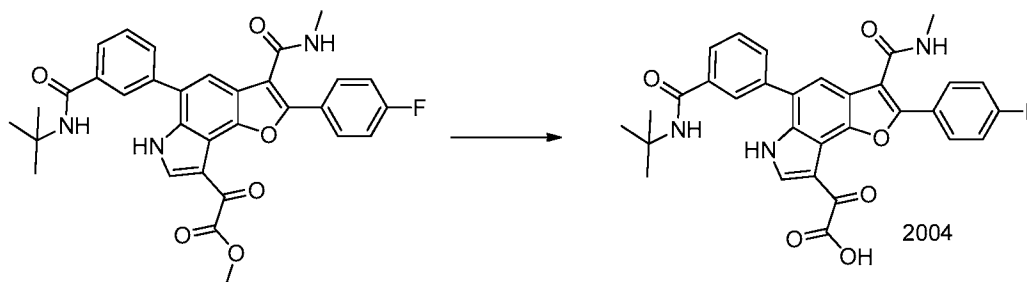
5

To a suspension of 5-(3-(tert-butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (70 mg) in CH₂Cl₂ (20 mL) was added methyl 2-chloro-2-oxoacetate (70.9 mg). The mixture was stirred at room temperature for 6 hours. The reaction was quenched with saturated NH₄Ac aqueous solution and extracted with

10 CH₂Cl₂. The organic layer was washed with H₂O, brine, dried over MgSO₄ and concentrated to give a residue which was purified by preparative HPLC system.

2003	
MS (M+H) ⁺ Calcd.	570.2
MS (M+H) ⁺ Observ.	570.2
Retention Time	2.12 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	10
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

Preparation of Compound 2004:

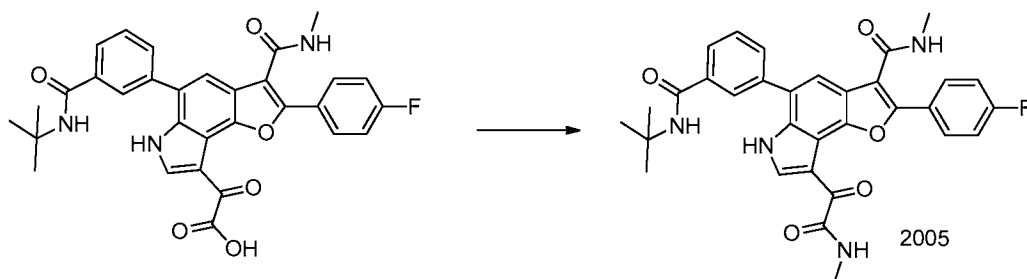


- 5 To a suspension of methyl 2-(5-(3-(tert-butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-8-yl)-2-oxoacetate (70 mg) in THF (6 mL) and water (2 mL) was added NaOH (0.49 mL, 1M). The mixture was heated at 80°C for 6 hours. The mixture was acidified to pH ~ 5 and extracted with EtOAc (2 x 20 mL). The organic layer was washed with brine and concentrated to give compound 2004.

10

2004	
MS (M+H) ⁺ Calcd.	556.2
MS (M+H) ⁺ Observ.	556.3
Retention Time	1.26 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	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

Preparation of Compounds 2005, 2006 and 2007:



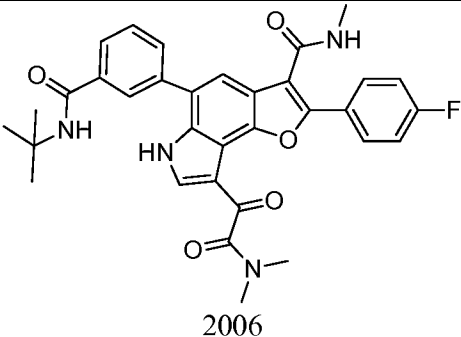
To a solution of 2-(5-(3-(tert-butylcarbamoyl)phenyl)-2-(4-fluorophenyl)-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-8-yl)-2-oxoacetic acid (35 mg), methanamine hydrochloride (17.01 mg) and HCTU (31.3 mg) in DMF (1.5 mL) was added DIPEA (0.066 mL). The mixture was stirred at room temperature for 16 hours. The product

5 2005 was isolated by preparative HPLC system.

2005	
MS (M+H) ⁺ Calcd.	569.2
MS (M+H) ⁺ Observ.	569.3
Retention Time	1.36 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	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

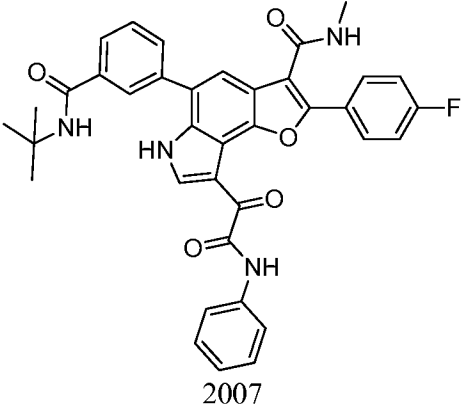
Compound 2006 was prepared via the same procedure towards 2005, using dimethylamine hydrochloride as the starting material.

10

 2006	
MS (M+H) ⁺ Calcd.	583.2
MS (M+H) ⁺ Observ.	583.2
Retention Time	1.25 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	2 min
Flow Rate	1 mL/min

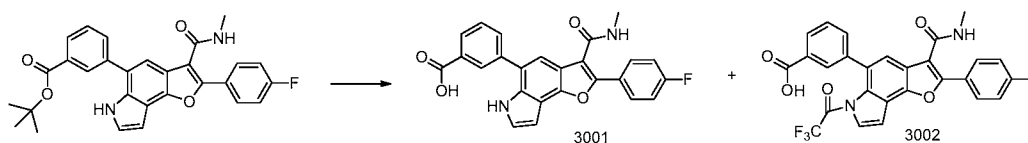
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

Compound 2007 was prepared via the same procedure towards 2005, using aniline as the starting material.

 2007	
MS (M+H) ⁺ Calcd.	631.2
MS (M+H) ⁺ Observ.	631.3
Retention Time	1.90 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	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

5

Preparation of Compounds 3001 and 3002:

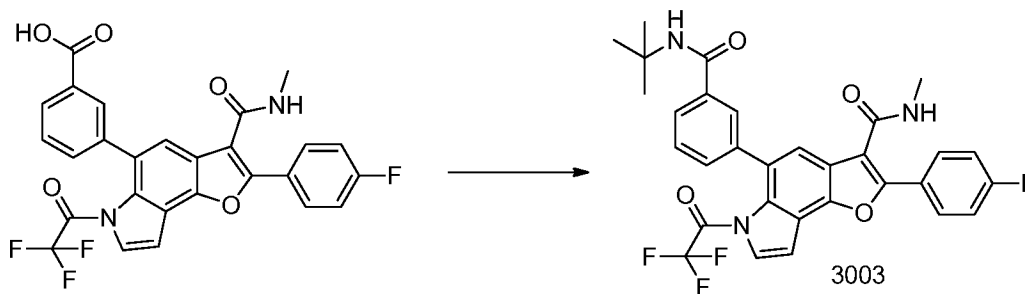


- 10 TFA (1 mL) was added into a solution of tert-butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-5-yl)benzoate in CH₂Cl₂ at room temperature. The reaction was stirred at room temperature for 24 hours. The solvents were removed

under vacuum and the residue was purified by preparative HPLC system to give compound 3001 and compound 3002.

3001	
MS (M+H) ⁺ Calcd.	429.1
MS (M+H) ⁺ Observ.	428.9
Retention Time	2.09 min
3002	
MS (M+H) ⁺ Calcd.	525.1
MS (M+H) ⁺ Observ.	524.9
Retention Time	2.31 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

5 Preparation of Compound 3003:



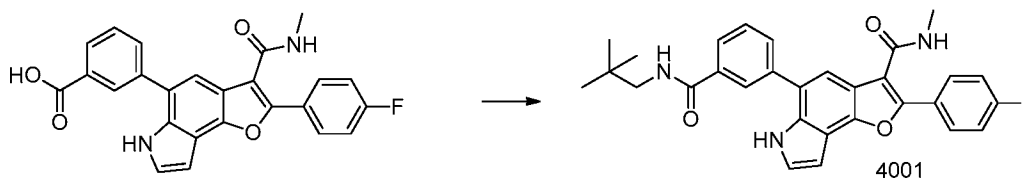
- To a solution of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(2,2,2-trifluoroacetyl)-6H-furo[2,3-e]indol-5-yl)benzoic acid (6 mg) and 2-methylpropan-2-amine (8.37 mg) in DMF (2 mL) was added HATU (6.53 mg) and DIPEA (0.016 mL). The mixture was stirred at room temperature for 4 hours. The mixture was purified by preparative HPLC system.

3003	
MS (M+H) ⁺ Calcd.	580.2
MS (M+H) ⁺ Observ.	580.1
Retention Time	2.16 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	30
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

Preparation of Compounds 4001 - 4022:

The typical procedure, preparation of compound 4001:

5



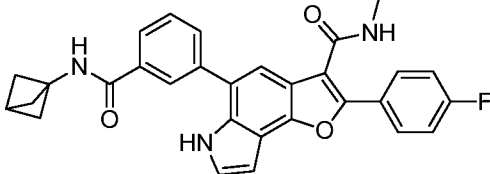
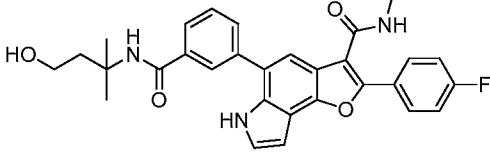
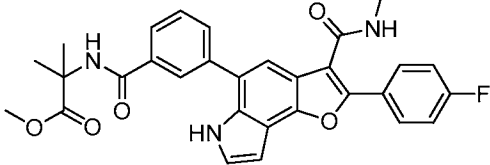
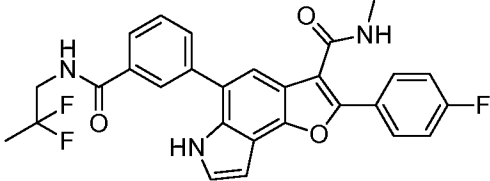
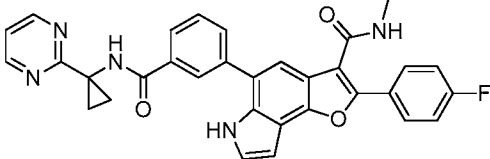
iPr₂NEt (0.25 mL) and HCTU (58 mg) were added into the solution of 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6H-furo[2,3-e]indol-5-yl)benzoic acid (30 mg) and 2,2-dimethylpropan-1-amine (12.2 mg) in DMF (2 mL). The reaction was stirred at room temperature for 24 hours, and the product was isolated by using preparative HPLC system.

