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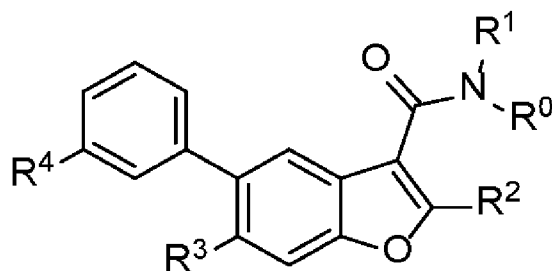
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I

(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:

BENZOFURAN COMPOUNDS FOR THE TREATMENT OF HEPATITIS C

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application No. 62/118048 filed February 19, 2015, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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).

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 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 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.

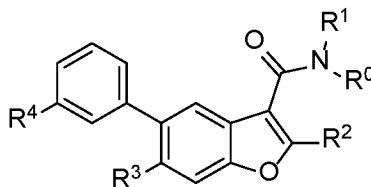
HCV-796, an HCV NS5B inhibitor, has shown an ability to reduce HCV RNA levels in patients. The viral RNA levels decreased transiently and then rebounded during dosing when treatment was with the compound as a single agent

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
 5 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
 10 mechanism of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, or bioavailability. Also needed are new formulations and methods of treatment which utilize these compounds.

SUMMARY OF THE INVENTION

15 There are disclosed compounds of Formula I



I

wherein

20

R^0 and R^1 are independently hydrogen or methyl;

R^2 is optionally substituted aryl with 0-2 halo;

R^4 is COOR^{101} or $\text{CON}(\text{R}^{102})(\text{R}^{103})$;

R^{101} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl with 0-2 substituents

25 selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} and R^{103} are each independently hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , NH_2 , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, $\text{S}(\text{O})_2\text{R}^{104}$, $\text{S}(\text{O})_2\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{OR}^{104}\text{CONR}^{105}\text{R}^{106}$,

30 $\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{108}\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, C_1 - C_6 alkyl, halo substituted phenyl, phenyl, C_1 - C_3 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl,

5 COOR¹⁰⁴-NHCO C_1 - C_3 alkyl;

R^{104} is hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{107} and R^{108} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

15 R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, -COO C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $NR^{201}R^{202}$,

R^{201} is selected from the group of hydrogen, -SO₂ C_1 - C_3 alkyl, alkenyl, alkyne, haloalkyl, haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl, cyanoalkynyl, cycloalkyl, halocycloalkyl, (haloalkyl)cycloalkyl, (halocycloalkyl)cycloalkyl, cyanocycloalkyl, (cyanoalkyl)cycloalkyl, (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl, (hydroxyalkyl)cycloalkyl, (hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl, (alkoxyalkyl)cycloalkyl, and

25 (alkoxycycloalkyl)cycloalkyl;

R^{202} is selected from the group of CN(C_1 - C_6 alkyl), C_3 - C_6 cycloalkyl(C_1 - C_6 alkyl), halo(C_1 - C_6 alkyl)_n, halo(C_2 - C_6 alkenyl)_n, CF_3CF_2 (C_1 - C_6 alkyl)_n, CF_3 (C_1 - C_6 alkyl)_n, alkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl, cyanoalkynyl, cycloalkyl, halocycloalkyl, (haloalkyl)cycloalkyl, (halocycloalkyl)cycloalkyl, cyanocycloalkyl, (cyanoalkyl)cycloalkyl, (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl, (hydroxyalkyl)cycloalkyl, (hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl, (alkoxyalkyl)cycloalkyl, and (alkoxycycloalkyl)cycloalkyl;

30

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

The invention also relates to pharmaceutical compositions comprising a
5 compound of Formula I, including a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier.

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.

10 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
embodiments, hereinafter described.

15 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:

20 “Hydrogen” or “H” refers to hydrogen, including its isotopes, such as deuterium.

“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,”

25 “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
30 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 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.

Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R. 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.

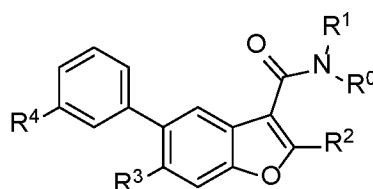
10 The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents.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

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
25 stereoisomers can be made using methods known in the art. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods commonly known in the art. The use of wedges or hashes in the depictions of molecular structures in the following schemes and tables is intended only to indicate relative stereochemistry, and should not be interpreted as implying
30 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.

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



I

wherein

R^0 and R^1 are independently hydrogen or methyl;

R^2 is optionally substituted aryl with 0-2 halo;

R^4 is COOR^{101} or $\text{CON}(\text{R}^{102})(\text{R}^{103})$;

R^{101} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} and R^{103} are each independently hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , NH_2 , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, $\text{S}(\text{O})_2\text{R}^{104}$, $\text{S}(\text{O})_2\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{OR}^{104}\text{CONR}^{105}\text{R}^{106}$,

$\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{108}\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo

substituted phenyl, phenyl, C₁-C₃ alkoxy C₁-C₃ alkyl, hydroxy C₁-C₃ alkyl,
COOR¹⁰⁴-NHCO C₁-C₃ alkyl;

R¹⁰⁴ is hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted
C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and
5 haloalkoxy;

R¹⁰⁵ and R¹⁰⁶ are each independently hydrogen, optionally substituted C₁-C₆
alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from
halo, hydroxyl, alkoxy, and haloalkoxy; or

R¹⁰⁷ and R¹⁰⁸ are each independently hydrogen, optionally substituted C₁-C₆
10 alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from
halo, hydroxyl, alkoxy, and haloalkoxy; or

R¹⁰ and R¹¹ are independently hydrogen or C₁-C₆ alkyl;

R¹² is substituted C₁-C₆ alkynyl, C₃-C₈ cycloalkyl, -COO C₁-C₆ alkyl, phenyl
or CF₂CF₃;

15 R³ is NR²⁰¹R²⁰²;

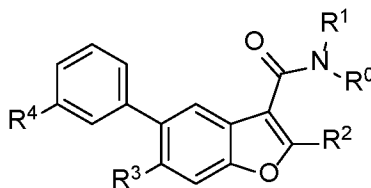
R²⁰¹ is selected from the group of hydrogen, -SO₂ C₁-C₃ alkyl, alkenyl,
alkynyl, haloalkyl, haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl,
cyanoalkynyl, cycloalkyl, halocycloalkyl, (haloalkyl)cycloalkyl,
(halocycloalkyl)cycloalkyl, cyanocycloalkyl, (cyanoalkyl)cycloalkyl,
20 (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl, (hydroxyalkyl)cycloalkyl,
(hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl, (alkoxyalkyl)cycloalkyl, and
(alkoxycycloalkyl)cycloalkyl;;

R²⁰² is selected from the group of CN(C₁-C₆ alkyl), C₃-C₆ cycloalkyl(C₁-C₆
alkyl), halo(C₁-C₆ alkyl)_n, halo(C₂-C₆ alkenyl)_n, CF₃CF₂(C₁-C₆ alkyl)_n, CF₃ (C₁-C₆
25 alkyl)_n, alkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkenyl, alkynyl, haloalkyl,
haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl, cyanoalkynyl, cycloalkyl,
halocycloalkyl, (haloalkyl)cycloalkyl, (halocycloalkyl)cycloalkyl, cyanocycloalkyl,
(cyanoalkyl)cycloalkyl, (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl,
(hydroxyalkyl)cycloalkyl, (hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl,
30 (alkoxyalkyl)cycloalkyl, and (alkoxycycloalkyl)cycloalkyl;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment of the invention, there is disclosed a compound of Formula I



I

wherein

R^0 is hydrogen;

R^1 is methyl;

R^2 is phenyl substituted with 1-2 halo;

R^4 is COOR^{101} or $\text{CON}(\text{R}^{102})(\text{R}^{103})$;

R^{101} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} and R^{103} are each independently hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , NH_2 , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, $\text{S}(\text{O})_2\text{R}^{104}$, $\text{S}(\text{O})_2\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{OR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{108}\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo substituted phenyl, phenyl, $\text{C}_1\text{-C}_3$ alkoxy $\text{C}_1\text{-C}_3$ alkyl, hydroxy $\text{C}_1\text{-C}_3$ alkyl, $\text{COOR}^{104}\text{-NHCO}$ $\text{C}_1\text{-C}_3$ alkyl;

R^{104} is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{107} and R^{108} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

5 R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-COO$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $NR^{201}R^{202}$;

R^{201} is hydrogen or SO_2 C_1 - C_3 alkyl;

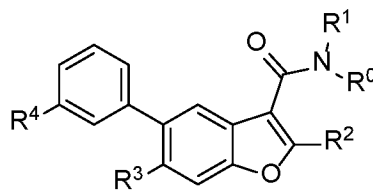
10 R^{202} is CN C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, halo (C_1 - C_6 alkyl) $_n$, halo (C_2 - C_6 alkenyl) $_n$, $CF_3CF_2(C_1$ - C_6 alkyl) $_n$ or CF_3 (C_1 - C_6 alkyl) $_n$;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment of the invention, there is disclosed a compound of

15 Formula I



I

wherein

R^0 is hydrogen;

20 R^1 is methyl;

R^2 is phenyl substituted with fluoro;

R^4 is $COOR^{101}$ or $CONH(R^{103})$;

R^{101} is hydrogen or optionally substituted C_1 - C_3 alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

25 R^{103} is hydrogen, $-(CR^{10}R^{11})R^{12}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, with 0-3 substituents selected from halo, CN , CF_3 , OH , OR^{104} , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring
30 optionally substituted with 0-3 substituents selected from OH , C_1 - C_6 alkyl, halo

substituted phenyl, phenyl, C₁-C₃ alkoxy C₁-C₃ alkyl, hydroxy C₁-C₃ alkyl,
COOR¹⁰⁴-NHCO C₁-C₃ alkyl;

R¹⁰⁴ is hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted
C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and
5 haloalkoxy;

R¹⁰⁵ and R¹⁰⁶ are each independently hydrogen, optionally substituted C₁-C₆
alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from
halo, hydroxyl, alkoxy, and haloalkoxy; or

R¹⁰ and R¹¹ are independently hydrogen or C₁-C₆ alkyl;

10 R¹² is substituted C₁-C₆ alkynyl, C₃-C₈ cycloalkyl, -COO C₁-C₆ alkyl, phenyl
or CF₂CF₃;

R³ is NR²⁰¹R²⁰²;

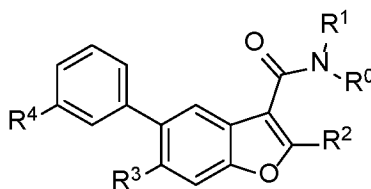
R²⁰¹ is hydrogen or SO₂ C₁-C₃ alkyl;

R²⁰² is CN C₁-C₆ alkyl, C₃-C₆ cycloalkyl C₁-C₆ alkyl, halo (C₁-C₆ alkyl)_n, halo
15 (C₂-C₆ alkenyl)_n, CF₃CF₂(C₁-C₆ alkyl)_n or CF₃ (C₁-C₆ alkyl)_n;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment of the invention, there is disclosed a compound of
20 Formula I



I

wherein

R⁰ is hydrogen;

25 R¹ is methyl;

R² is phenyl substituted with fluoro;

R⁴ is COOR¹⁰¹ or CONH(R¹⁰³);

R¹⁰¹ is hydrogen or C₁-C₃ alkyl;

R^{103} is hydrogen, $-(CR^{10}R^{11})R^{12}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7
 5 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, C_1 - C_6 alkyl, halo substituted phenyl, phenyl, C_1 - C_3 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl, $COOR^{104}$ -NHCO C_1 - C_3 alkyl;

R^{104} is hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted
 10 C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

15 R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-COO$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $NR^{201}R^{202}$;

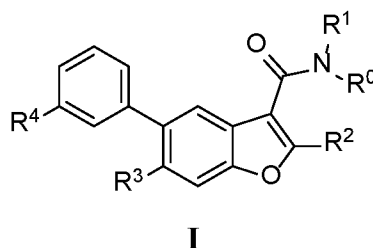
R^{201} is SO_2 C_1 - C_3 alkyl;

20 R^{202} is CN C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, halo $(C_1$ - C_6 alkyl) $_n$, halo $(C_2$ - C_6 alkenyl) $_n$, $CF_3CF_2(C_1$ - C_6 alkyl) $_n$ or CF_3 $(C_1$ - C_6 alkyl) $_n$;

n is 1, 2 or 3;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

25 In another embodiment of the invention, there is disclosed a compound of Formula I



wherein

30 R^0 is hydrogen;

R^1 is methyl;

R^2 is  ;

R^4 is COOR^{101} or $\text{CONH}(\text{R}^{103})$;

R^{101} is hydrogen or $\text{C}_1\text{-C}_3$ alkyl;

5 R^{103} is hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7
 10 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo substituted phenyl, phenyl, $\text{C}_1\text{-C}_3$ alkoxy $\text{C}_1\text{-C}_3$ alkyl, hydroxy $\text{C}_1\text{-C}_3$ alkyl, $\text{COOR}^{104}\text{-NHCO}$ $\text{C}_1\text{-C}_3$ alkyl;

R^{104} is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and
 15 haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{10} and R^{11} are independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

20 R^{12} is substituted $\text{C}_1\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{COO}$ $\text{C}_1\text{-C}_6$ alkyl, phenyl or CF_2CF_3 ;

R^3 is $\text{NR}^{201}\text{R}^{202}$;

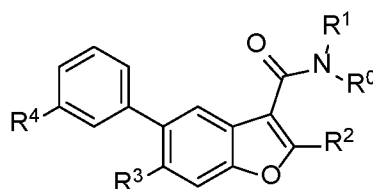
R^{201} is SO_2 $\text{C}_1\text{-C}_3$ alkyl;

R^{202} is CN $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl $\text{C}_1\text{-C}_6$ alkyl, halo $(\text{C}_1\text{-C}_6 \text{ alkyl})_n$, halo
 25 $(\text{C}_2\text{-C}_6 \text{ alkenyl})_n$, $\text{CF}_3\text{CF}_2(\text{C}_1\text{-C}_6 \text{ alkyl})_n$ or $\text{CF}_3 (\text{C}_1\text{-C}_6 \text{ alkyl})_n$;

n is 1, 2 or 3;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

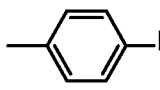
In another embodiment of the invention, there is disclosed a compound of
 30 Formula I

**I**

wherein

R^0 is hydrogen;

5 R^1 is methyl;

R^2 is  ;

R^4 is COOR^{101} or $\text{CONH}(R^{103})$;

R^{101} is hydrogen or methyl;

R^{103} is hydrogen, $-(\text{CR}^{10}R^{11})R^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , $\text{NR}^{105}R^{106}$, COOR^{104} , $\text{CONR}^{105}R^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo substituted phenyl, phenyl, $\text{C}_1\text{-C}_3$ alkoxy $\text{C}_1\text{-C}_3$ alkyl, hydroxy $\text{C}_1\text{-C}_3$ alkyl, $\text{COOR}^{104}\text{-NHCO}$ $\text{C}_1\text{-C}_3$ alkyl;

R^{104} is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

20 R^{105} and R^{106} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{10} and R^{11} are independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^{12} is substituted $\text{C}_1\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{COO}$ $\text{C}_1\text{-C}_6$ alkyl, phenyl or CF_2CF_3 ;

R^3 is $\text{NR}^{201}R^{202}$;

R^{201} is SO_2CH_3 ;

R^{202} is $-\text{CH}_3\text{CN}$, $-\text{CH}_3$ cyclopropyl, $-(\text{CH}_2)_2\text{F}$, $-(\text{CH}_2)_3\text{F}$, $-\text{NH}(\text{CH}_2)_3\text{F}$, $-\text{CHF}_2$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}=\text{CHF}_2$, $-(\text{CH}_2)_2\text{CF}_3$;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

In a further embodiment, there are disclosed the exemplified compounds of the invention.

5

Pharmaceutical Compositions and Methods of Treatment

The compounds according to the various embodiments herein set forth demonstrate activity against HCV NS5B, and can be useful in treating HCV and HCV infection. Therefore, another aspect of the invention is a composition
10 comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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
15 anti-HCV activity is an interferon or a ribavirin. Another aspect of the invention is wherein the interferon is selected from 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
20 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 consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell
25 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 HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B
30 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, 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.