4001	
MS (M+H) ⁺ Calcd.	498.2
MS (M+H) ⁺ Observ.	498.0
Retention Time	2.34 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

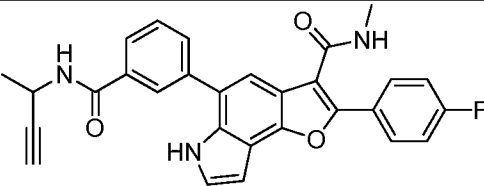
Compounds 4002 – 4022 were prepared via the same procedure towards compound 4001, using the corresponding amines as the starting materials. LC condition for compound 4002 – 4022 was the same for compound 4001.

5

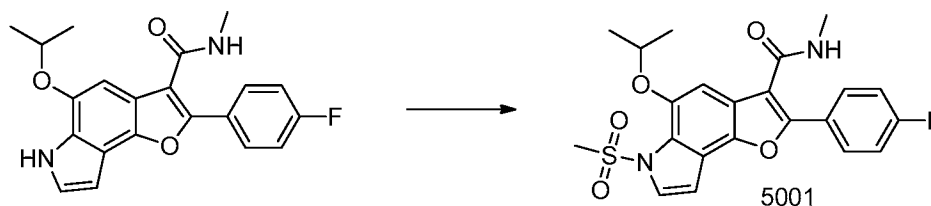
Cmpd #	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4002		494.2	494.0	2.30
4003		514.2	514.0	2.20
4004		528.2	528.0	2.22
4005		506.2	505.9	2.20
4006		546.2	546.0	2.18

Cmpd #	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4007		610.1	610.0	2.33
4008		514.2	514.0	2.12
4009		594.2	594.0	2.39
4010		580.2	580.0	2.38
4011		526.2	526.0	2.13
4012		540.2	540.0	2.13
4013		494.2	494.0	2.14

Cmpd #	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4014		493.3	493.1	2.23
4015		570.2	570.1	2.28
4016		560.2	560.1	2.40
4017		534.2	534.0	2.49
4018		522.2	522.0	2.19
4019		508.2	508.0	2.25
4020		569.2	569.0	2.17

Cmpd #	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4021		480.2	480.0	2.15
4022		495.2	495.1	2.16

Preparation of Compounds 5001, 5003 - 5006:



5

To a solution of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (20 mg) and NaH (4.37 mg) in THF (2 mL) was added methanesulfonyl chloride (12.51 mg). The mixture was stirred at room temperature for 16 hours. The reaction was quenched with aqueous NaHCO₃ solution and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with brine and concentrated. The residue was purified by preparative HPLC system.

10

5001	
MS (M+H) ⁺ Calcd.	445.1
MS (M+H) ⁺ Observ.	445.1
Retention Time	1.48 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA

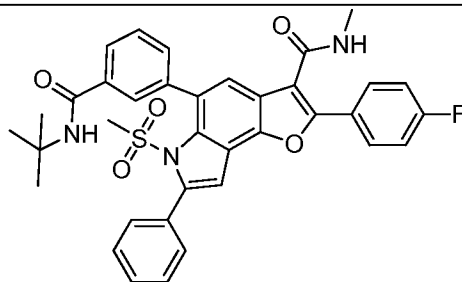
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	50
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

Compounds 5003 - 5005 were prepared via the same procedure towards compound 5001, using the corresponding furo[2,3-e]indoles as the starting materials.

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

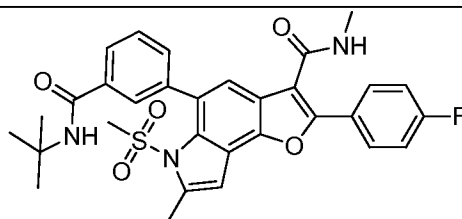
5

5003	
MS (M+H) ⁺ Calcd.	576.2
MS (M+H) ⁺ Observ.	576.4
Retention Time	1.86 min



5004

MS (M+H) ⁺ Calcd.	638.2
MS (M+H) ⁺ Observ.	638.4
Retention Time	1.77 min

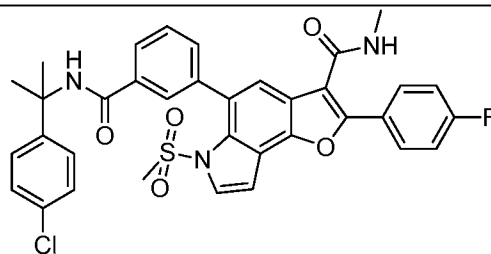


5005

MS (M+H) ⁺ Calcd.	576.2
MS (M+H) ⁺ Observ.	576.4
Retention Time	1.65 min

Compound 5006 was prepared via the same procedure towards compound 5001, using the corresponding furo[2,3-e]indoles as the starting materials.

5



5006

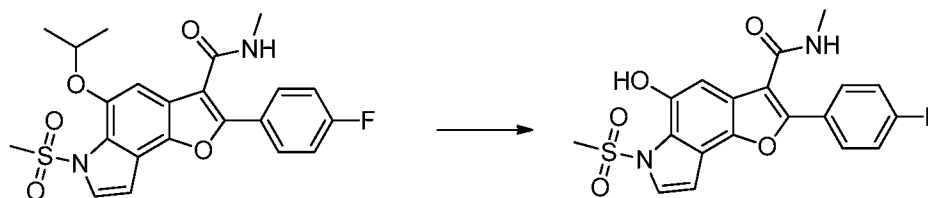
MS (M+H) ⁺ Calcd.	658.2
MS (M+H) ⁺ Observ.	658.2
Retention Time	2.36 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min

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

Preparation of Compound 5002:

Step 1:

5

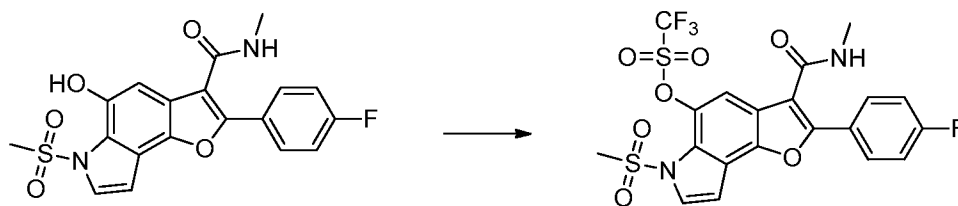


To a solution of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6-(methylsulfonyl)-6H-furo[2,3-e]indole-3-carboxamide (18 mg) in CH₂Cl₂ (5 mL) was added trichloroborane (0.12 mL) at -78°C. The mixture was warmed to room temperature and stirred for 16 hours. The mixture was diluted with 20 mL of CH₂Cl₂ and washed with 5% NaHCO₃ aqueous solution, brine, dried over MgSO₄ and concentrated to give 2-(4-fluorophenyl)-5-hydroxy-N-methyl-6-(methylsulfonyl)-6H-furo[2,3-e]indole-3-carboxamide.

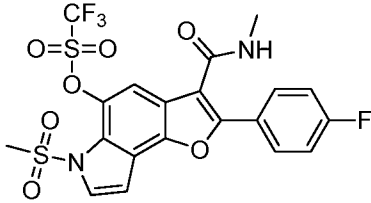
MS (M+H) ⁺ Calcd.	403.1
MS (M+H) ⁺ Observ.	403.0
Retention Time	1.87 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	10
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

15

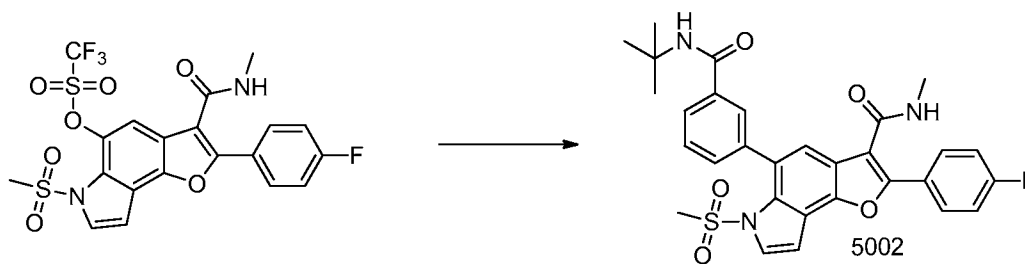
Step 2:



- 5 To a solution of 2-(4-fluorophenyl)-5-hydroxy-N-methyl-6-(methylsulfonyl)-6H-furo[2,3-e]indole-3-carboxamide (12 mg) and NEt_3 (0.025 mL) in CH_2Cl_2 (5 mL) was added a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (53.3 mg) in 1 mL of CH_2Cl_2 dropwise at 0°C . The mixture was stirred at 0°C for 1 hour and then at room temperature for 2 days.
- 10 The reaction was quenched with aqueous 5% NaHCO_3 solution and extracted with CH_2Cl_2 (10 mL). The organic layer was washed with water, brine (5 mL), dried over MgSO_4 and concentrated. The residue was purified by preparative HPLC system.

	
MS (M+H) ⁺ Calcd.	535.0
MS (M+H) ⁺ Observ.	535.0
Retention Time	2.02 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	10
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

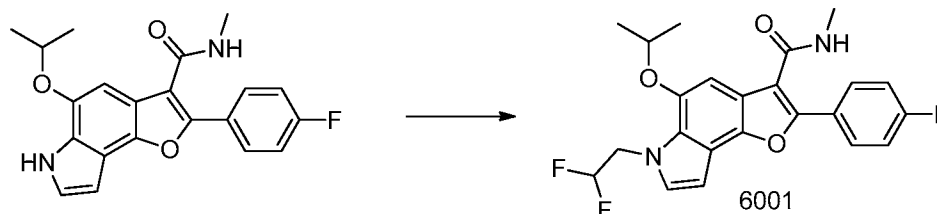
Step 3:



To a mixture of 2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(methylsulfonyl)-6H-furo[2,3-e]indol-5-yl trifluoromethanesulfonate (4.2 mg), (3-(tert-butylcarbamoyl)phenyl)boronic acid (2.61 mg) and Cs_2CO_3 (7.68 mg) in dioxane (2 mL) and water (0.40 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (1.36 mg). The mixture was flushed with nitrogen and then heated at 90°C for 16 hours. The mixture was diluted with water and extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine, dried over MgSO_4 and concentrated. The residue was purified by preparative HPLC system.

5002	
MS (M+H) ⁺ Calcd.	562.2
MS (M+H) ⁺ Observ.	562.2
Retention Time	2.13 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	10
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

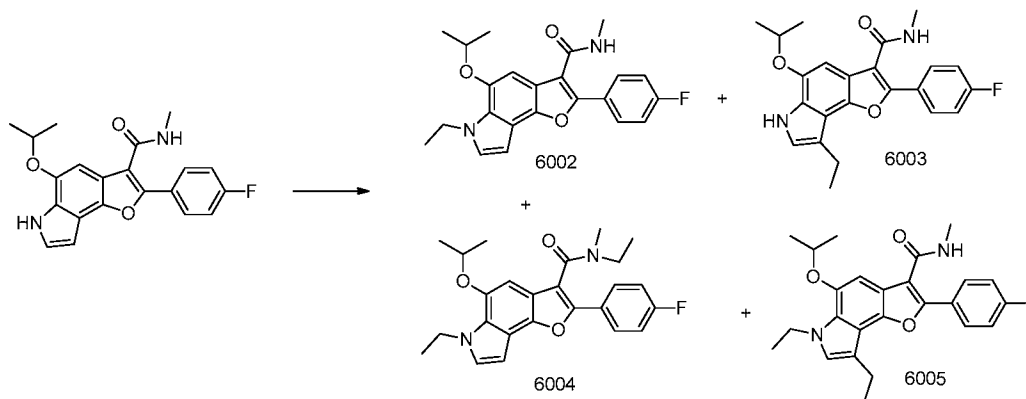
Preparation of Compounds 6001:



- 5 To a solution of 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (20 mg) and NaH (4.37 mg) in THF (2 mL) was added 2-bromo-1,1-difluoroethane (15.82 mg). The mixture was stirred at room temperature for 16 hours. The reaction was quenched with aqueous NaHCO₃ solution and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with brine and concentrated. The
- 10 residue was purified by preparative HPLC system.

6001	
MS (M+H) ⁺ Calcd.	431.2
MS (M+H) ⁺ Observ.	431.1
Retention Time	2.28 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

Preparation of Compounds 6002 – 6005:



- 5 NaH (92 mg, 60%) was added into a solution of EtI (358 mg) and 2-(4-fluorophenyl)-5-isopropoxy-N-methyl-6H-furo[2,3-e]indole-3-carboxamide (560 mg) in THF (10 mL). The reaction was stirred at room temperature for 24 hour, before being quenched by MeOH. Then, products were isolated by preparative HPLC system.

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

10

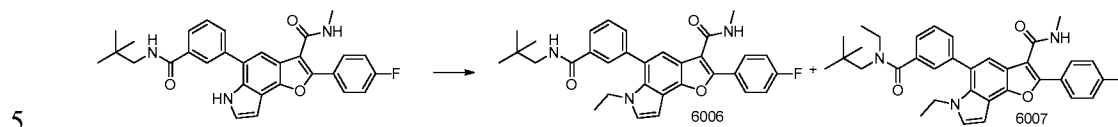
6002	
MS (M+H) ⁺ Calcd.	395.2
MS (M+H) ⁺ Observ.	395.1
Retention Time	2.27 min

6003	
MS (M+H) ⁺ Calcd.	395.2
MS (M+H) ⁺ Observ.	395.1
Retention Time	2.31 min

6004	
MS (M+H) ⁺ Calcd.	423.2
MS (M+H) ⁺ Observ.	423.2
Retention Time	2.46 min

6005	
MS (M+H) ⁺ Calcd.	423.2
MS (M+H) ⁺ Observ.	423.2
Retention Time	2.60 min

Preparation of Compounds 6006 and 6007:



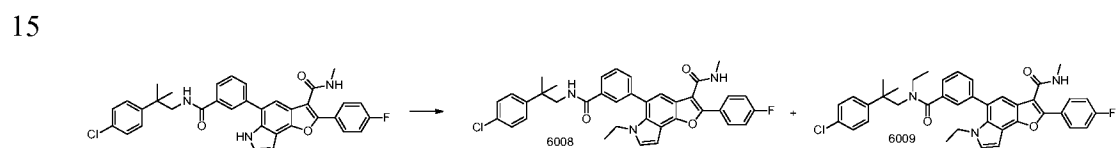
Compounds 6006 and 6007 were prepared via the same procedure towards compounds 6002 - 6005, using 2-(4-fluorophenyl)-N-methyl-5-(3-(neopentylcarbamoyl)phenyl)-6H-furo[2,3-e]indole-3-carboxamide as the starting materials. LC condition for 6006/6007 was the same as that for 6002 - 6005.

10

6006	
MS (M+H) ⁺ Calcd.	526.2
MS (M+H) ⁺ Observ.	526.2
Retention Time	2.48 min

6007	
MS (M+H) ⁺ Calcd.	554.3
MS (M+H) ⁺ Observ.	554.2
Retention Time	2.56 min

Preparation of Compounds 6008 and 6009:



Compounds 6008 and 6009 were prepared via the same procedure towards compounds 6002 - 6005, using 5-(3-((2-(4-chlorophenyl)-2-methylpropyl)carbamoyl)phenyl)-2-(4-

fluorophenyl)-N-methyl-6H-furo[2,3-e]indole-3-carboxamide as the starting materials.

LC condition for 6008/6009 was the same as that for 6002 – 6005.

6008	
MS (M+H) ⁺ Calcd.	622.2
MS (M+H) ⁺ Observ.	622.2
Retention Time	2.58 min

6009	
MS (M+H) ⁺ Calcd.	650.3
MS (M+H) ⁺ Observ.	650.3
Retention Time	2.65 min

5

Biological Methods

The compound demonstrated activity against HCV NS5B as determined in the following HCV RdRp assays.

10

HCV NS5B RdRp cloning, expression, and purification. The cDNA encoding NS5B proteins of HCV genotype 1b (Con1), a genotype 1b variant with amino acid 316 mutated from cysteine to asparagine, and genotype 2a (JFH-1), were cloned into the pET21a expression vector. Each untagged protein was expressed with an 18 amino acid C-terminal truncation to enhance the solubility. The E. coli competent cell line BL21(DE3) was used for expression of the protein. Cultures were grown at 37 °C for ~ 4 hours until the cultures reached an optical density of 2.0 at 600 nm. The cultures were cooled to 20 °C and induced with 1 mM IPTG. Fresh ampicillin was added to a final concentration of 50 µg/mL and the cells were grown overnight at 20 °C.

20

Cell pellets (3L) were lysed for purification to yield 15-24 mgs of purified NS5B. The lysis buffer consisted of 20 mM Tris-HCl, pH 7.4, 500 mM NaCl, 0.5% triton X-100, 1 mM DTT, 1mM EDTA, 20% glycerol, 0.5 mg/mL lysozyme, 10 mM MgCl₂, 15 ug/mL deoxyribonuclease I, and Complete TM protease inhibitor tablets (Roche). After addition of the lysis buffer, frozen cell pellets were resuspended using a tissue homogenizer. To reduce the viscosity of the sample, aliquots of the lysate were sonicated on ice using a microtip attached to a Branson sonicator. The sonicated lysate was centrifuged at 100,000 x g for 30 minutes at 4 °C and filtered through a 0.2 µm filter unit (Corning).

25

The protein was purified using two sequential chromatography steps: Heparin sepharose CL-6B and polyU sepharose 4B. The chromatography buffers were identical to the lysis buffer but contained no lysozyme, deoxyribonuclease I, MgCl_2 or protease inhibitor and the NaCl concentration of the buffer was adjusted according to the requirements for charging the protein onto the column. Each column was eluted with a NaCl gradient which varied in length from 5-50 column volumes depending on the column type. After the final chromatography step, the resulting purity of the enzyme is >90% based on SDS-PAGE analysis. The enzyme was aliquoted and stored at -80°C .

HCV NS5B RdRp enzyme assay. An on-bead solid phase homogeneous assay was used in a 384-well format to assess NS5B inhibitors (Wang Y-K, Rigat K, Roberts S, and Gao M (2006) Anal Biochem, 359: 106-111). The biotinylated oligo dT₁₂ primer was captured on streptavidin-coupled imaging beads (GE, RPNQ0261) by mixing primer and beads in 1X buffer and incubating at room temperature for three hours. Unbound primer was removed after centrifugation. The primer-bound beads were resuspended in 3X reaction mix (20 mM Hepes buffer, pH 7.5, dT primer coupled beads, poly A template, ^3H -UTP, and RNase inhibitor (Promega N2515)). Compounds were serially diluted 1:3 in DMSO and aliquoted into assay plates. Equal volumes (5 μL) of water, 3X reaction mix, and enzyme in 3X assay buffer (60 mM Hepes buffer, pH 7.5, 7.5 mM MgCl_2 , 7.5 mM KCl, 3 mM DTT, 0.03 mg/mL BSA, 6 % glycerol) were added to the diluted compound on the assay plate. Final concentration of components in 384-well assay: 0.36 nM template, 15 nM primer, 0.29 μM ^3H -UTP (0.3 μCi), 1.6 U/ μL RNase inhibitor, 7 nM NS5B enzyme, 0.01 mg/mL BSA, 1 mM DTT, and 0.33 $\mu\text{g}/\mu\text{L}$ beads, 20 mM Hepes buffer, pH 7.5, 2.5 mM MgCl_2 , 2.5 mM KCl, and 0.1 % DMSO.