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.

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 interferon alpha 2B, pegylated interferon alpha, consensus interferon, 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.

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 interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response,

interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

Another aspect of the invention is the method wherein the other compound having anti-HCV activity is effective to inhibit the function of a target selected from the group consisting of HCV metalloprotease, HCV serine protease, HCV
5 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
10 having anti-HCV activity is effective to inhibit the function of target in the HCV life cycle other than the HCV NS5B protein.

“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.

15 “Patient” means a person infected with the HCV virus and suitable for therapy as understood by practitioners in the field of hepatitis and HCV infection.

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

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

Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg.

Generally, other agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 0.25-1000 mg/unit.

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

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

Some examples of compounds suitable for compositions and methods 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

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN

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

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

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
Intron A and Zadaxin	Interferon	IFN- α 2b/ α 1-thymosin	RegeneRx Biopharma. Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
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 n1	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

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	serine protease inhibitor	Schering Plough
TMS-435	Antiviral	serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium
BI-201335	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	serine protease inhibitor	Merck
PF-00868554	Antiviral	replicase inhibitor	Pfizer
ANA598	Antiviral	Non-Nucleoside NS5B Polymerase Inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Non-Nucleoside Replicase Inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA

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

The compounds may be made by methods known in the art, including those described below. Some reagents and intermediates are known in the art. Other

5 reagents and intermediates can be made by methods known 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 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

10 conventions used in the art.

Abbreviations used in the schemes generally follow conventions used in the art. Chemical abbreviations used in the specification and examples are defined as follows: "NaHMDS" for sodium bis(trimethylsilyl)amide; "DMF" for N,N-dimethylformamide; "MeOH" for methanol; "NBS" for N-bromosuccinimide; "Ar"

15 for aryl; "TFA" for trifluoroacetic acid; "LAH" for lithium aluminum hydride; "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention

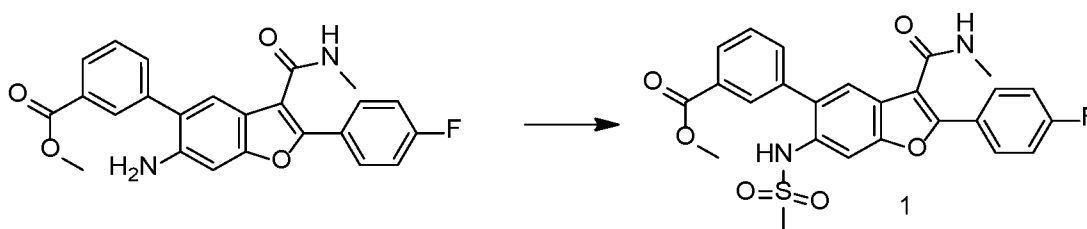
time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "EDTA" for ethylenediaminetetraacetic acid; "Et₂O" for diethyl ether; "DMAP" for 4-dimethylaminopyridine; "DCE" for 1,2-dichloroethane; "ACN" for acetonitrile; "DME" for 1,2-dimethoxyethane; "HOBt" for 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 Acquity™ automated preparative HPLC system.

Examples:

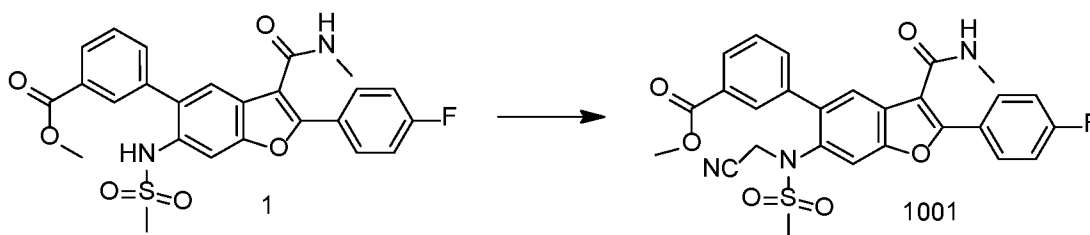
Preparation of Intermediate 1:



Pyridine (0.133 mL) and methanesulfonyl chloride (0.189 g) were added into a solution of ethyl 3-(6-amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)benzoate (0.23 g) in CH₂Cl₂ (5 mL). The reaction was stirred at room temperature for 16 hours. After removal of solvents under vacuum, the residue was purified by preparative HPLC system.

Compound 1	
MS (M+H) ⁺ Calcd.	497.1

MS (M+H) ⁺ Observ.	497.0
Retention Time	3.45 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 50mm 3um

Preparation of 1001:

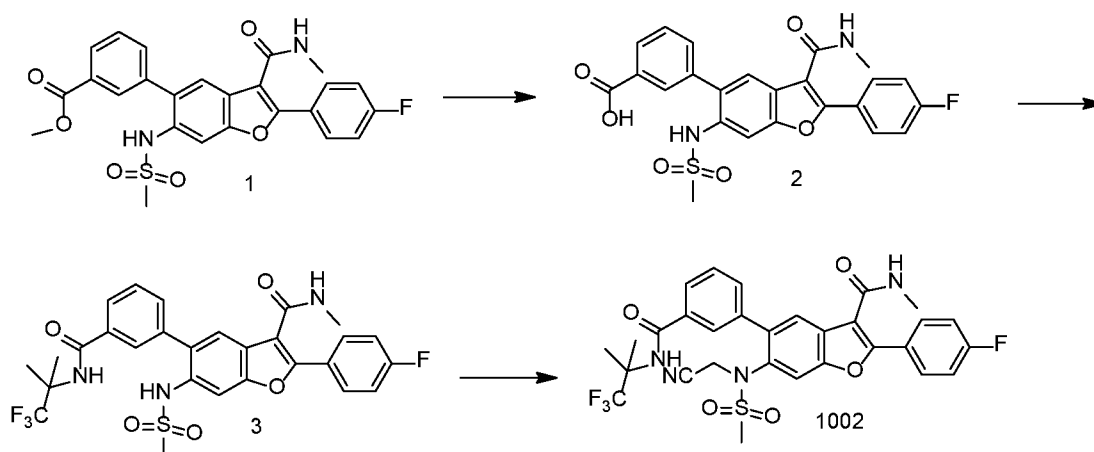
5

2-Iodoacetonitrile (6.72 mg) and Cs₂CO₃ (0.013 g) were added into a solution of methyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(methylsulfonamido)benzofuran-5-yl)benzoate (0.020 g) in DMF (2 mL). The reaction was stirred at room temperature for 1 hour. After removal of solvents under vacuum, the residue was purified by preparative HPLC system.

10

1001	
MS (M+H) ⁺ Calcd.	536.1
MS (M+H) ⁺ Observ.	536.0
Retention Time	1.94 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 1002:

5

Step 1: K_2CO_3 (0.021g) was added into a solution of Compound 1 (0.025 g) in methanol (3 mL) and water (1 mL). The reaction was heated at 70°C for 1 hour. After removal of solvents under vacuum, the residue was purified by preparative

10 HPLC system to give Compound 2.

Compound 2	
MS (M+H) ⁺ Calcd.	483.1
MS (M+H) ⁺ Observ.	483.0
Retention Time	3.21 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 50mm 3um

Step 2: $i\text{Pr}_2\text{NEt}$ (0.013 g) and HATU (0.026 g) were added into a solution of Compound 2 (0.025 g) and 1,1,1-trifluoro-2-methylpropan-2-amine (7.90 mg) in DMF (1 mL). The reaction was stirred at room temperature for 16 hours. Compound 3 was isolated by preparative HPLC system.

Compound 3	
MS (M+H) ⁺ Calcd.	592.2
MS (M+H) ⁺ Observ.	592.2
Retention Time	3.69 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 50mm 3um

Step 3: Cs_2CO_3 (0.033 g) and 2-iodoacetonitrile (0.017 g) were added into a solution of Compound 3 (0.020 g, 0.034 mmol) in DMF (1 mL). The reaction was stirred at

room temperature for 1 hour. Compound 1002 was isolated by preparative HPLC system.

1002	
MS (M+H) ⁺ Calcd.	631.2
MS (M+H) ⁺ Observ.	631.2
Retention Time	2.08 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 2001:

Compound 2001 was prepared via the same procedure synthesizing Compound 1001, using (iodomethyl)cyclopropane as alkylation agent with reaction time 48 hours.

2001	
MS (M+H) ⁺ Calcd.	551.2
MS (M+H) ⁺ Observ.	551.3
Retention Time	1.80 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100

Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

Preparation of 2002:

Compound 2002 was prepared from Compound 2001, via the same procedure
 5 synthesizing Compound 2, with reaction time 3 hours.

2002	
MS (M+H) ⁺ Calcd.	537.1
MS (M+H) ⁺ Observ.	537.1
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	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

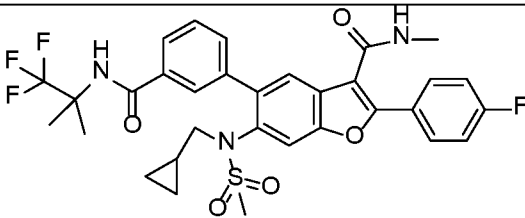
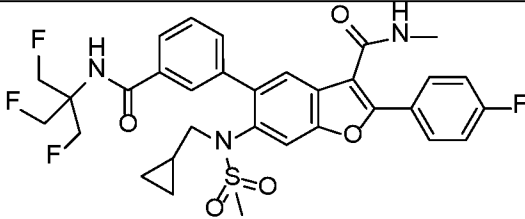
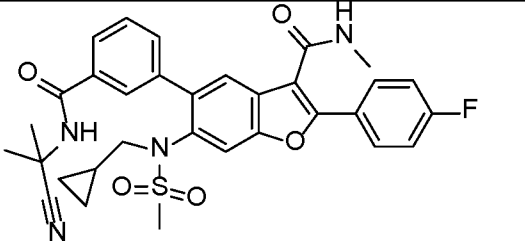
General procedure of amide formation, preparation of 2003, 2004, 2005 and 2006:

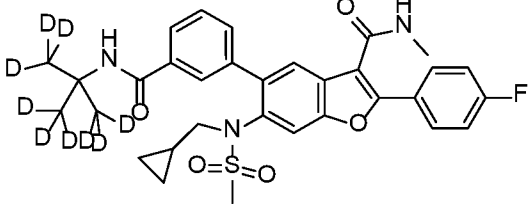
10

iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 2002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The

reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was isolated by preparative HPLC system.

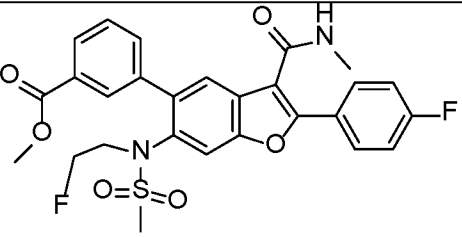
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 x 30mm 3um

Cmpd#	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
2003		646.2	646.2	2.20
2004		646.2	646.2	2.13
2005		603.2	603.2	2.02

Cmpd#	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
2006		601.3	601.3	2.19

Preparation of 3001:

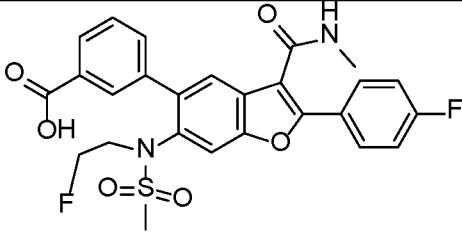
Compound 3001 was prepared via the same procedure synthesizing Compound 1001,
 5 using 1-fluoro-2-iodoethane as alkylation agent with reaction time 16 hours.

 3001	
MS (M+H) ⁺ Calcd.	543.1
MS (M+H) ⁺ Observ.	543.3
Retention Time	3.03 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate

Column	Phenomenex LUNA C18, 30x2, 3u
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Preparation of 3002:

Compound 3002 was prepared from Compound 3001, via the same procedure
 5 synthesizing Compound 2, with reaction time 1 hour.

 3002	
MS (M+H) ⁺ Calcd.	529.1
MS (M+H) ⁺ Observ.	529.1
Retention Time	3.38 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 50mm 3um

General procedure of amide formation, preparation of 3003 – 3044:

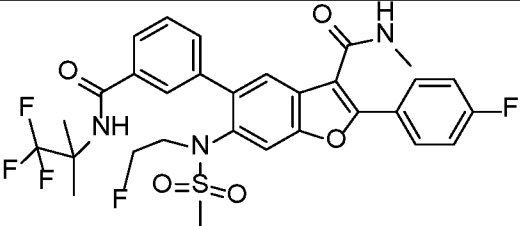
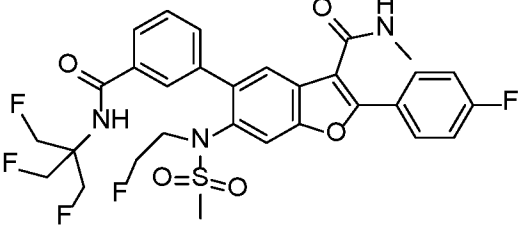
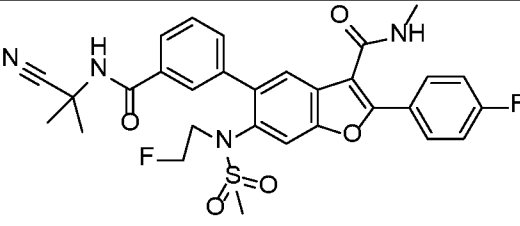
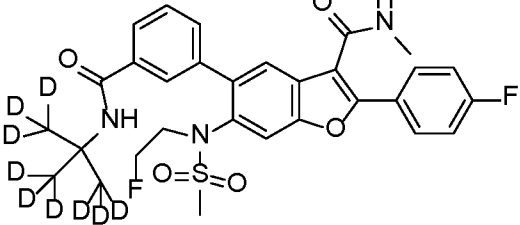
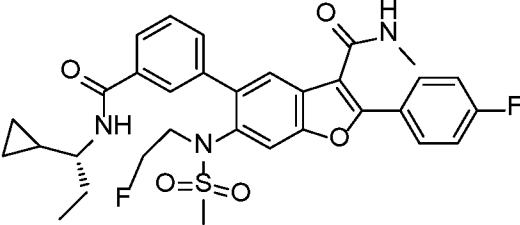
- 10 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 3002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was isolated by preparative HPLC system.