Reactions were allowed to proceed for 24 hours at 30°C and terminated by the addition of 50 mM EDTA (5 μL). After incubating for at least 15 minutes, plates were read on an Amersham LEADseeker multimodality imaging system.

IC_{50} values for compounds were determined using ten different [I]. IC_{50} values were calculated from the inhibition using the four-parameter logistic formula $y = A + ((B -$

$A/(1+((C/x)^D)))$, where A and B denote minimal and maximal % inhibition, respectively, C is the IC_{50} , D is hill slope and x represents compound concentration.

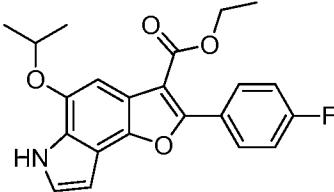
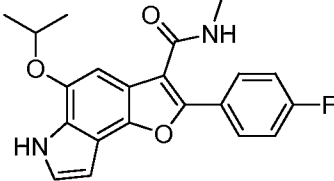
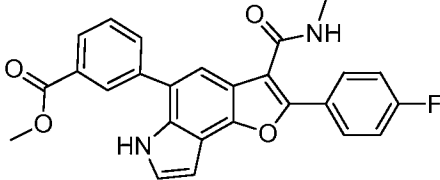
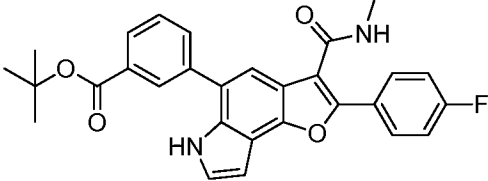
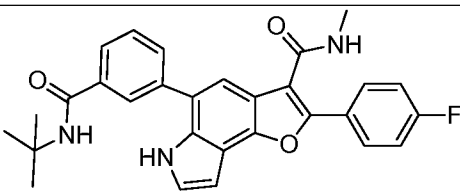
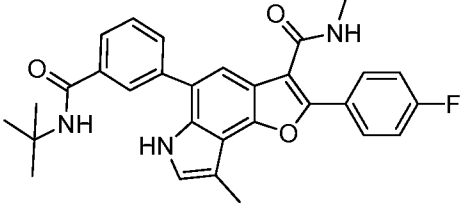
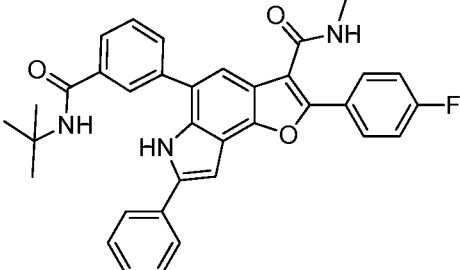
Cell lines. The cell lines used to evaluate compounds consist of a human
5 hepatocyte derived cell line (Huh-7) that constitutively expresses a genotype 1b (Con-1)
HCV replicon or a genotype 1b (Con-1) HCV replicon with an asparagine replacing the
cysteine at amino acid 316, or a genotype 2a (JFH-1) replicon, containing a Renilla
luciferase reporter gene. These cells were maintained in Dulbecco's modified Eagle
medium (DMEM) containing 10% FBS, 100 U/mL penicillin/streptomycin and 1.0
10 mg/mL G418.

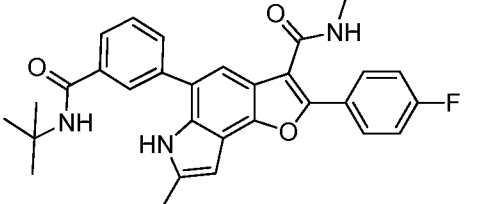
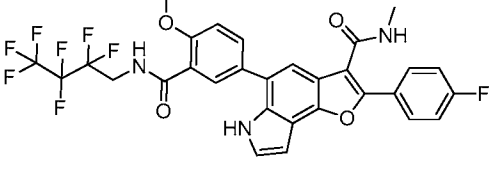
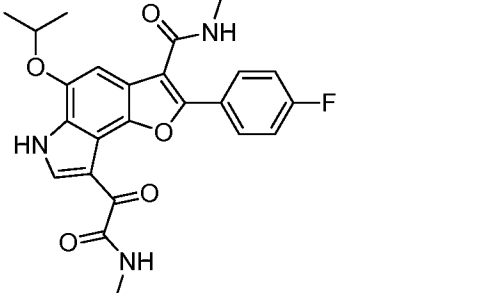
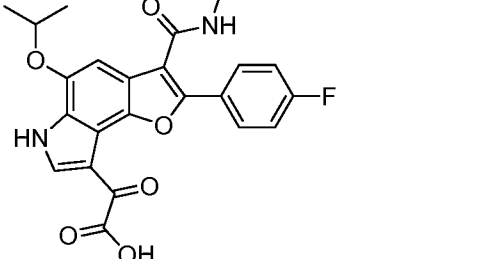
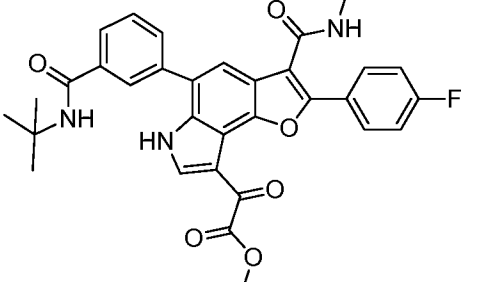
HCV replicon luciferase assay. To evaluate compound efficacy, titrated
compounds were transferred to sterile 384-well tissue culture treated plates, and the plates
were seeded with HCV replicon cells (50 μ L at a density of 2.4×10^3 cells/well) in
15 DMEM containing 4 % FBS (final DMSO concentration at 0.5 %). After 3 days
incubation at 37°C, cells were analyzed for Renilla Luciferase activity using the EnduRen
substrate (Promega cat #E6485) according to the manufacturer's directions. Briefly, the
EnduRen substrate was diluted in DMEM and then added to the plates to a final
concentration of 7.5 μ M. The plates were incubated for at least 1 h at 37°C then read on a
20 Viewlux Imager (PerkinElmer) using a luminescence program. The 50% effective
concentration (EC_{50}) was calculated using the four-parameter logistic formula noted
above.

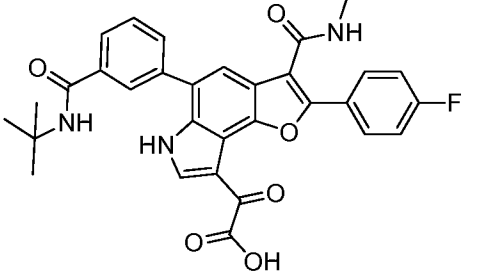
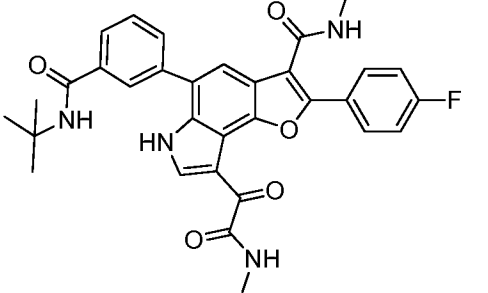
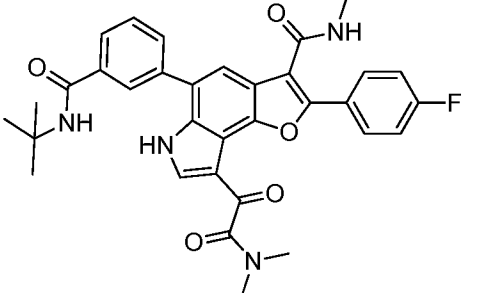
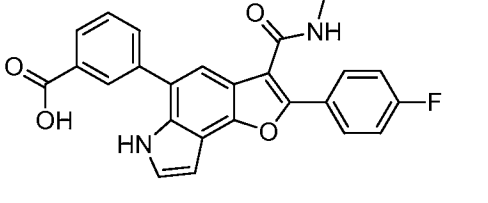
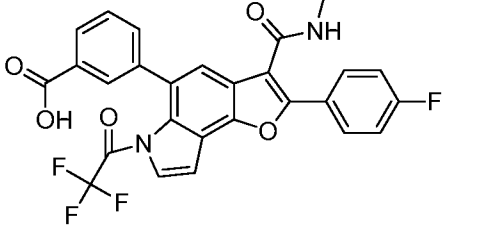
To assess cytotoxicity of compounds, Cell Titer-Blue (Promega) was added to the
25 EnduRen-containing plates and incubated for at least 4 hrs at 37°C. The fluorescence
signal from each well was read using a Viewlux Imager. All CC_{50} values were calculated
using the four-parameter logistic formula.