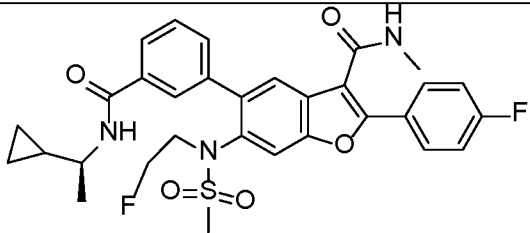
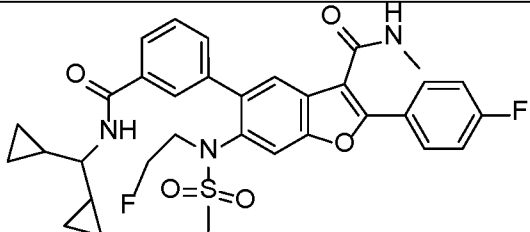
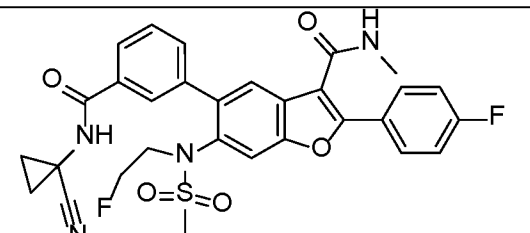
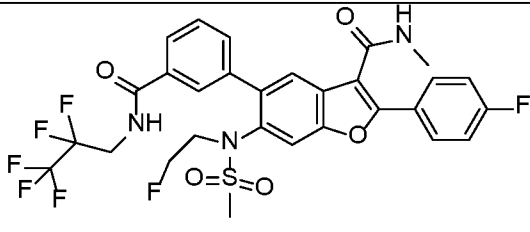
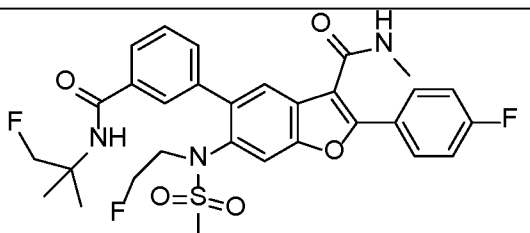
LC Condition A	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

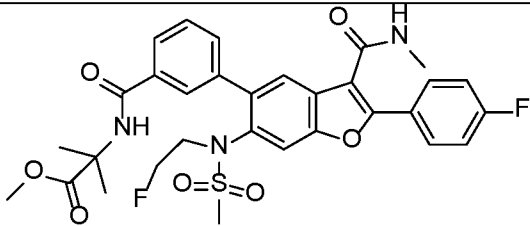
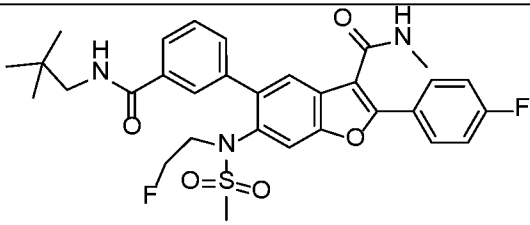
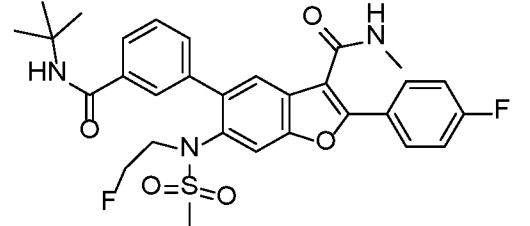
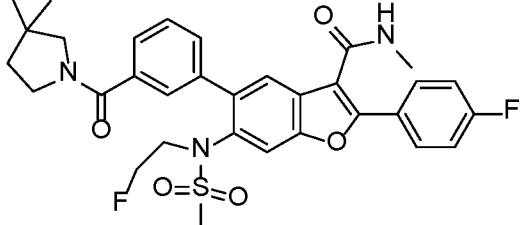
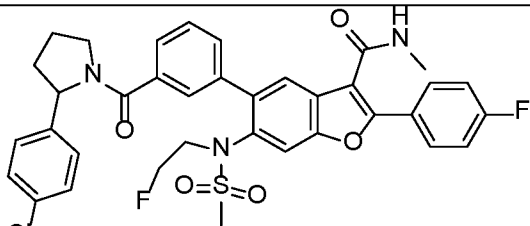
LC Condition B	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	PHENOMENEX-LUNA 2.0 X 50mm 3um

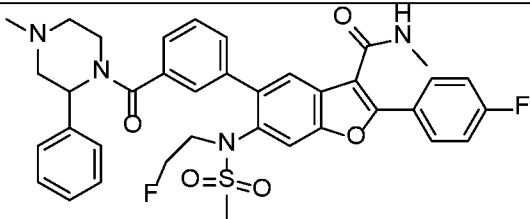
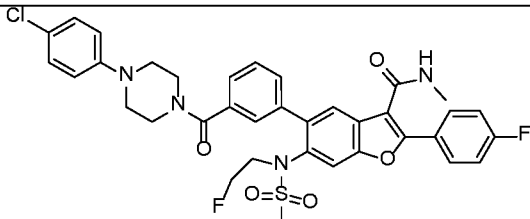
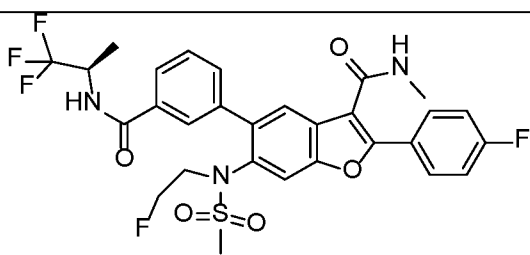
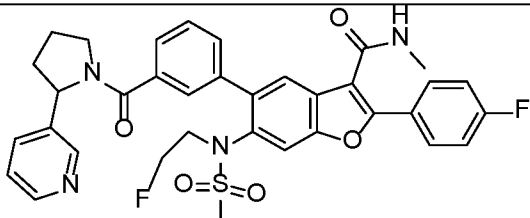
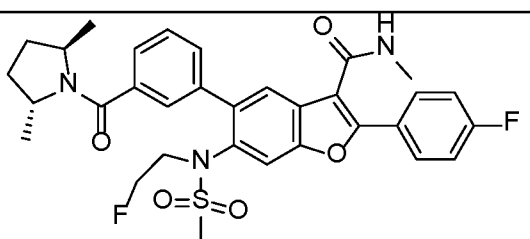
LC Condition C	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA

Column	PHENOMENEX-LUNA 2.0 X 30mm 3um
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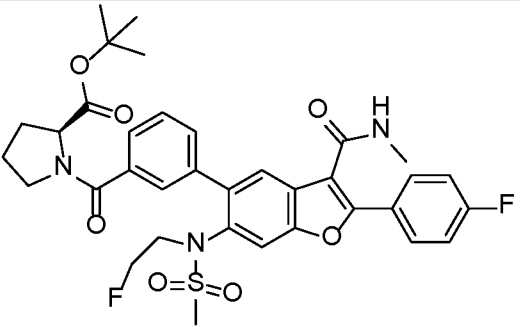
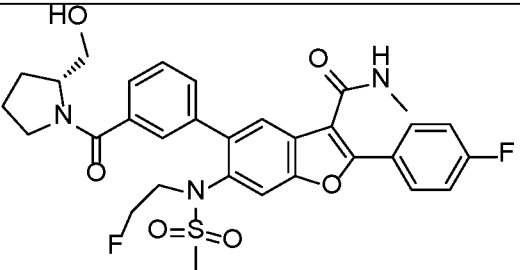
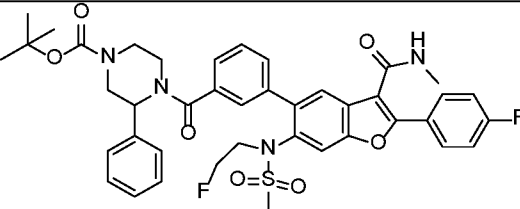
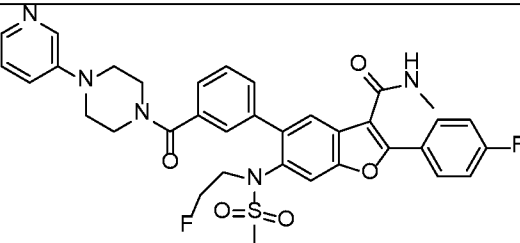
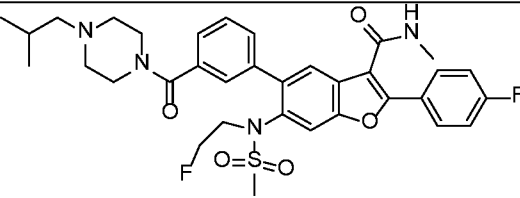
Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3003	A		638.2	638.3	1.80
3004	B		638.2	638.2	3.73
3005	C		595.2	595.2	1.92
3006	A		593.3	593.4	1.73
3007	A		610.2	610.4	1.80

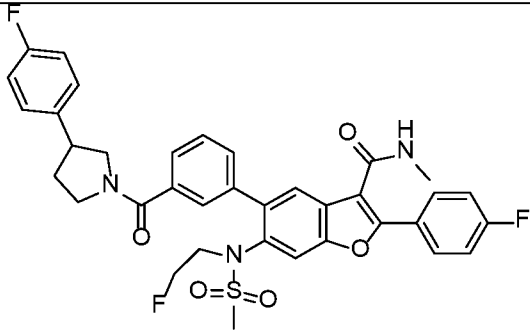
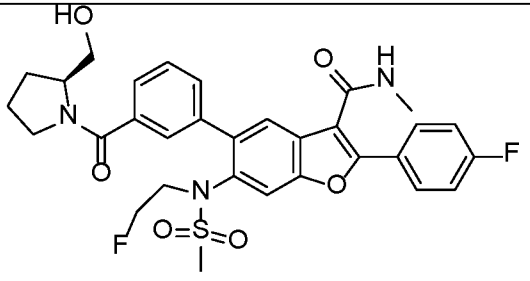
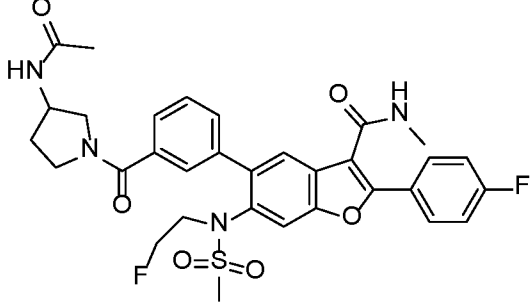
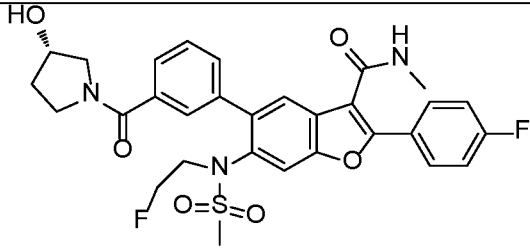
Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3009	A		596.2	596.4	1.73
3010	A		622.2	622.4	1.81
3011	C		593.2	593.2	1.87
3012	C		660.1	660.2	2.10
3013	C		602.2	602.2	2.06

Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3014	C		628.2	628.2	1.99
3015	C		598.2	598.2	2.18
3016	C		584.2	584.2	2.15
3017	C		610.2	610.2	2.13
3018	C		692.2	692.3	2.27

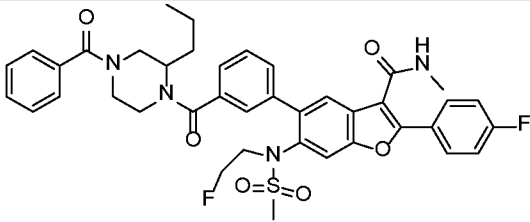
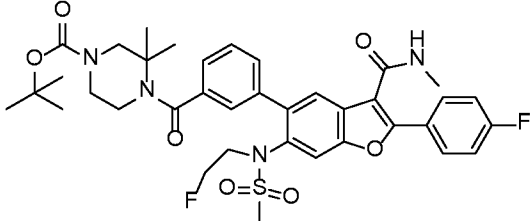
Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3019	C		687.2	687.3	1.85
3020	C		707.2	707.4	1.84
3021	C		624.2	624.0	2.06
3022	C		659.2	659.3	1.71
3023	C		610.2	610.3	2.17

Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3024	C		596.2	596.2	2.04
3025	C		673.2	673.3	2.14
3026	C		670.2	670.3	2.06
3027	C		610.2	610.2	2.12
3028	A		697.2	697.4	1.81

Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3029	C		682.2	682.3	2.17
3030	C		612.2	612.2	1.92
3031	C		773.3	773.4	2.30
3032	C		674.2	674.3	1.73
3033	C		653.3	653.3	1.77

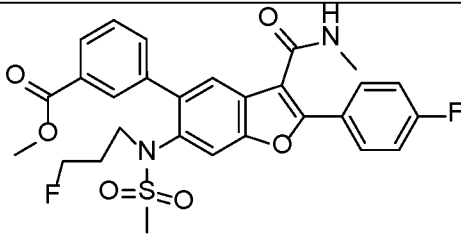
Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3034	C		676.2	676.3	2.20
3035	C		612.2	612.2	1.93
3036	A		639.2	639.4	1.45
3037	A		598.2	598.4	1.47

Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3038	A		697.2	697.6	1.70
3039	C		598.2	598.1	1.84
3040	C		692.2	692.1	2.26
3041	C		640.2	640.1	1.94
3042	A		683.2	683.5	1.68

Cmpd#	LC method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
3043	C		743.3	743.3	2.10
3044	A		725.3	725.6	1.83

Preparation of 4001:

Compound 4001 was prepared via the same procedure synthesizing Compound 1001,
 5 using 1-fluoro-3-iodopropane as alkylation agent with reaction time 72 hours.

 4001	
MS (M+H) ⁺ Calcd.	557.2
MS (M+H) ⁺ Observ.	557.4
Retention Time	1.73 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0

Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

Preparation of 4002:

- Compound 4002 was prepared from Compound 4001, via the same procedure
 5 synthesizing Compound 2, with reaction time 2 hours and reaction temperature 90°C.

4002	
MS (M+H) ⁺ Calcd.	543.1
MS (M+H) ⁺ Observ.	543.1
Retention Time	1.91 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 30mm 3um

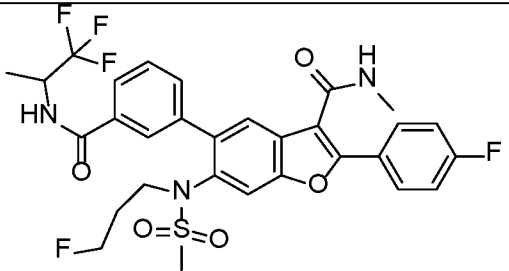
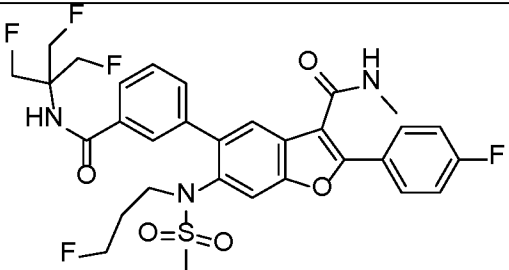
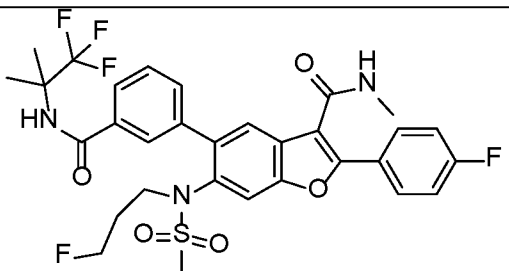
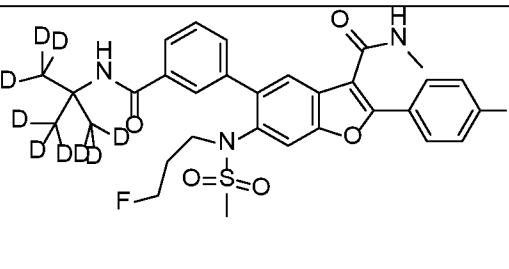
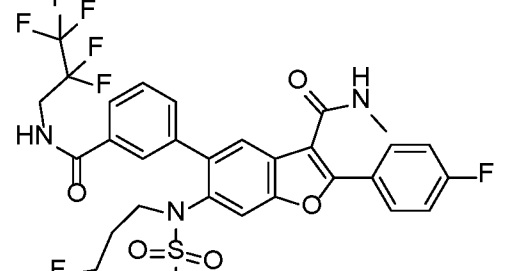
General procedure of amide formation, preparation of 4003 – 4030:

- 10 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 4002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The

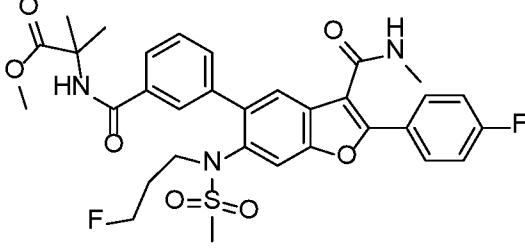
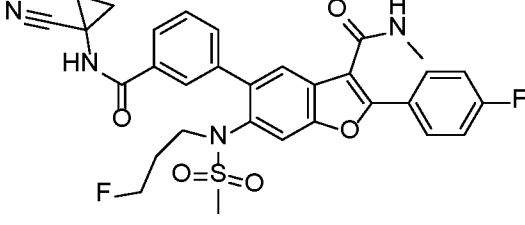
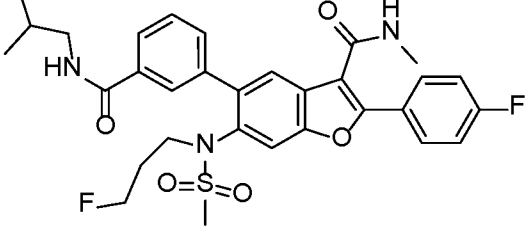
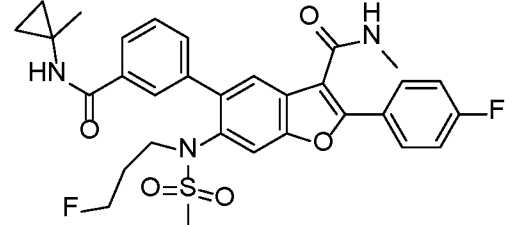
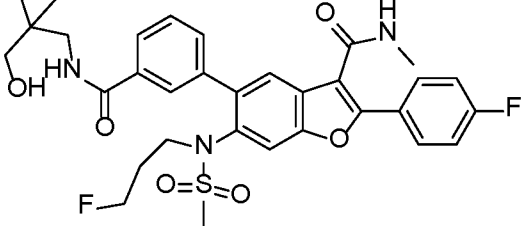
reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was isolated by preparative HPLC system.

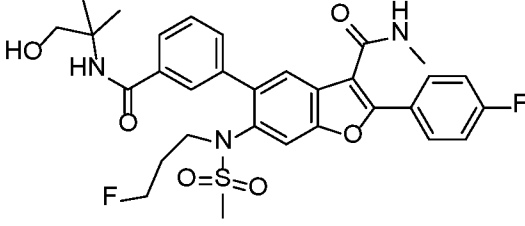
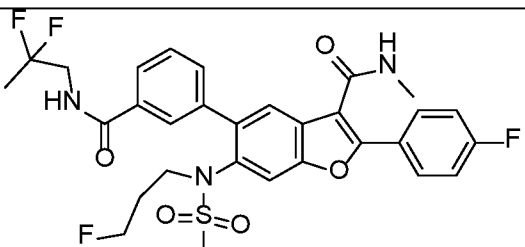
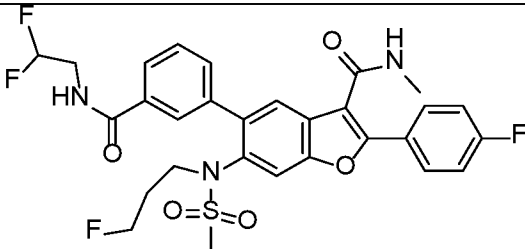
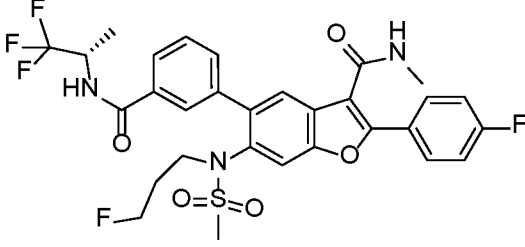
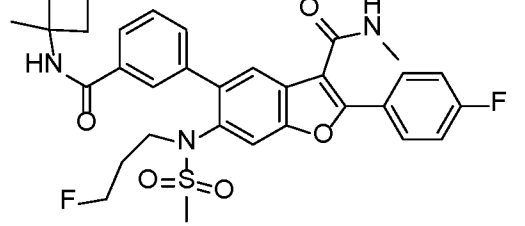
LC Condition A	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

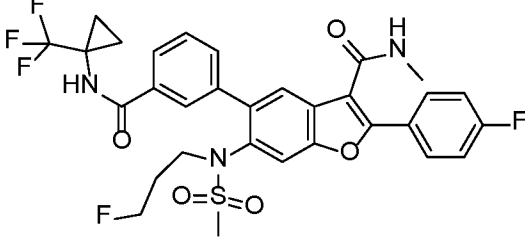
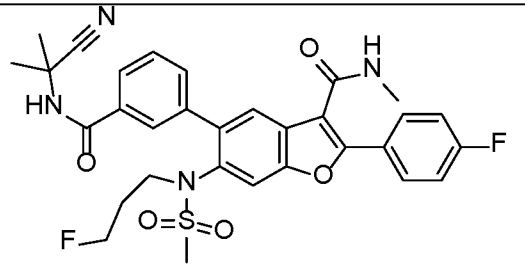
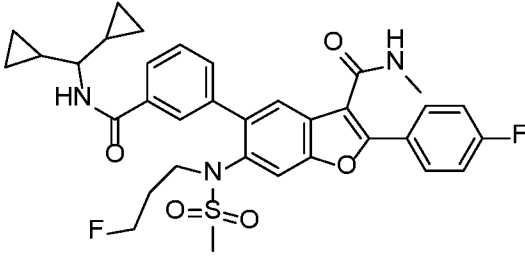
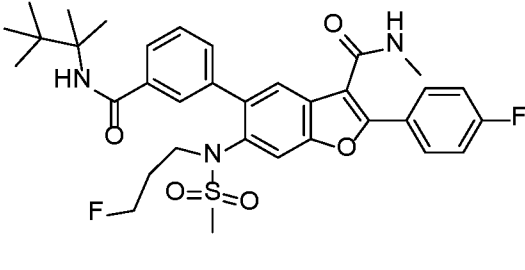
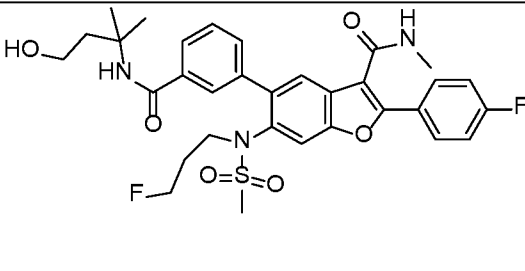
LC Condition B	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 30mm 3um

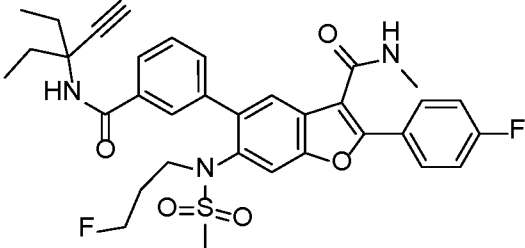
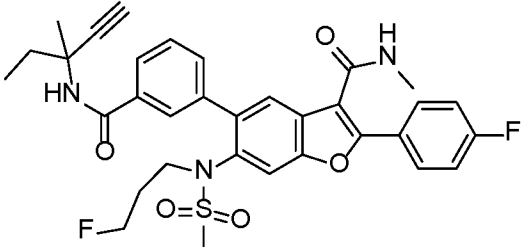
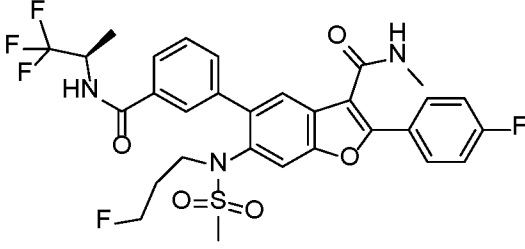
Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4003	B		638.2	638.1	2.07
4004	B		652.2	652.2	2.03
4005	B		652.2	652.2	2.14
4006	B		607.3	607.2	2.11
4007	B		674.2	674.1	2.10

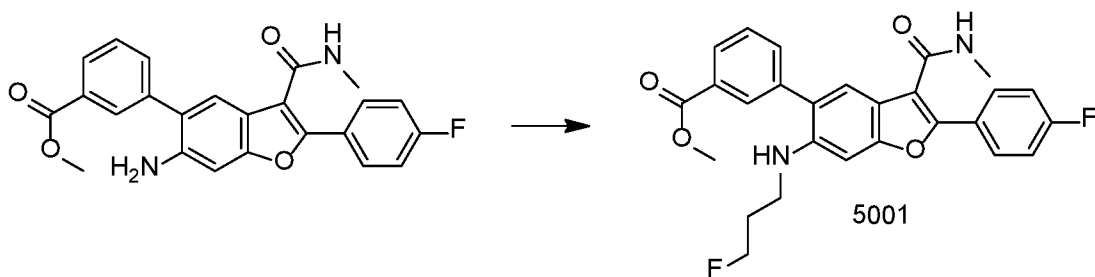
Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4008	B		616.2	616.2	2.08
4009	A		612.2	612.5	1.78
4010	A		624.2	624.3	1.71
4011	A		598.2	598.4	1.76
4012	A		608.2	608.4	1.71

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4013	A		642.2	642.4	1.69
4014	A		607.2	607.3	1.63
4015	A		598.2	598.4	1.73
4016	B		596.2	596.1	1.99
4017	A		628.2	628.4	1.74

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4018	A		614.2	614.4	1.78
4019	B		620.2	620.1	2.07
4020	B		606.2	606.1	2.03
4021	A		638.2	638.4	1.87
4022	B		610.2	610.1	2.20

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4023	B		650.2	650.1	2.17
4024	B		609.2	609.1	2.02
4025	B		636.2	636.1	2.25
4026	B		640.3	640.2	2.37
4027	B		628.2	628.1	2.08

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
4028	B		636.2	636.1	2.24
4029	B		622.2	622.1	2.21
4030	B		638.2	638.1	2.21

Preparation of 5001:

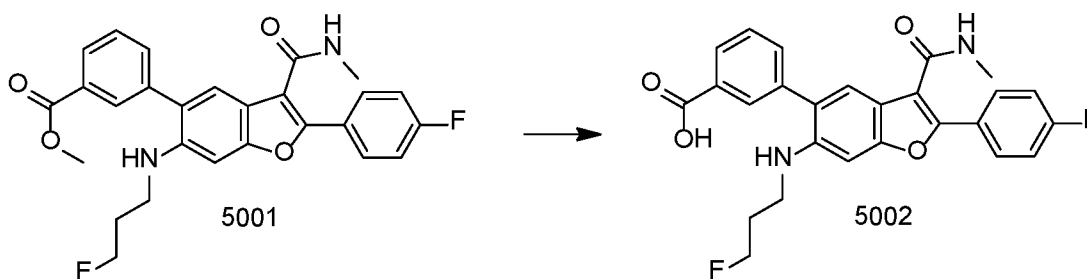
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Cs₂CO₃ (0.156 g) and 1-fluoro-3-iodopropane (0.449 g) were added into a solution of methyl 3-(6-amino-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-

yl)benzoate (0.20 g) in DMF (1 mL). The reaction was stirred at room temperature for 16 hours. Compound 5001 was isolated by preparative HPLC system.

5001	
MS (M+H) ⁺ Calcd.	479.2
MS (M+H) ⁺ Observ.	479.4
Retention Time	1.92 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

5 Preparation of 5002:



- 10 To a suspension of Compound 5001 (75 mg) in THF (5 mL) and water (1 mL) was added NaOH (1 mL, 1 M). The mixture was heated at 80 °C for 4 hours, before being cooled and acidified with 1N HCl to pH ~ 3. The precipitate was collected by filtration to give Compound 5002.

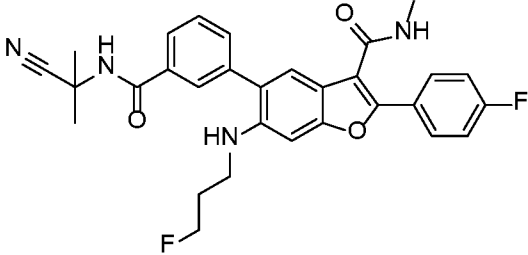
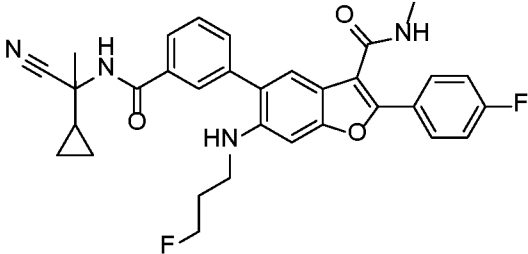
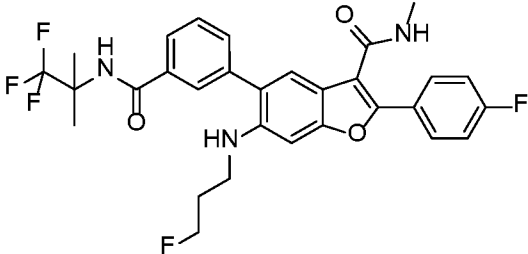
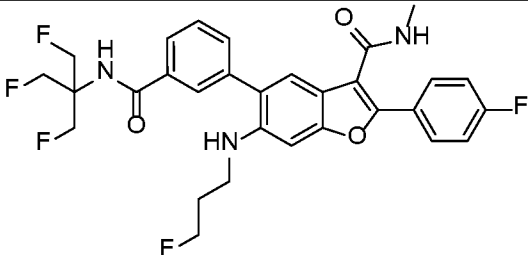
5002	
MS (M+H) ⁺ Calcd.	465.2
MS (M+H) ⁺ Observ.	465.0
Retention Time	1.90 min
LC Condition	
Solvent A	90% Water -10% Methanol-0.1% TFA
Solvent B	10% Water -90% Methanol-0.1% TFA
Start % B	30
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 30mm 3um

General procedure of amide formation, preparation of 5003 – 5006:

- 5 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 5002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was 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	50
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA

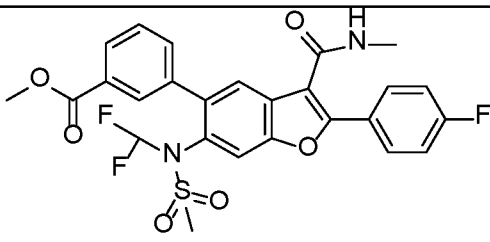
Column	PHENOMENEX-LUNA 2.0 X 30mm 3um
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Cmpd#	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
5003		531.2	531.1	1.46
5004		557.2	557.1	1.56
5005		574.2	574.1	1.80
5006		574.2	574.1	1.69

Preparation of 6001:

Compound 6001 was prepared via the same procedure synthesizing Compound 1001, using difluoriodomethane as alkylation agent with reaction time 48 hours.

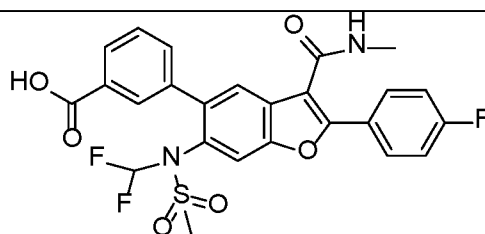
5

 6001	
MS (M+H) ⁺ Calcd.	547.1
MS (M+H) ⁺ Observ.	547.2
Retention Time	1.75 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

Preparation of 6002:

Compound 6002 was prepared from Compound 6001, via the same procedure synthesizing Compound 2, with reaction time 15 minutes.

10

**6002**

MS (M+H) ⁺ Calcd.	533.1
MS (M+H) ⁺ Observ.	533.3
Retention Time	2.12 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 50x2, 3u

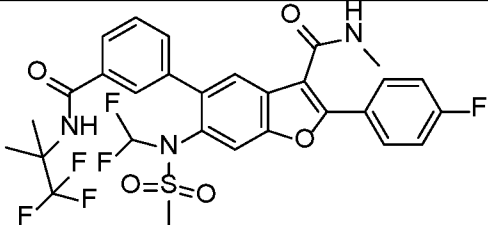
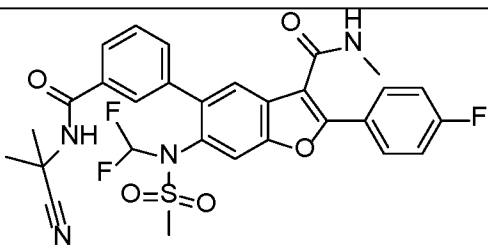
General procedure of amide formation, preparation of 6003 – 6006:

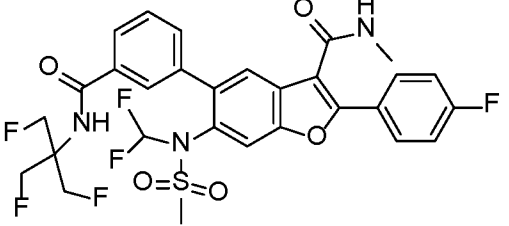
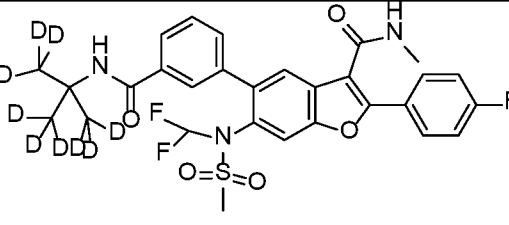
- 5 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 6002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was isolated by preparative HPLC system.