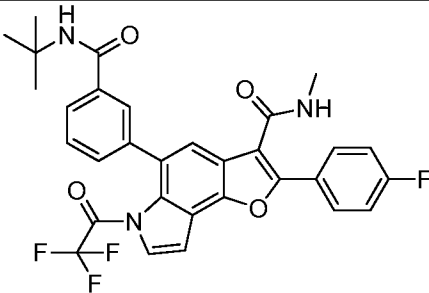
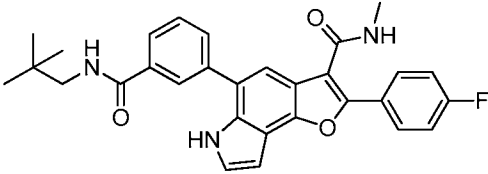
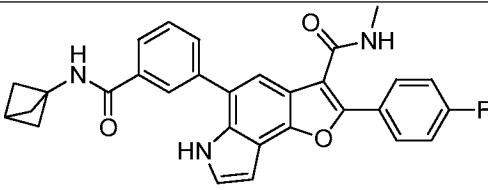
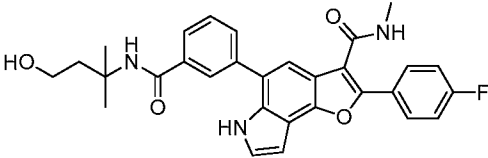
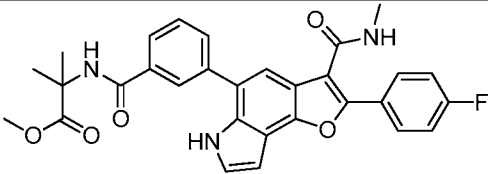
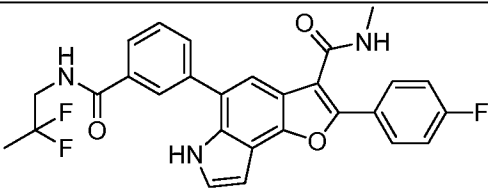
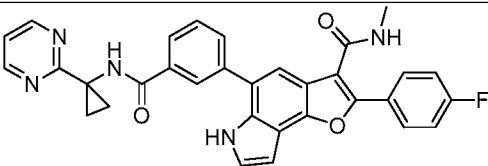
Compound EC_{50} data is expressed as A: < 100 nM; B = 100-1000 nM; C > 1000
nM). Representative data for compounds is reported in Table 2.

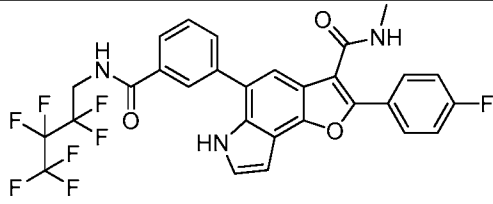
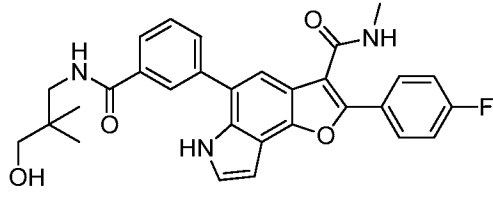
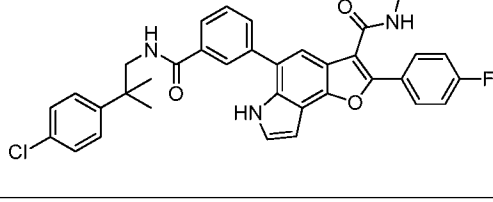
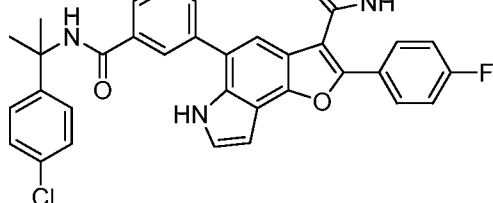
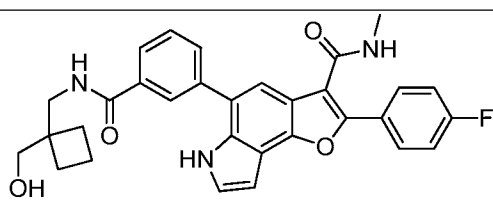
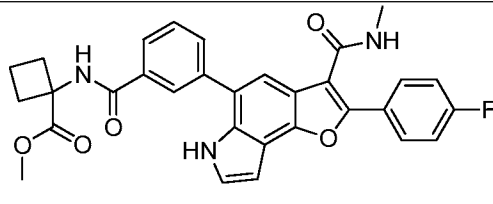
Table 2

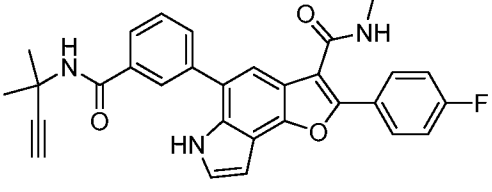
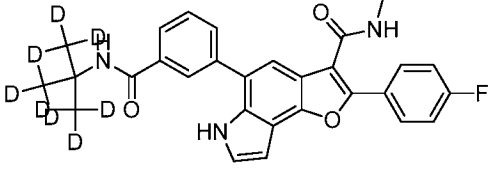
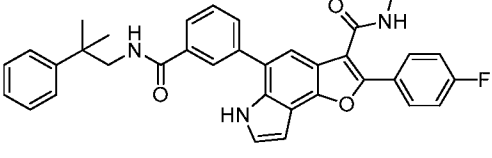
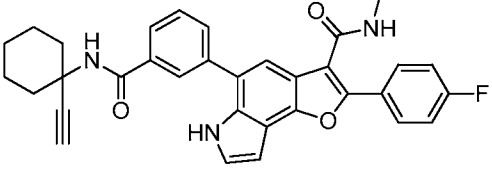
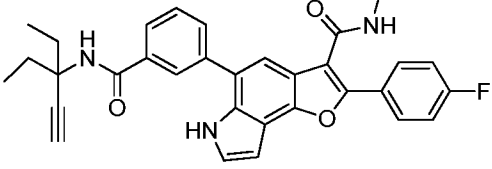
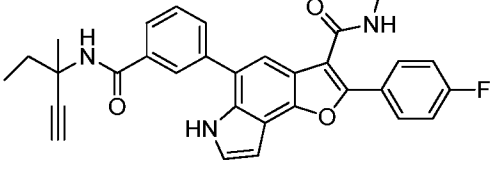
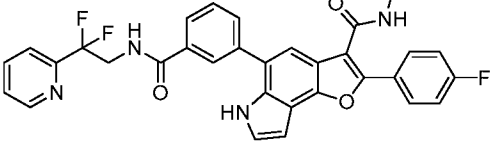
Cmpd#	Structure	EC ₅₀ (uM) 1b
1001		C
1002		C
1003		1.46 C
1004		B
1005		0.050 A
1006		0.51 B
1007		B

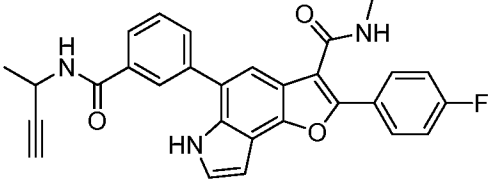
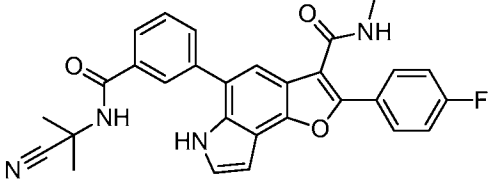
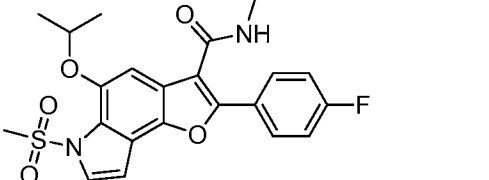
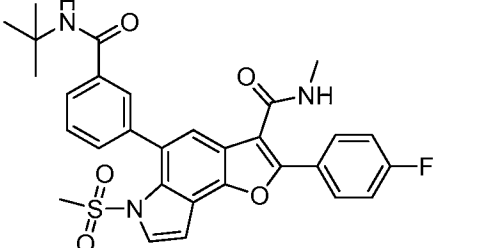
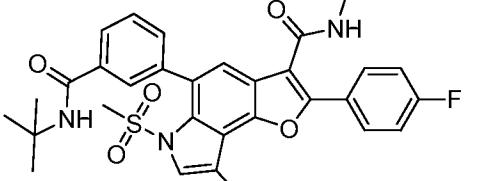
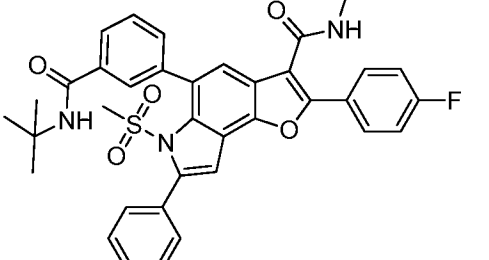
Cmpd#	Structure	EC ₅₀ (uM) 1b
1008		B
1009		A
2001		C
2002		C
2003		0.44 B

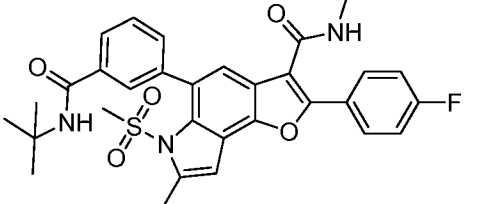
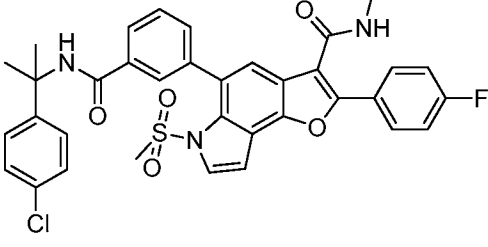
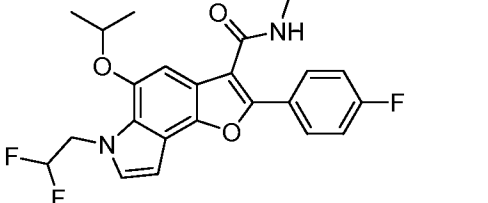
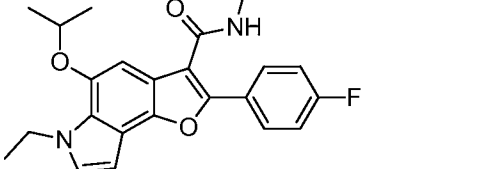
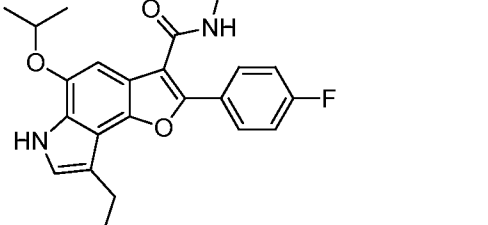
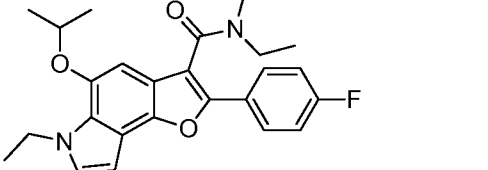
Cmpd#	Structure	EC ₅₀ (uM) 1b C
2004		C
2005		5.16 C
2006		C
3001		C
3002		C

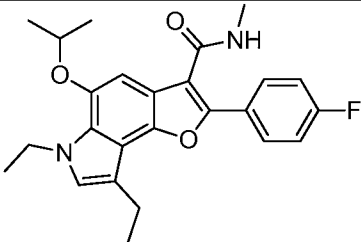
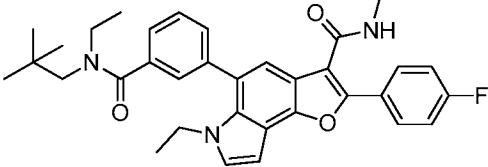
Cmpd#	Structure	EC ₅₀ (uM) 1b
3003		0.20 B
4001		0.083 A
4002		A
4003		A
4004		A
4005		0.15 B
4006		A

Cmpd#	Structure	EC ₅₀ (uM) 1b
4007		0.049 A
4008		0.13 B
4009		B
4010		0.027 A
4011		B
4012		B

Cmpd#	Structure	EC ₅₀ (uM) 1b
4013		A
4014		A
4016		B
4017		B
4018		A
4019		B
4020		B

Cmpd#	Structure	EC ₅₀ (uM) 1b
4021		B
4022		0.015 A
5001		C
5002		A
5003		C
5004		B

Cmpd#	Structure	EC ₅₀ (uM) 1b C
5005		C
5006		A
6001		C
6002		C
6003		C
6004		C

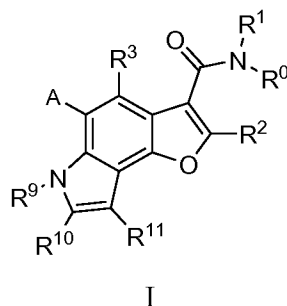
Cmpd#	Structure	EC ₅₀ (uM) 1b C
6005		C
6007		B

It will be evident to one skilled in the art that the present invention 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 and range of equivalency of the claims are therefore intended to be embraced therein.

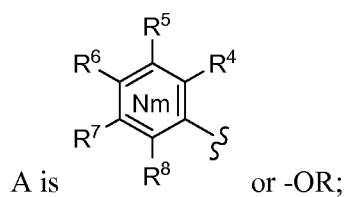
CLAIMS

We claim:

1. A compound of Formula I, including pharmaceutically acceptable salts thereof:



wherein



R is alkyl, cycloalkyl, alkenyl, cyclokenyl or alkynyl;

m is 0 or 1;

R⁰, R¹ is methyl or ethyl;

R² is phenyl that is independently substituted with 0-2 halo or methoxy or is para substituted with W-Ar¹;

W is -O- or -NH-;

Ar¹ is phenyl or para-halophenyl;

R³ is hydrogen, halo, or alkyl;

R^4 , R^5 , R^6 , R^7 , R^8 are each independently selected from the group of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, halocycloalkyl, hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxyalkyl, alkoxy, hydroxyalkyloxy, alkoxyalkyloxy, Ar^2 , $COOR^{101}$ and $CON(R^{102})(R^{103})$;

R^{101} is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} , R^{103} are each independently selected from the group of hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkyl alkynyl, cyclic ether, cyclic amine, lactame, fused bicyclic alkyl, bridged bicyclic alkyl, spiro bicyclic alkyl, fused bicyclic ether, bridged bicyclic ether, spiro bicyclic ether, fused bicyclic amine, bridged bicyclic amine and spiro bicyclic amine, with 0-3 substituents selected from the group of halo, OH, OR^{104} , NH_2 , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, $S(O)_2R^{104}$, $S(O)_2NR^{105}R^{106}$, $NR^{104}CONR^{105}R^{106}$, $OR^{104}CONR^{105}R^{106}$, $C(=NR^{107})NR^{105}R^{106}$, $NR^{108}C(=NR^{107})NR^{105}R^{106}$, haloalkoxy, Ar^2 , $O-Ar^2$, and $NR^{105}-Ar^2$; or

R^{102} and R^{103} can form a ring by joining two atoms, one from each of R^{102} and R^{103} ; or

R^{102} and R^{103} can form a bicyclic or tricyclic ring by joining multiple atoms from each of R^{102} and R^{103} ;

Ar^2 is phenyl, 5-membered heterocyclic or 6-membered heterocyclic (aromatic or nonaromatic) ring, and is substituted with 0-3 substituents selected from the group of cyano, halo, alkyl, cycloalkyl, haloalkyl, OH, OR^{104} , haloalkoxy, NH_2 , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, $S(O)_2R^{104}$, $S(O)_2NR^{105}R^{106}$, and $NR^{104}CONR^{105}R^{106}$;

R^{104} is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} , R^{106} are each independently hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{105} and R^{106} can form a ring by joining two atoms, one from each of R^{105} and R^{106} ;

R^{107} , R^{108} are each independently selected from the group of hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{107} and R^{108} can form a ring by joining two atoms, one from each of R^{107} and R^{108} ;

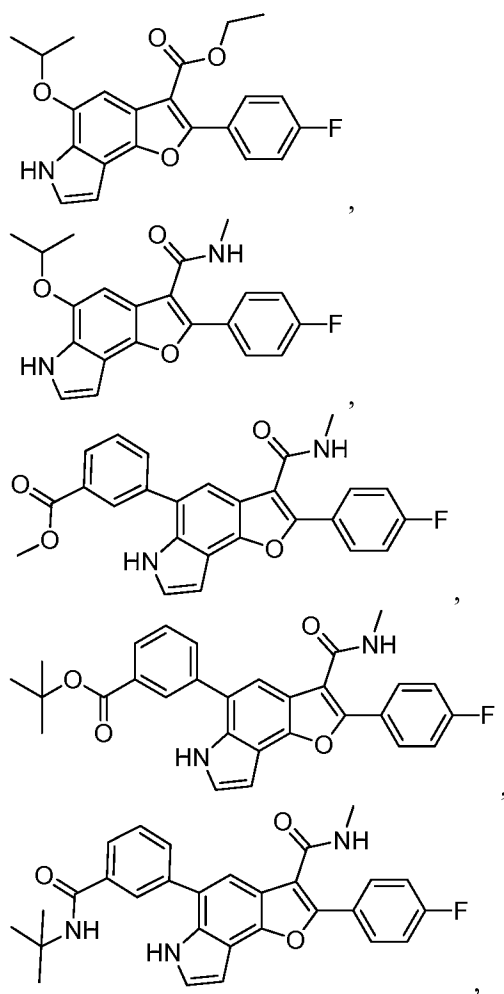
R^9 is hydrogen, R^{201} , COR^{201} or SO_2R^{201} ;

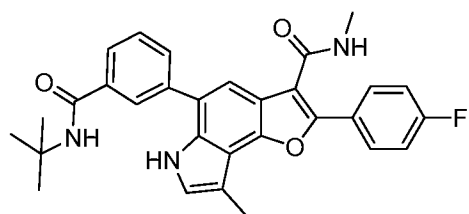
R^{201} is hydrogen, alkyl or cycloalkyl with 0-3 substituents selected from the group of halo, hydroxyl, alkoxy, haloalkoxy, phenyl and heterocyclic;

R^{10} , R^{11} are each independently selected from the group of hydrogen, alkyl, cycloalkyl, ester, amide, 2-keto acid, 2-keto ester, 2-keto amide, phenyl and heterocyclic, with 0-3 substituents selected from halo, hydroxyl, alkoxy, haloalkoxy, ester, amide, oxalate, oxalamide, phenyl and heterocyclic.

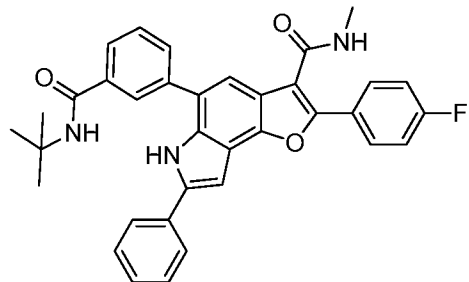
2. A compound of claim 1 wherein m is 0.
3. A compound of claim 1 wherein R^2 is phenyl which is substituted with one halo group.
4. A compound of claim 2 wherein said halo group is fluoro.
5. A compound of claim 1 wherein R^4 , R^5 , R^6 , R^7 , R^8 are independently selected from the group of $COOR^{101}$ and $CON(R^{102})(R^{103})$.
6. A compound of claim 5 wherein R^7 is selected from the group of $COOR^{101}$ and $CON(R^{102})(R^{103})$.