LC Condition A	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100

Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

LC Condition B	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 50x2, 3u

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
6003	B		642.1	642.4	3.35
6004	A		599.2	599.3	1.71

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
6005	A		642.1	642.4	1.79
6006	A		597.2	597.4	1.75

Preparation of 7001:

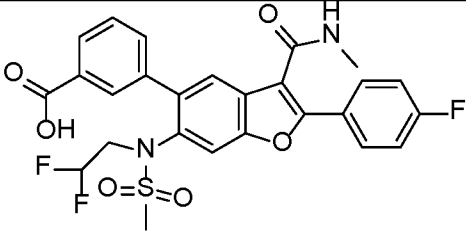
Compound 7001 was prepared via the same procedure synthesizing Compound 1001,
 5 using 1,1-difluoro-2-iodoethane as alkylation agent with reaction time 48 hours.

7001	
MS (M+H) ⁺ Calcd.	561.1
MS (M+H) ⁺ Observ.	561.1
Retention Time	3.71 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA

Column	PHENOMENEX-LUNA 2.0 X 50mm 3um
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Preparation of 7002:

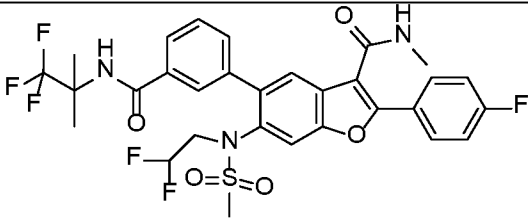
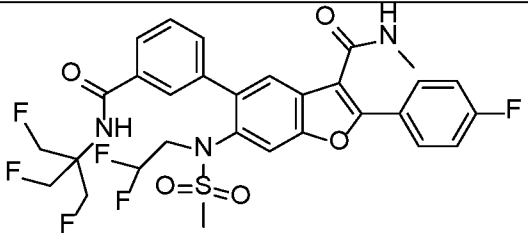
Compound 7002 was prepared from Compound 7001, via the same procedure
 5 synthesizing Compound 2, with reaction time 1 hour.

 7002	
MS (M+H) ⁺ Calcd.	547.1
MS (M+H) ⁺ Observ.	547.0
Retention Time	3.49 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 50mm 3um

General procedure of amide formation, preparation of 7003 and 7004:

- 10 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 7002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was 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

Cmpd#	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
7003		656.2	656.1	2.14
7004		656.1	656.1	2.10

Preparation of 8001:

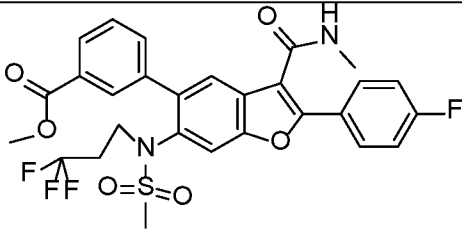
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Compound 8001 was prepared via the same procedure synthesizing Compound 1001, using 1-bromo-1,1-difluoro-3-iodopropane as alkylation agent with reaction time 16 hours.

8001	
MS (M+H) ⁺ Calcd.	573.1
MS (M+H) ⁺ Observ.	573.1
Retention Time	3.86 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	4 min
Flow Rate	0.8 mL/min
Wavelength	220
Solvent Pair	Water - Methanol- TFA
Column	PHENOMENEX-LUNA 2.0 X 50mm 3um

Preparation of 9001:

Compound 9001 was prepared via the same procedure synthesizing Compound 1001,
 5 using 1,1,1-trifluoro-3-iodopropane as alkylation agent with reaction time 72 hours.

 9001	
MS (M+H) ⁺ Calcd.	593.1
MS (M+H) ⁺ Observ.	593.4
Retention Time	1.83 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate

Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

Preparation of 9002:

- Compound 9002 was prepared from Compound 9001, via the same procedure
 5 synthesizing Compound 2, with reaction time 1 hour at 90°C.

9002	
MS (M+H) ⁺ Calcd.	579.1
MS (M+H) ⁺ Observ.	579.3
Retention Time	1.38 min
LC Condition	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

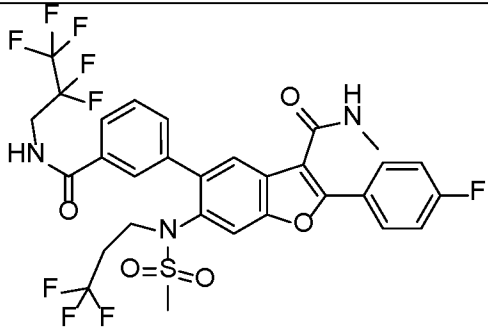
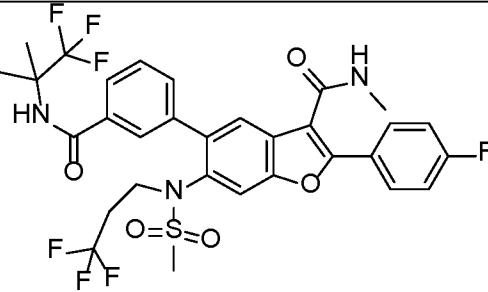
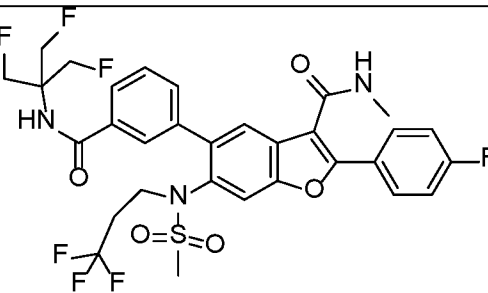
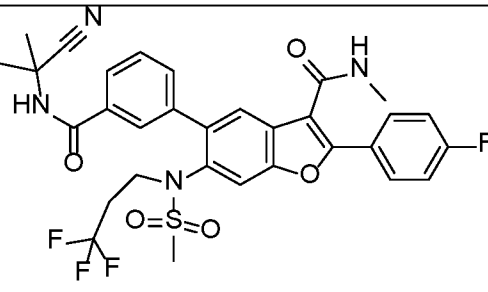
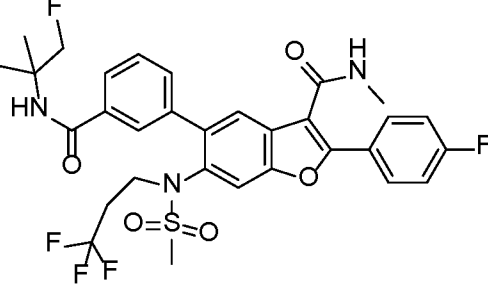
General procedure of amide formation, preparation of 9003 - 9007:

- 10 iPr₂NEt or Et₃N (2 eq.) and HATU or HCTU or DEBPT (1.3 eq.) were added into a solution of Compound 9002 (1 eq.) and amine (1.3 eq.) in DMF or THF. The

reaction was stirred at room temperature or 85°C for 30 minutes to 72 hours. The desired product was isolated by preparative HPLC system.

LC Condition A	
Solvent A	5 % ACN: 95% Water : 10mM Ammonium Acetate
Solvent B	95 % ACN: 5% Water : 10mM Ammonium Acetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Acetate
Column	Phenomenex LUNA C18, 30x2, 3u

LC Condition B	
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

Cmpd#	LC Method	Structure	MS (M+H) ⁺ Calcd.	MS (M+H) ⁺ Observ.	Retention Time (min)
9003	B		710.1	710.1	2.24
9004	B		688.2	688.2	2.24
9005	B		688.2	688.2	2.16
9006	A		645.2	645.4	1.81
9007	A		652.2	652.5	1.86

Biological Methods

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

5

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.

10

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).

20

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, MgCl₂ 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

30

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 MgCl₂, 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 µg/µL beads, 20 mM Hepes buffer, pH 7.5, 2.5 mM MgCl₂, 2.5 mM KCl, and 0.1 % DMSO.

20

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.

IC₅₀ values for compounds were determined using ten different [I]. IC₅₀ 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 IC₅₀, D is hill slope and x represents compound concentration.

30

Cell lines. The cell lines used to evaluate compounds consist of a human 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,

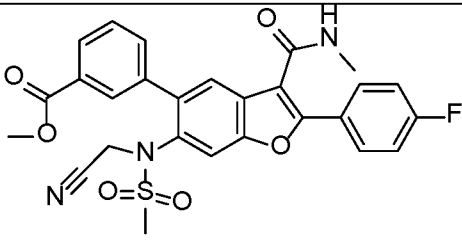
containing a Renilla luciferase reporter gene. These cells were maintained in Dulbecco's modified Eagle medium (DMEM) containing 10% FBS, 100 U/mL penicillin/streptomycin and 1.0 mg/mL G418.

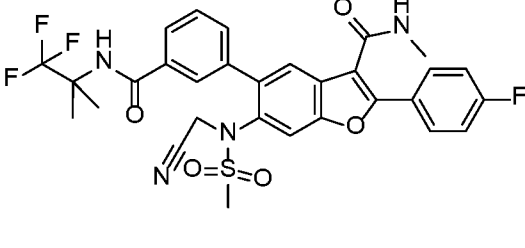
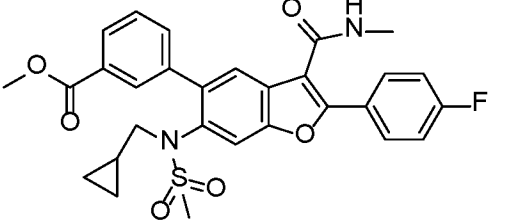
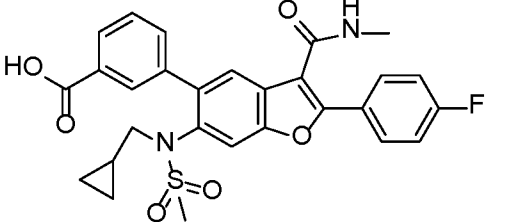
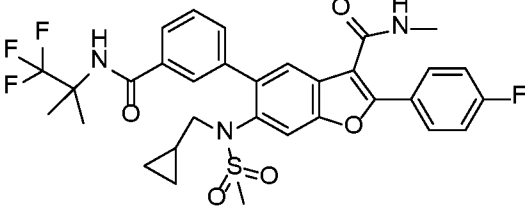
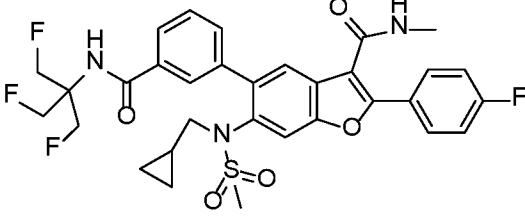
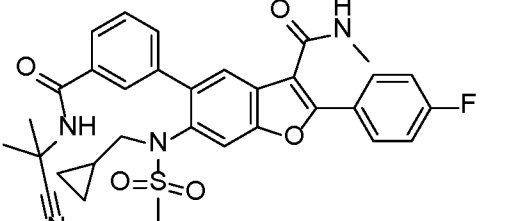
5 *HCV replicon luciferase assay.* To evaluate compound efficacy, titrated compounds were transferred to sterile 384-well tissue culture treated plates, and the plates were seeded with HCV replicon cells (50 μ L at a density of 2.4×10^3 cells/well) in DMEM containing 4 % FBS (final DMSO concentration at 0.5 %). After 3 days incubation at 37°C, cells were analyzed for Renilla Luciferase activity
 10 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 Viewlux Imager (PerkinElmer) using a luminescence program. The 50% effective concentration (EC₅₀) was calculated using the four-
 15 parameter logistic Formula noted above.

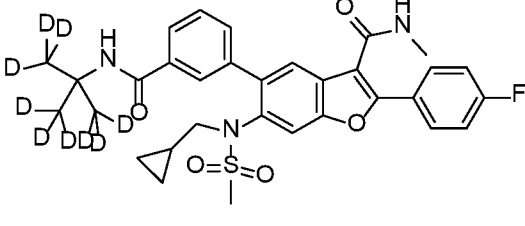
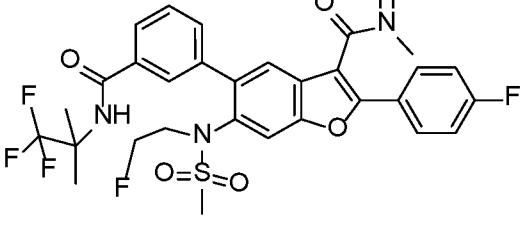
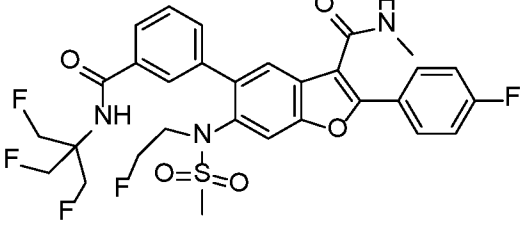
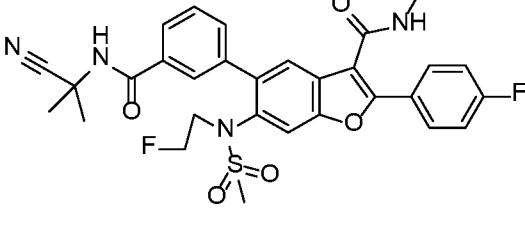
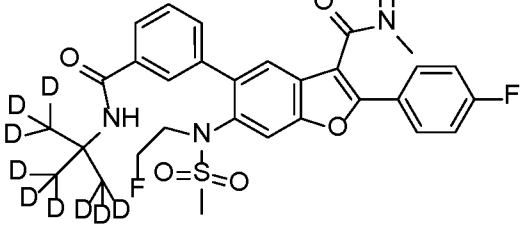
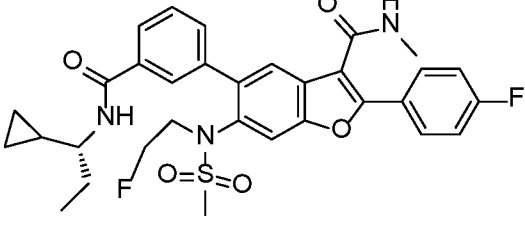
To assess cytotoxicity of compounds, Cell Titer-Blue (Promega) was added to the EnduRen-containing plates and incubated for at least 4 hrs at 37°C. The fluorescence signal from each well was read using a Viewlux Imager. All CC₅₀ values were calculated using the four-parameter logistic Formula.

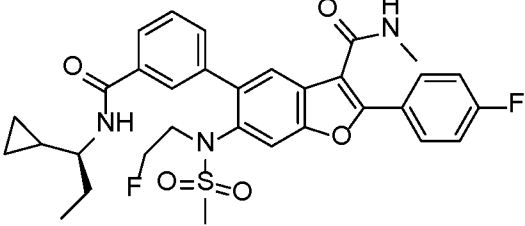
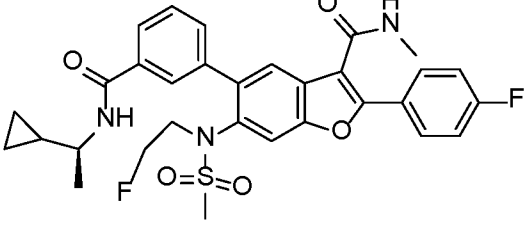
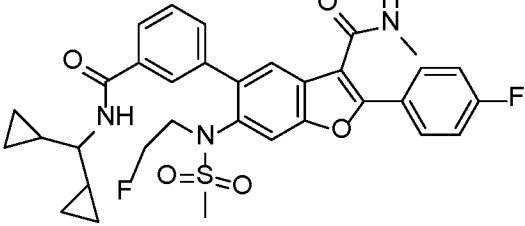
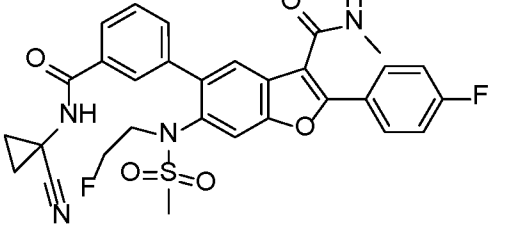
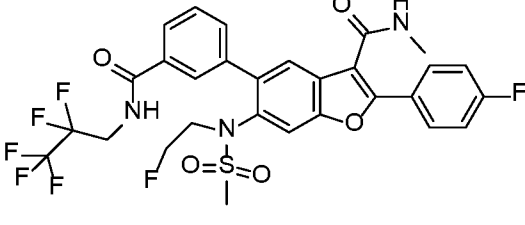
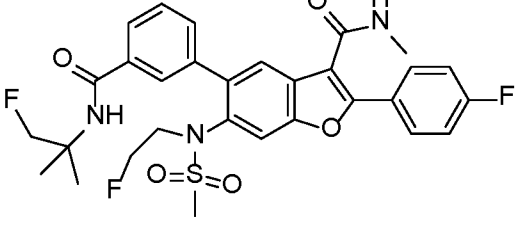
20 Compound EC₅₀ data is expressed as A: < 100 nM; B = 100-1000 nM; C > 1000 nM). Representative data for compounds are reported in Table 2.