7. A compound of claim 5 wherein R^{102} , R^{103} are each independently selected from the group of hydrogen, alkyl, and haloalkyl.
8. A compound of claim 1 wherein R^9 is SO_2R^{201} .
9. A compound of claim 1 wherein m is 0, R^2 is phenyl which is substituted with one fluoro group, and R^7 is $CON(R^{102})(R^{103})$.
10. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

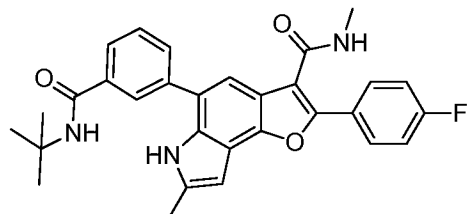




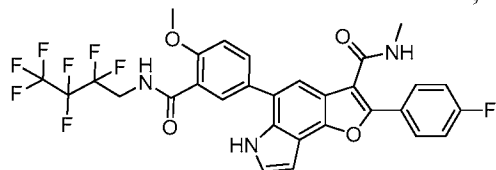
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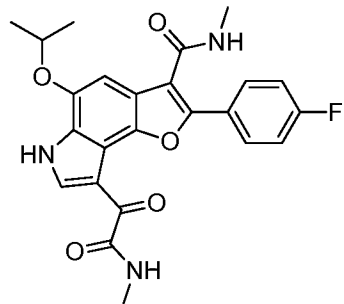
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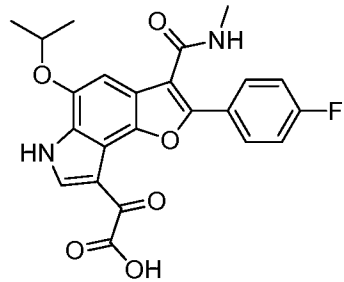
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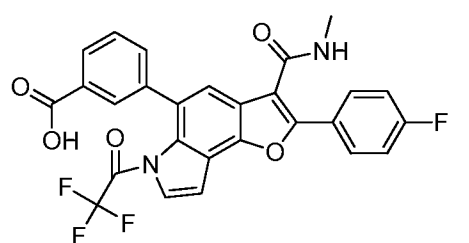
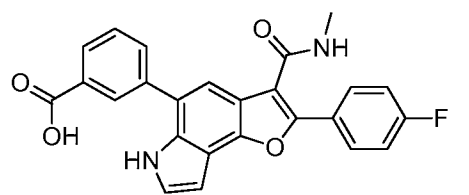
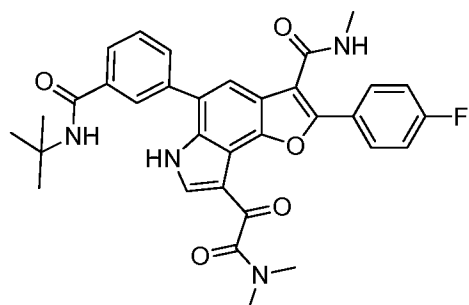
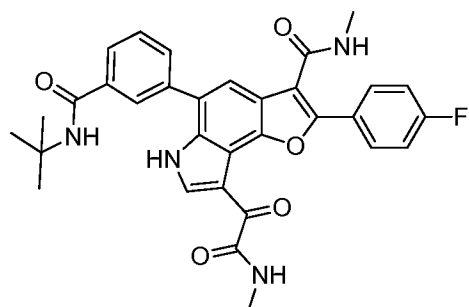
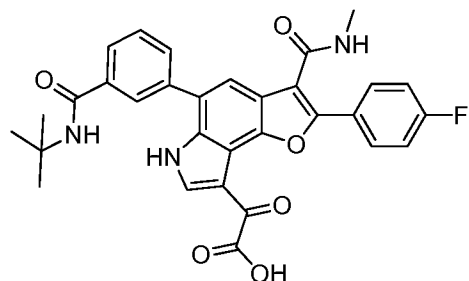
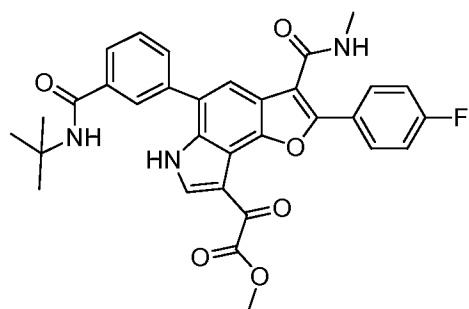
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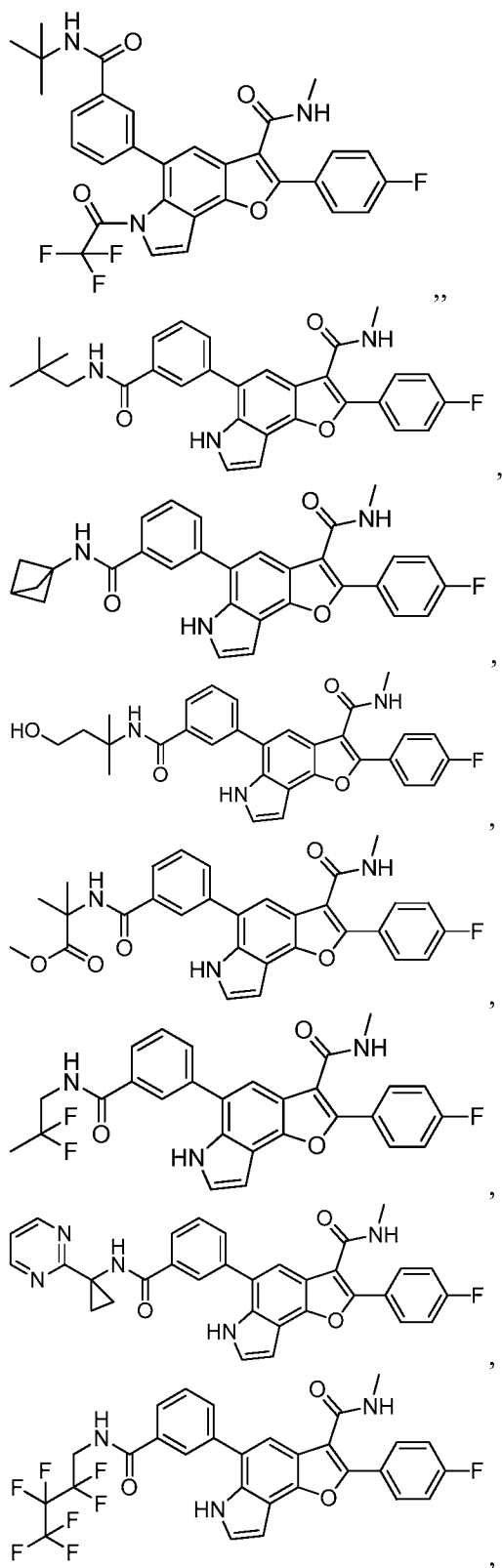


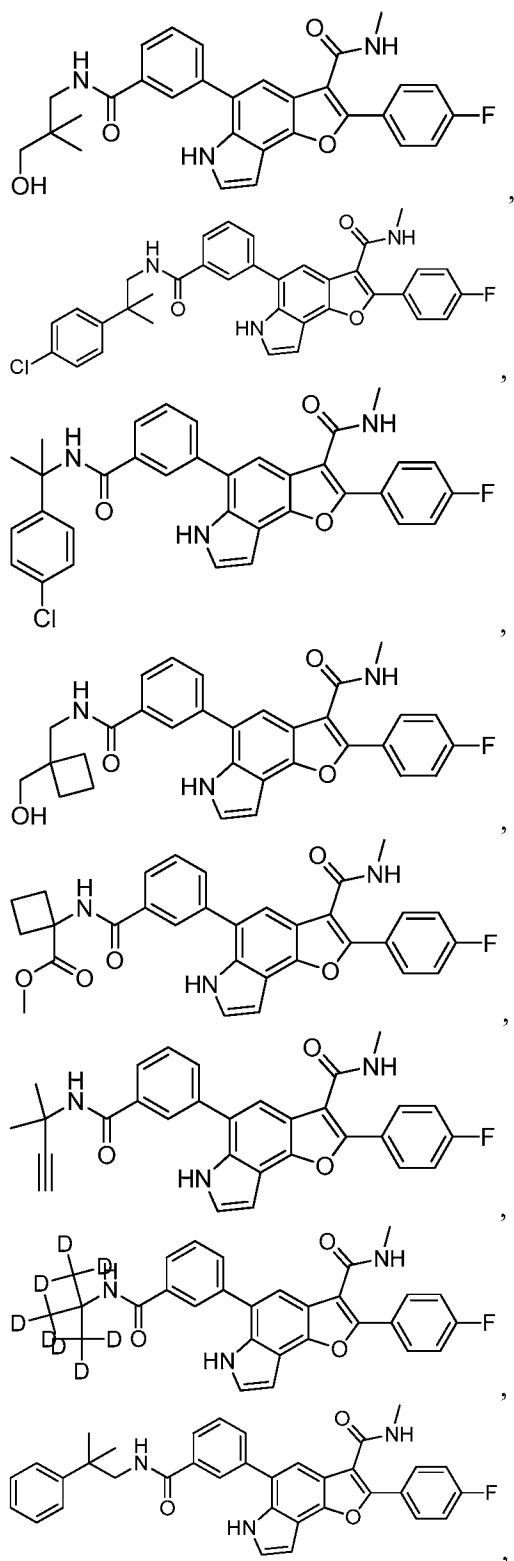
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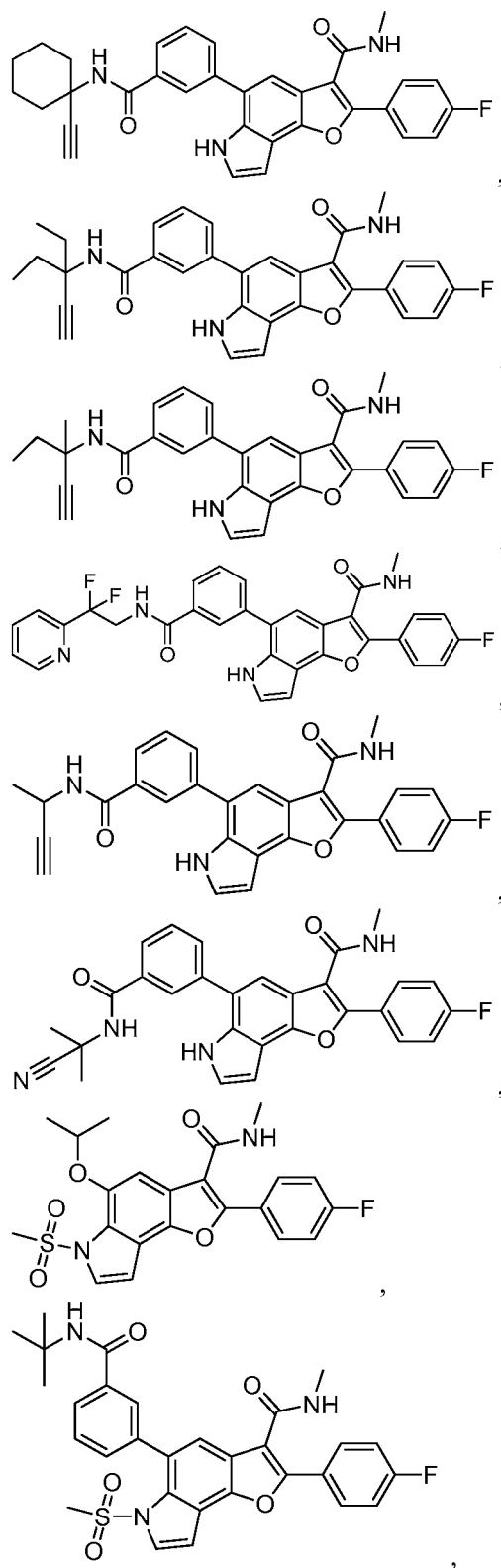