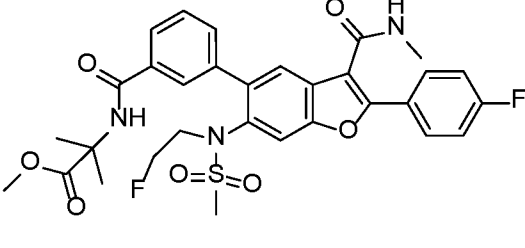
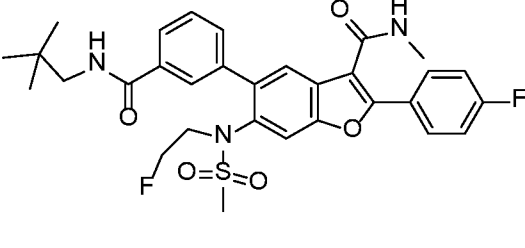
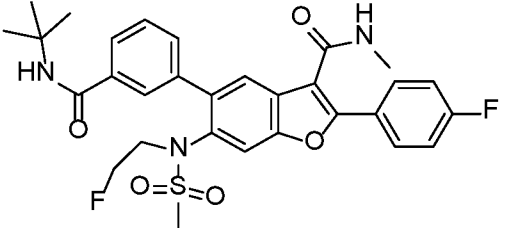
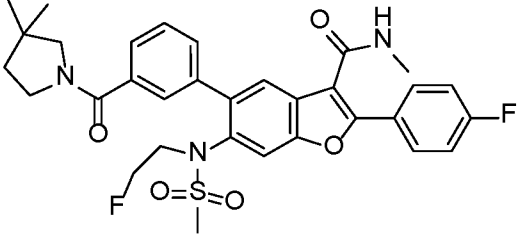
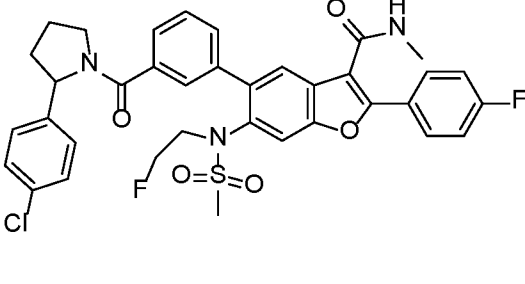
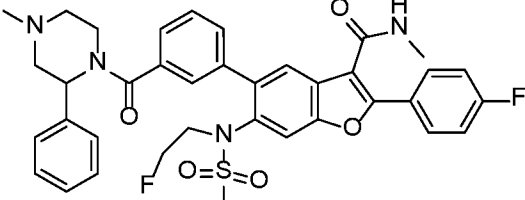
Table 2

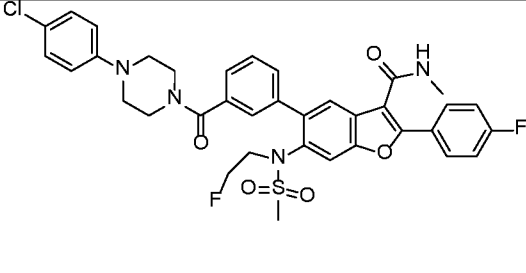
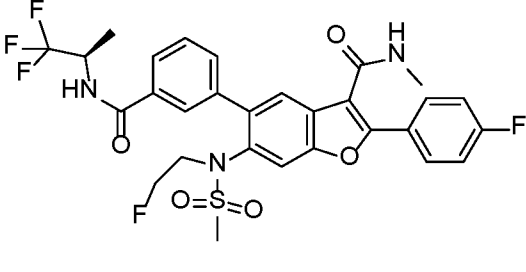
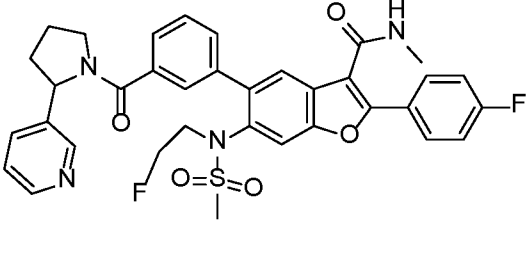
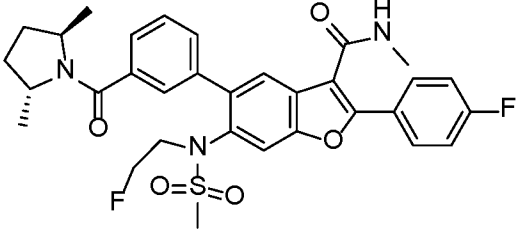
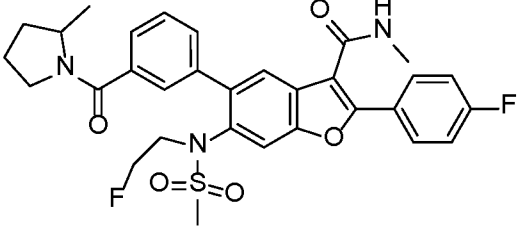
Cmpd#	Structure	EC ₅₀ (μ M) 1b
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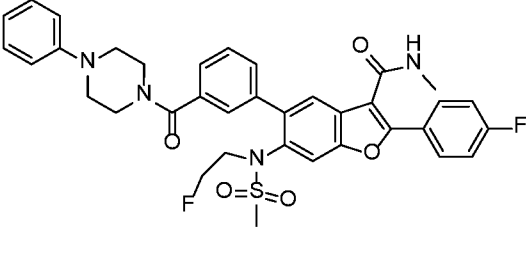
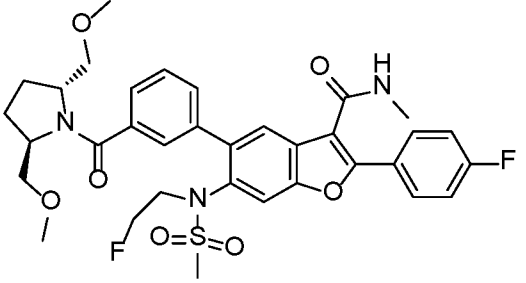
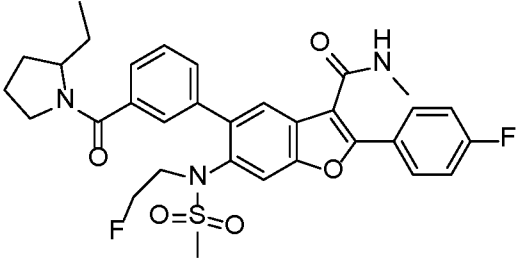
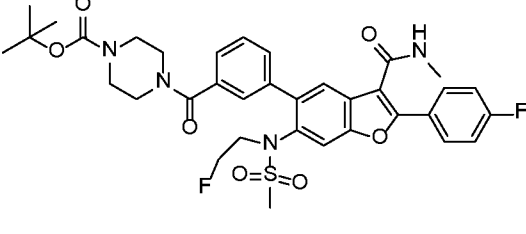
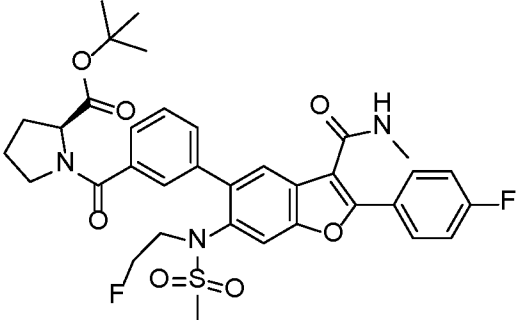
Cmpd#	Structure	EC ₅₀ (uM) 1b
1002		A
2001		A
2002		7.5550 C
2003		A
2004		A
2005		0.0147 A

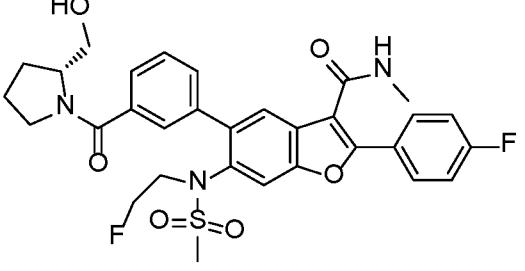
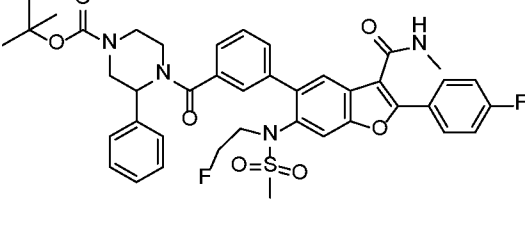
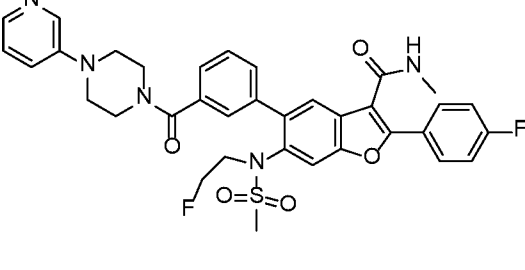
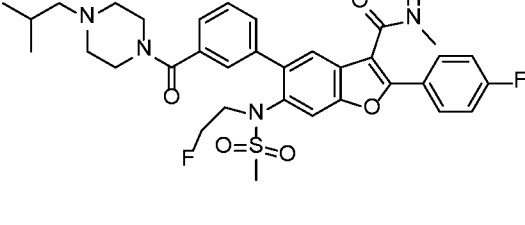
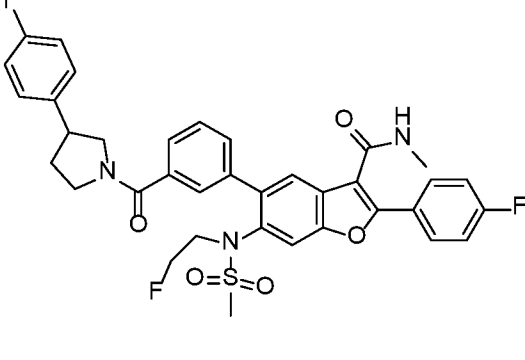
Cmpd#	Structure	EC ₅₀ (uM) 1b
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3003		A
3004		A
3005		0.0050 A
3006		A
3007		0.0057 A

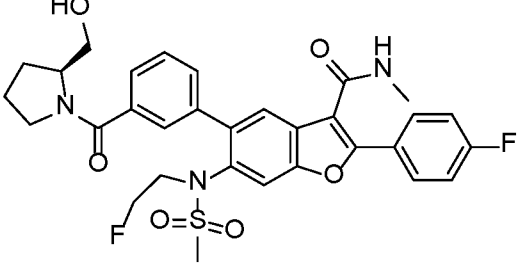
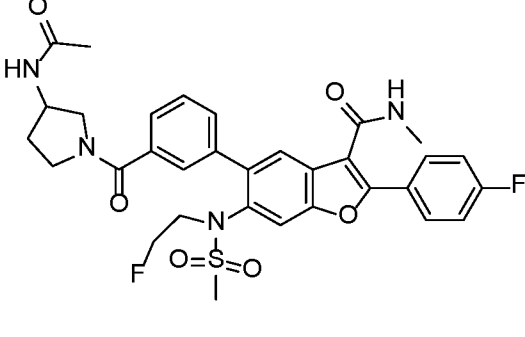
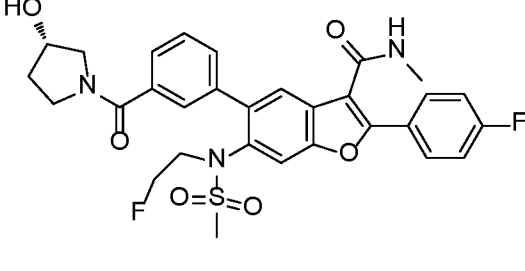
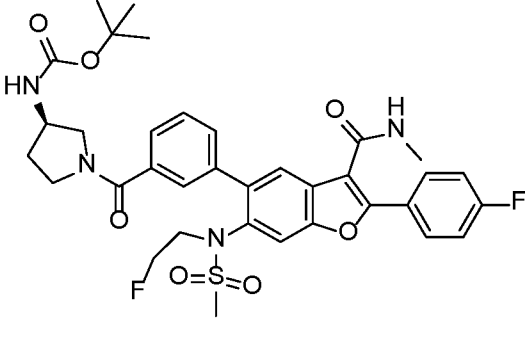
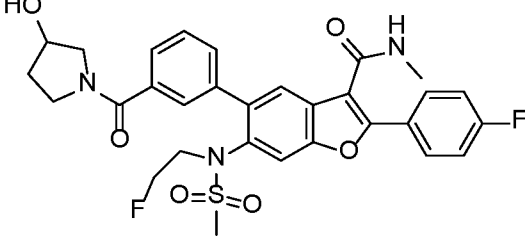
Cmpd#	Structure	EC ₅₀ (uM) 1b
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3009		A
3010		0.0056 A
3011		A
3012		0.0032 A
3013		A

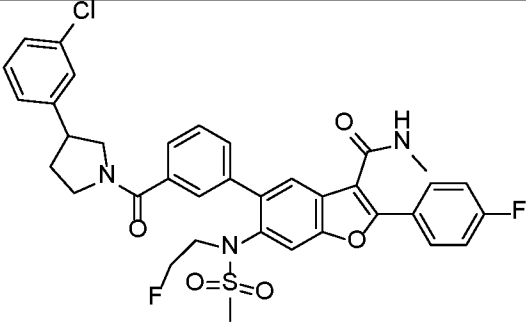
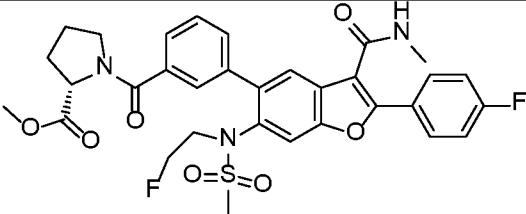
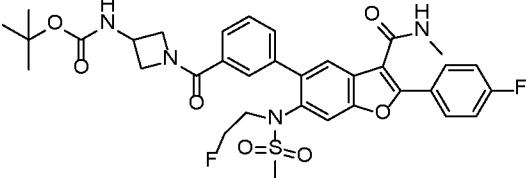
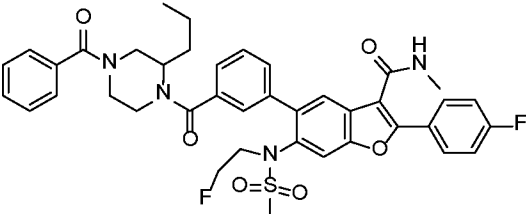
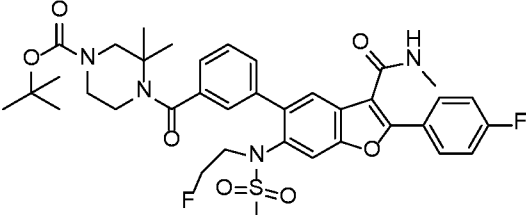
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3014		A
3015		A
3016		A
3017		0.0063 A
3018		A
3019		A

Cmpd#	Structure	EC ₅₀ (uM) 1b
3020		0.0094 A
3021		A
3022		A
3023		A
3024		A

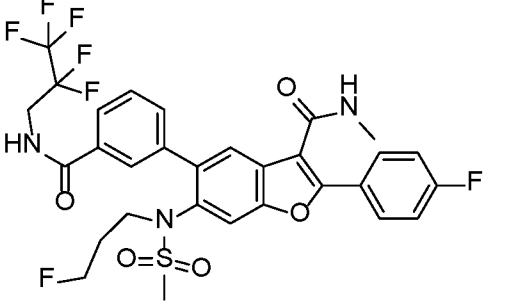
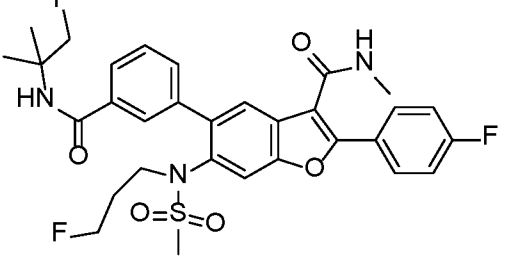
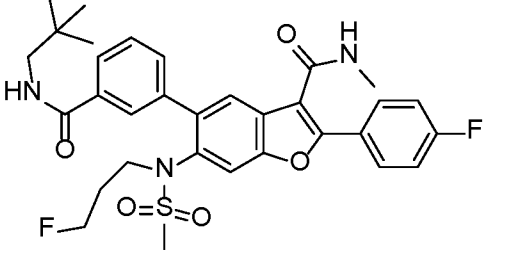
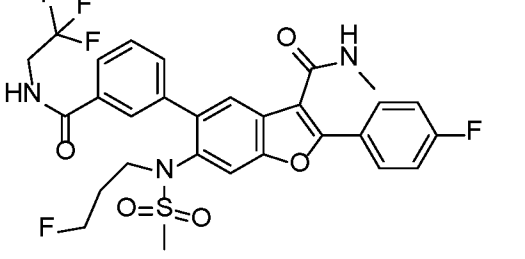
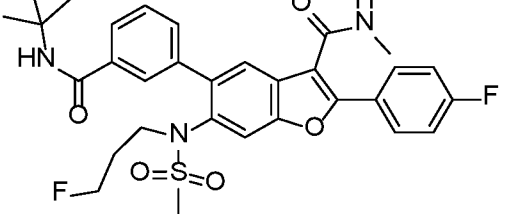
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3026		0.3320 B
3027		A
3028		A
3029		A

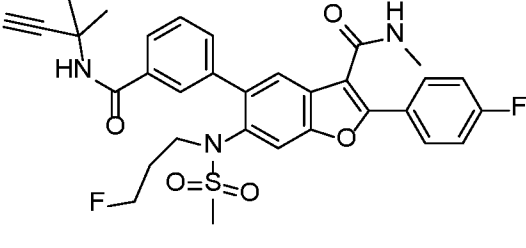
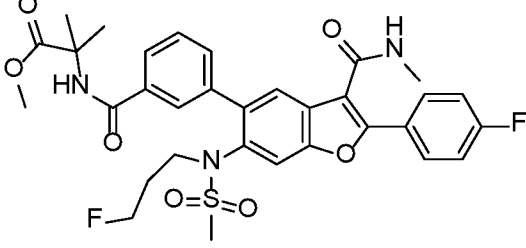
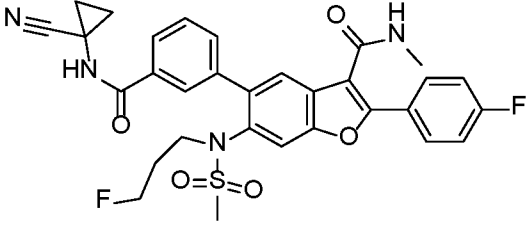
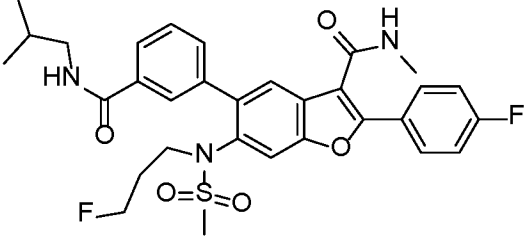
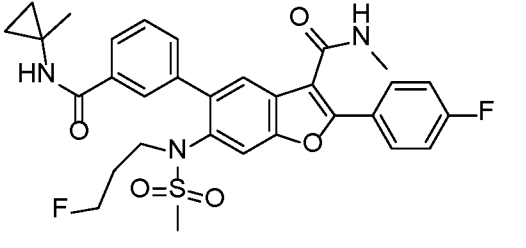
Cmpd#	Structure	EC ₅₀ (uM) 1b
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3031		A
3032		2.6380 C
3033		A
3034		0.0117 A

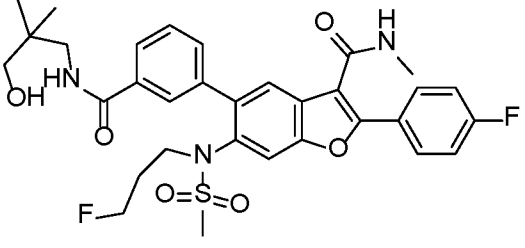
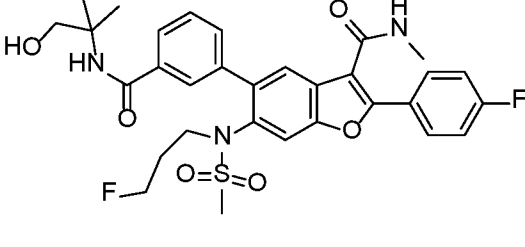
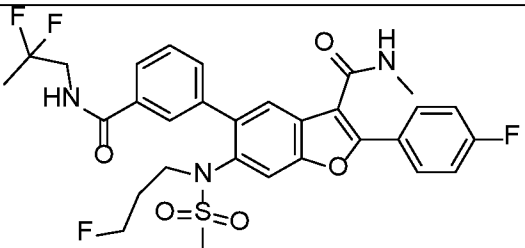
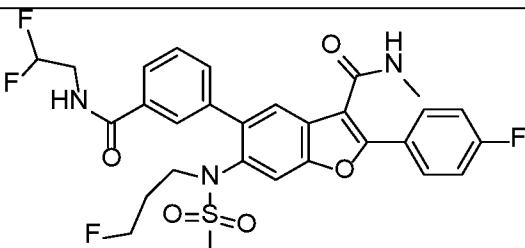
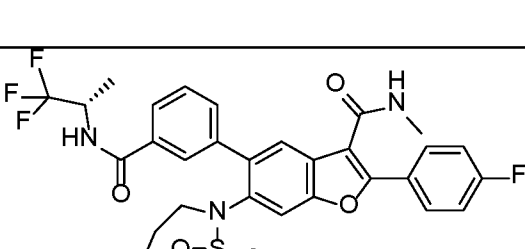
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3036		C
3037		C
3038		A
3039		1.6080 C

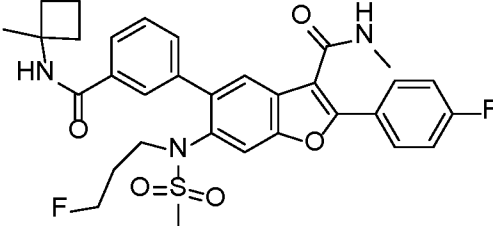
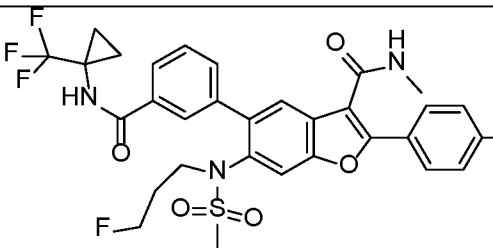
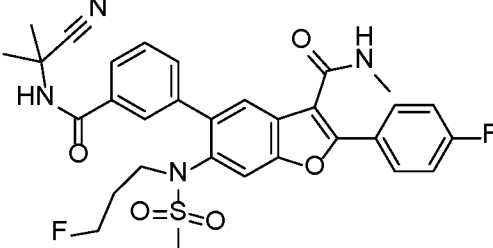
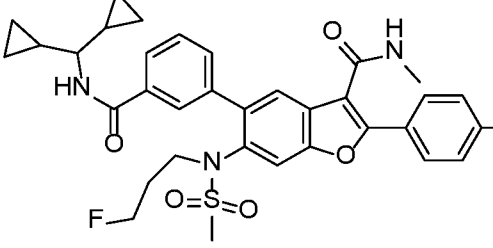
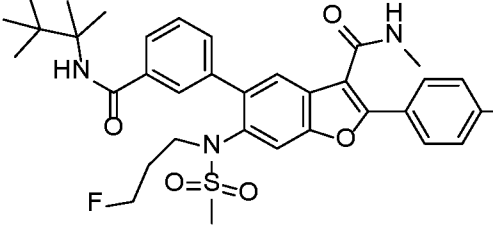
Cmpd#	Structure	EC ₅₀ (uM) 1b
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3041		B
3042		0.1381 B
3043		A
3044		A

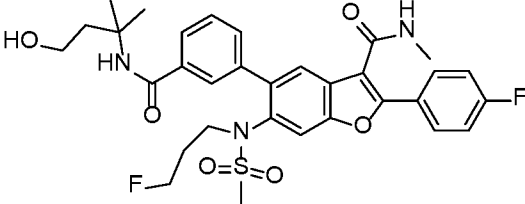
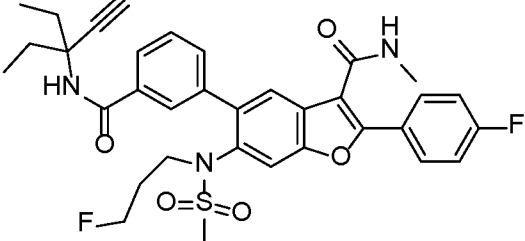
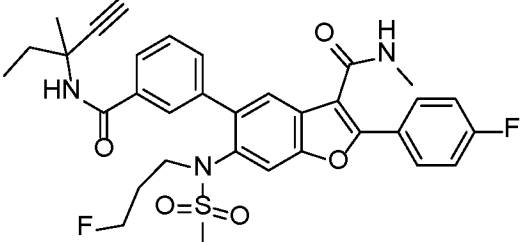
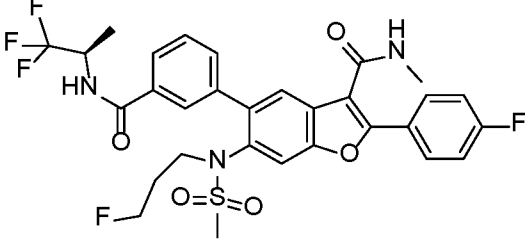
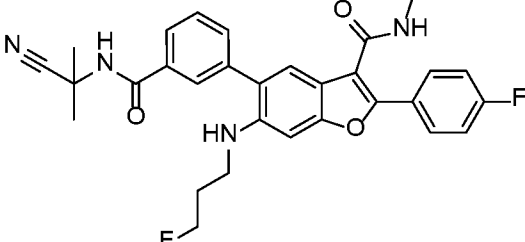
Cmpd#	Structure	EC ₅₀ (uM) 1b
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4003		0.0093 A
4004		A
4005		A
4006		A

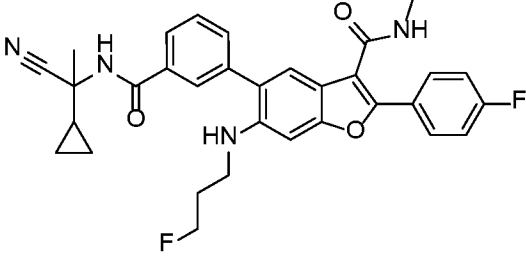
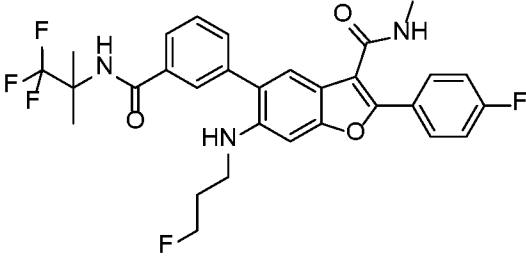
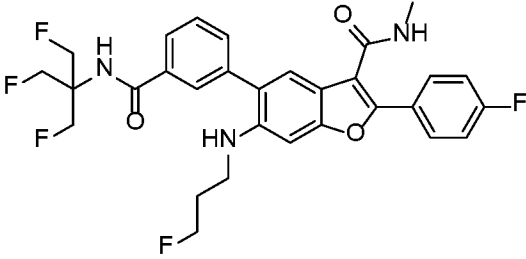
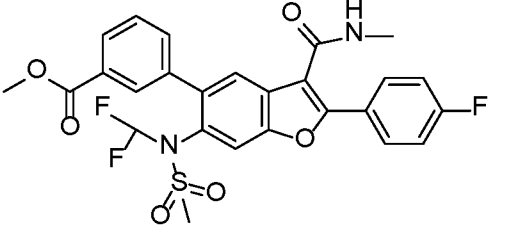
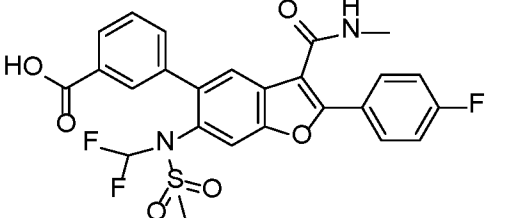
Cmpd#	Structure	EC ₅₀ (uM) 1b
4007		0.0053 A
4008		A
4009		A
4010		A
4011		A

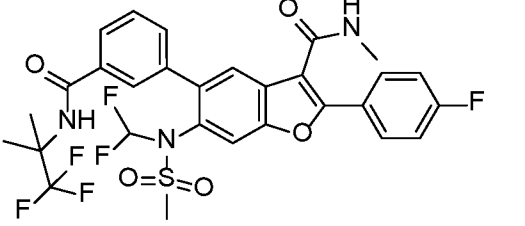
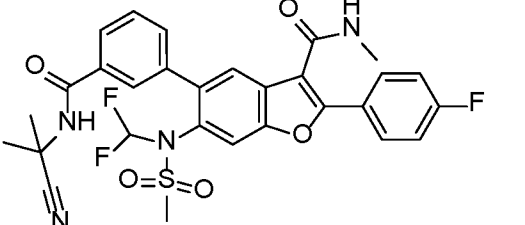
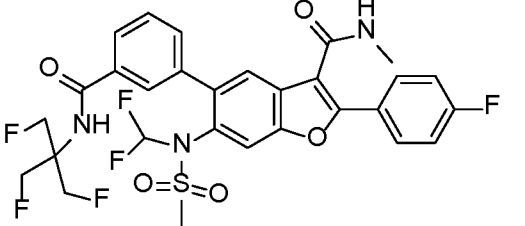
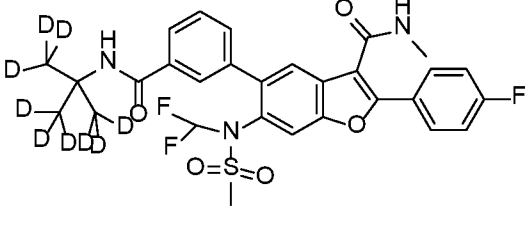
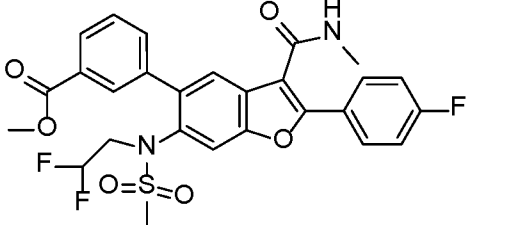
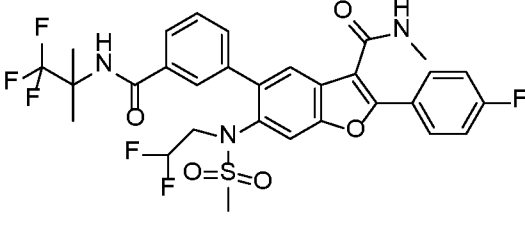
Cmpd#	Structure	EC ₅₀ (uM) 1b
4012		0.0080 A
4013		A
4014		A
4015		0.0075 A
4016		A