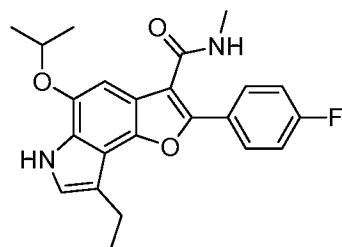
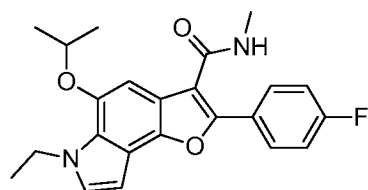
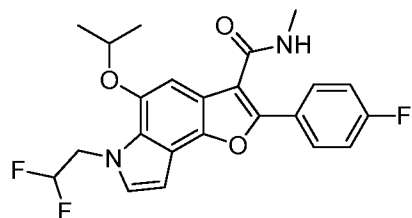
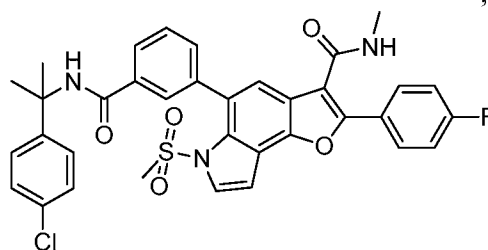
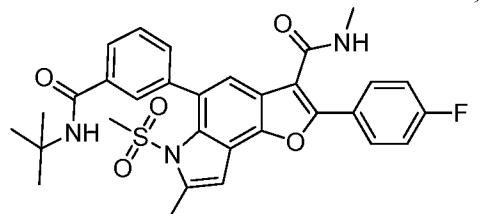
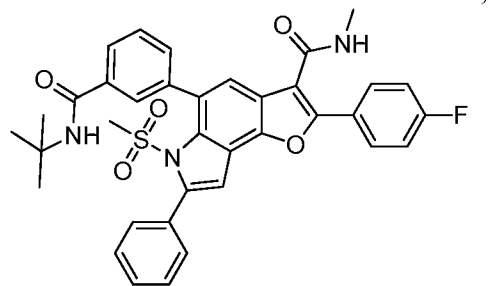
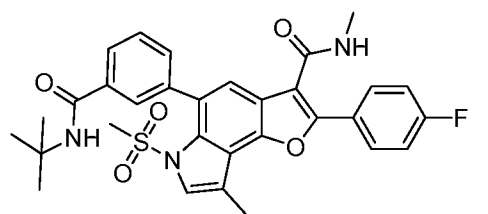
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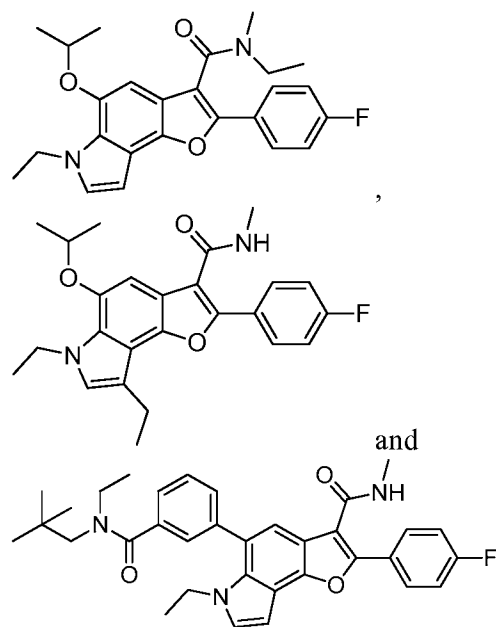




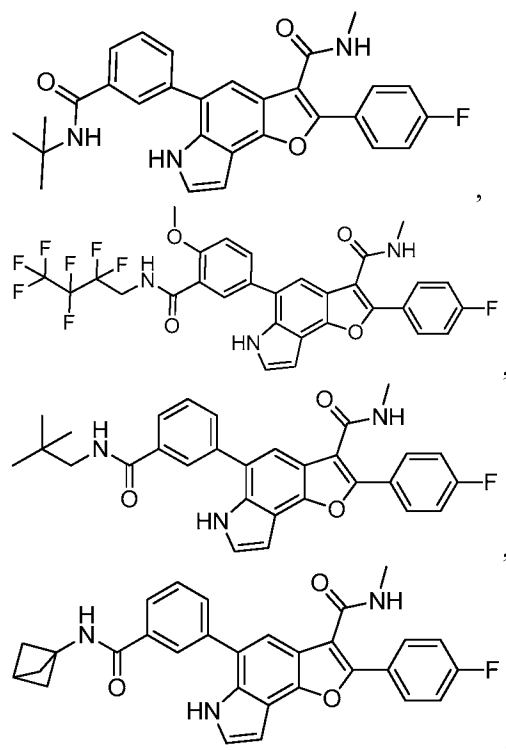


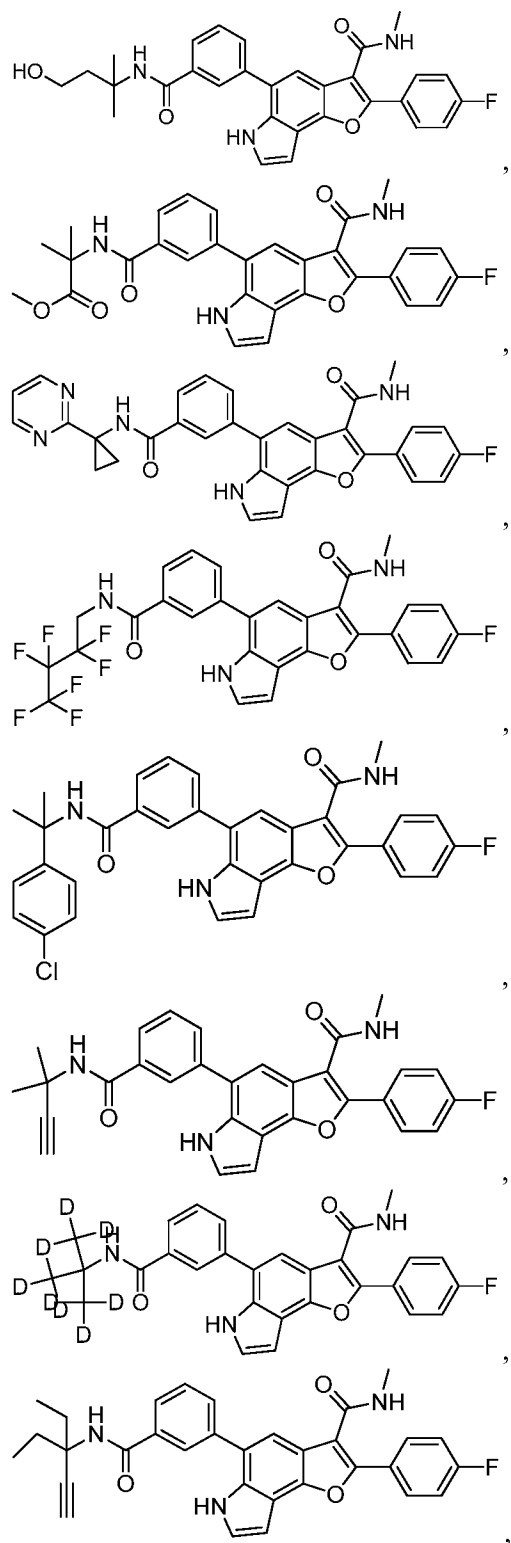


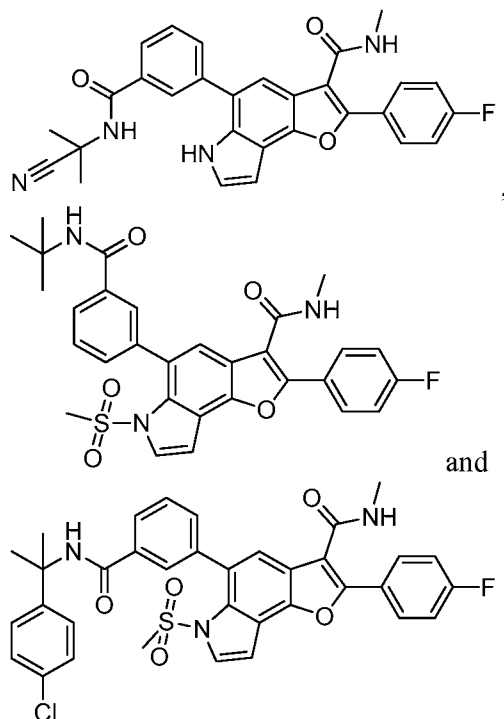




11. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:







12. A composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient and/or diluent.
13. A composition comprising a compound of claim 10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient and/or diluent.
14. A composition comprising a compound of claim 11 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient and/or diluent.
15. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 1 to a patient.
16. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 10 to a patient.
17. A method of treating hepatitis C infection comprising administering a therapeutically effective amount of a compound of claim 11 to a patient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/021641

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D491/048 A61K31/407 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, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/101022 A1 (HOFFMANN LA ROCHE [CH]; LABADIE SHARADA SHENVI [US]) 20 August 2009 (2009-08-20) cited in the application the whole document	1-17
A	WO 2012/058125 A1 (PRESIDIO PHARMACEUTICALS INC [US]; ZHONG MIN [US]) 3 May 2012 (2012-05-03) cited in the application the whole document	1-17
A	WO 2009/152200 A1 (SCHERING CORP [US]; VENKATRAMAN SRIKANTH [US]) 17 December 2009 (2009-12-17) the whole document	1-17



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

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"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

20 May 2015

Date of mailing of the international search report

01/06/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/021641

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