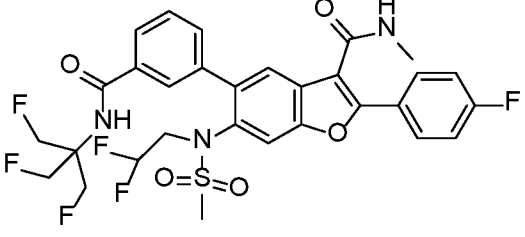
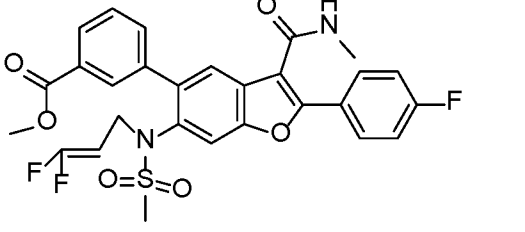
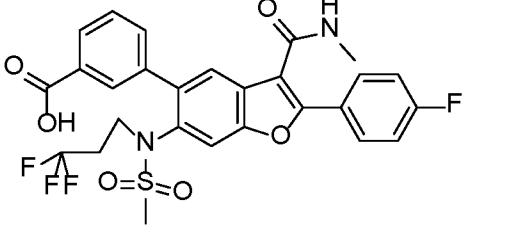
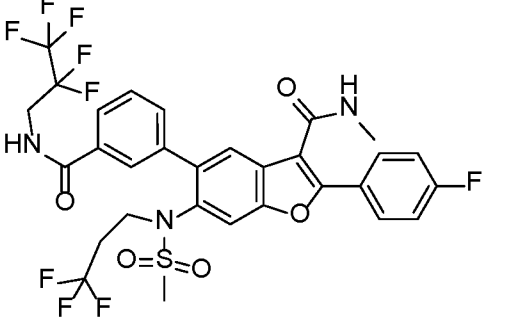
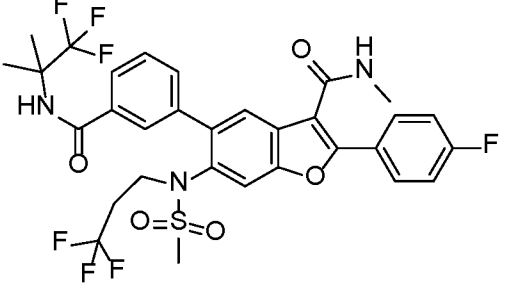
Cmpd#	Structure	EC ₅₀ (uM) 1b
4017		A
4018		A
4019		0.0098 A
4020		A
4021		A

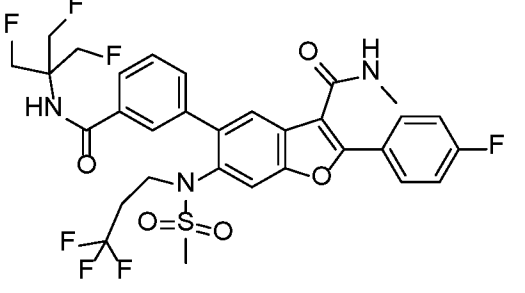
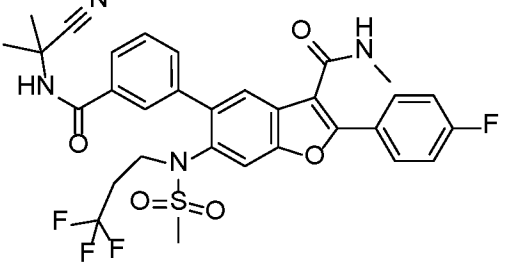
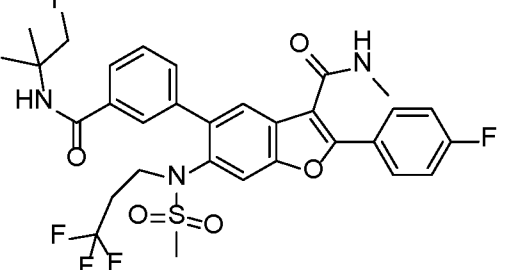
Cmpd#	Structure	EC ₅₀ (uM) 1b
4022		0.0077 A
4023		A
4024		A
4025		A
4026		A

Cmpd#	Structure	EC ₅₀ (uM) 1b
4027		A
4028		0.0056 A
4029		0.0059 A
4030		A
5003		A

Cmpd#	Structure	EC ₅₀ (uM) 1b
5004		A
5005		A
5006		0.0094 A
6001		A
6002		>10.00 00 C

Cmpd#	Structure	EC ₅₀ (uM) 1b
6003		0.0095 A
6004		A
6005		A
6006		A
7001		A
7003		A

Cmpd#	Structure	EC ₅₀ (uM) 1b
7004		A
8001		A
9002		C
9003		0.0076 A
9004		0.0106 A

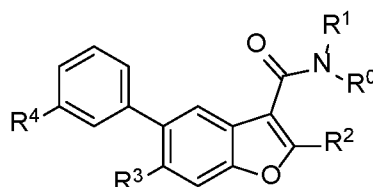
Cmpd#	Structure	EC ₅₀ (uM) 1b
9005		A
9006		A
9007		A

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore
 5 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



I

wherein

R^0 and R^1 are independently hydrogen or methyl;

R^2 is optionally substituted aryl with 0-2 halo;

R^4 is COOR^{101} or $\text{CON}(\text{R}^{102})(\text{R}^{103})$;

R^{101} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} and R^{103} are each independently hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , NH_2 , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, $\text{S}(\text{O})_2\text{R}^{104}$, $\text{S}(\text{O})_2\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{OR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{108}\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo substituted phenyl, phenyl, $\text{C}_1\text{-C}_3$ alkoxy $\text{C}_1\text{-C}_3$ alkyl, hydroxy $\text{C}_1\text{-C}_3$ alkyl, $\text{COOR}^{104}\text{-NHCO}$ $\text{C}_1\text{-C}_3$ alkyl;

R^{104} is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{107} and R^{108} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-COO$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $NR^{201}R^{202}$;

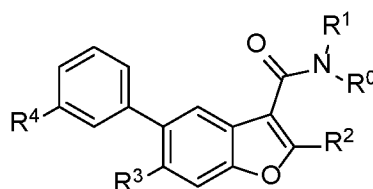
R^{201} is selected from the group of hydrogen, $-SO_2$ C_1 - C_3 alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl, cyanoalkynyl, cycloalkyl, halocycloalkyl, (haloalkyl)cycloalkyl, (halocycloalkyl)cycloalkyl, cyanocycloalkyl, (cyanoalkyl)cycloalkyl, (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl, (hydroxyalkyl)cycloalkyl, (hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl, (alkoxyalkyl)cycloalkyl, and (alkoxycycloalkyl)cycloalkyl;;

R^{202} is selected from the group of $CN(C_1$ - C_6 alkyl), C_3 - C_6 cycloalkyl(C_1 - C_6 alkyl), halo(C_1 - C_6 alkyl) $_n$, halo(C_2 - C_6 alkenyl) $_n$, $CF_3CF_2(C_1$ - C_6 alkyl) $_n$, CF_3 (C_1 - C_6 alkyl) $_n$, alkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, cyanoalkyl, cyanoalkenyl, cyanoalkynyl, cycloalkyl, halocycloalkyl, (haloalkyl)cycloalkyl, (halocycloalkyl)cycloalkyl, cyanocycloalkyl, (cyanoalkyl)cycloalkyl, (cyanocycloalkyl)cycloalkyl, hydroxycycloalkyl, (hydroxyalkyl)cycloalkyl, (hydroxycycloalkyl)cycloalkyl, alkoxycycloalkyl, (alkoxyalkyl)cycloalkyl, and (alkoxycycloalkyl)cycloalkyl;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

2. The compound according to claim 1



I

wherein

R^0 is hydrogen;

R^1 is methyl;

R^2 is phenyl substituted with 1-2 halo;

R^4 is COOR^{101} or $\text{CON}(\text{R}^{102})(\text{R}^{103})$;

R^{101} is hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{102} and R^{103} are each independently hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , NH_2 , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, $\text{S}(\text{O})_2\text{R}^{104}$, $\text{S}(\text{O})_2\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{OR}^{104}\text{CONR}^{105}\text{R}^{106}$, $\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, $\text{NR}^{108}\text{C}(=\text{NR}^{107})\text{NR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, $\text{C}_1\text{-C}_6$ alkyl, halo substituted phenyl, phenyl, $\text{C}_1\text{-C}_3$ alkoxy $\text{C}_1\text{-C}_3$ alkyl, hydroxy $\text{C}_1\text{-C}_3$ alkyl, $\text{COOR}^{104}\text{-NHCO}$ $\text{C}_1\text{-C}_3$ alkyl;

R^{104} is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{107} and R^{108} are each independently hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{10} and R^{11} are independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

R^{12} is substituted $\text{C}_1\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{COO}$ $\text{C}_1\text{-C}_6$ alkyl, phenyl or CF_2CF_3 ;

R^3 is $\text{NR}^{201}\text{R}^{202}$;

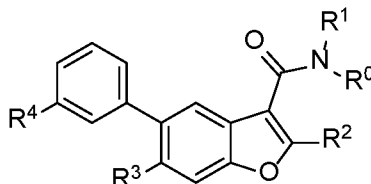
R^{201} is hydrogen or SO_2 $\text{C}_1\text{-C}_3$ alkyl;

R^{202} is CN C₁-C₆ alkyl, C₃-C₆ cycloalkyl C₁-C₆ alkyl, halo (C₁-C₆ alkyl)_n, halo (C₂-C₆ alkenyl)_n, CF₃CF₂(C₁-C₆ alkyl)_n or CF₃ (C₁-C₆ alkyl)_n;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound according to claim 2



I

wherein

R^0 is hydrogen;

R^1 is methyl;

R^2 is phenyl substituted with fluoro;

R^4 is COOR¹⁰¹ or CONH(R¹⁰³);

R^{101} is hydrogen or optionally substituted C₁-C₃ alkyl with 0-2 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{103} is hydrogen, -(CR¹⁰R¹¹)R¹², optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₈ cycloalkyl, with 0-3 substituents selected from halo, CN, CF₃, OH, OR¹⁰⁴, NR¹⁰⁵R¹⁰⁶, COOR¹⁰⁴, CONR¹⁰⁵R¹⁰⁶, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, C₁-C₆ alkyl, halo substituted phenyl, phenyl, C₁-C₃ alkoxy C₁-C₃ alkyl, hydroxy C₁-C₃ alkyl, COOR¹⁰⁴-NHCO C₁-C₃ alkyl;

R^{104} is hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{10} and R^{11} are independently hydrogen or C₁-C₆ alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-COO$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $NR^{201}R^{202}$;

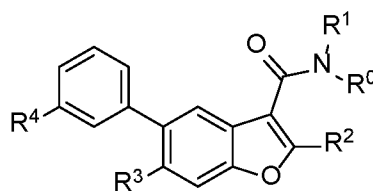
R^{201} is hydrogen or SO_2 C_1 - C_3 alkyl;

R^{202} is CN C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, halo (C_1 - C_6 alkyl) $_n$, halo (C_2 - C_6 alkenyl) $_n$, $CF_3CF_2(C_1$ - C_6 alkyl) $_n$ or CF_3 (C_1 - C_6 alkyl) $_n$;

n is 1, 2, 3 or 4;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

4. The compound according to claim 3



I

wherein

R^0 is hydrogen;

R^1 is methyl;

R^2 is phenyl substituted with fluoro;

R^4 is $COOR^{101}$ or $CONH(R^{103})$;

R^{101} is hydrogen or C_1 - C_3 alkyl;

R^{103} is hydrogen, $-(CR^{10}R^{11})R^{12}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, with 0-3 substituents selected from halo, CN , CF_3 , OH , OR^{104} , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH , C_1 - C_6 alkyl, halo substituted phenyl, phenyl, C_1 - C_3 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl, $COOR^{104}$ - $NHCO$ C_1 - C_3 alkyl;

R^{104} is hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy; or

R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-\text{COO}$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

R^3 is $\text{NR}^{201}\text{R}^{202}$;

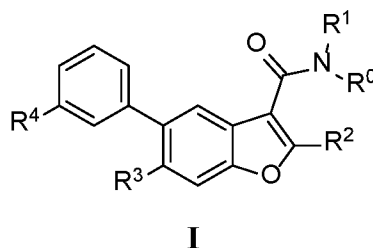
R^{201} is SO_2 C_1 - C_3 alkyl;

R^{202} is CN C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, halo (C_1 - C_6 alkyl) $_n$, halo (C_2 - C_6 alkenyl) $_n$, $\text{CF}_3\text{CF}_2(\text{C}_1$ - C_6 alkyl) $_n$ or CF_3 (C_1 - C_6 alkyl) $_n$;

n is 1, 2 or 3;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

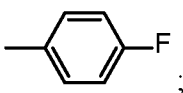
5. The compound according to claim 4



wherein

R^0 is hydrogen;

R^1 is methyl;

R^2 is ;

R^4 is COOR^{101} or $\text{CONH}(\text{R}^{103})$;

R^{101} is hydrogen or C_1 - C_3 alkyl;

R^{103} is hydrogen, $-(\text{CR}^{10}\text{R}^{11})\text{R}^{12}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, with 0-3 substituents selected from halo, CN , CF_3 , OH , OR^{104} , $\text{NR}^{105}\text{R}^{106}$, COOR^{104} , $\text{CONR}^{105}\text{R}^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH , C_1 - C_6 alkyl, halo

substituted phenyl, phenyl, C₁-C₃ alkoxy C₁-C₃ alkyl, hydroxy C₁-C₃ alkyl, COOR¹⁰⁴-NHCO C₁-C₃ alkyl;

R¹⁰⁴ is hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R¹⁰⁵ and R¹⁰⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or optionally substituted C₃-C₈ cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R¹⁰ and R¹¹ are independently hydrogen or C₁-C₆ alkyl;

R¹² is substituted C₁-C₆ alkynyl, C₃-C₈ cycloalkyl, -COO C₁-C₆ alkyl, phenyl or CF₂CF₃;

R³ is NR²⁰¹R²⁰²;

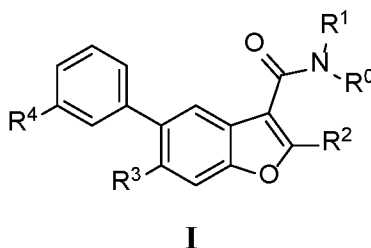
R²⁰¹ is SO₂ C₁-C₃ alkyl;

R²⁰² is CN C₁-C₆ alkyl, C₃-C₆ cycloalkyl C₁-C₆ alkyl, halo (C₁-C₆ alkyl)_n, halo (C₂-C₆ alkenyl)_n, CF₃CF₂(C₁-C₆ alkyl)_n or CF₃ (C₁-C₆ alkyl)_n;

n is 1, 2 or 3;

and/or a pharmaceutically acceptable salt or stereoisomer thereof.

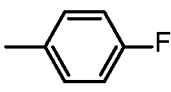
6. The compound according to claim 5



wherein

R⁰ is hydrogen;

R¹ is methyl;

R² is  ;

R⁴ is COOR¹⁰¹ or CONH(R¹⁰³);

R¹⁰¹ is hydrogen or methyl;

R^{103} is hydrogen, $-(CR^{10}R^{11})R^{12}$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, with 0-3 substituents selected from halo, CN, CF_3 , OH, OR^{104} , $NR^{105}R^{106}$, $COOR^{104}$, $CONR^{105}R^{106}$, haloalkoxy; or

R^{102} and R^{103} can be taken together with the nitrogen atom to form a 4-7 membered ring optionally containing 1-2 additional nitrogen atoms, said ring optionally substituted with 0-3 substituents selected from OH, C_1 - C_6 alkyl, halo substituted phenyl, phenyl, C_1 - C_3 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl, $COOR^{104}$ -NHCO C_1 - C_3 alkyl;

R^{104} is hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{105} and R^{106} are each independently hydrogen, optionally substituted C_1 - C_6 alkyl or optionally substituted C_3 - C_8 cycloalkyl with 0-3 substituents selected from halo, hydroxyl, alkoxy, and haloalkoxy;

R^{10} and R^{11} are independently hydrogen or C_1 - C_6 alkyl;

R^{12} is substituted C_1 - C_6 alkynyl, C_3 - C_8 cycloalkyl, $-COO$ C_1 - C_6 alkyl, phenyl or CF_2CF_3 ;

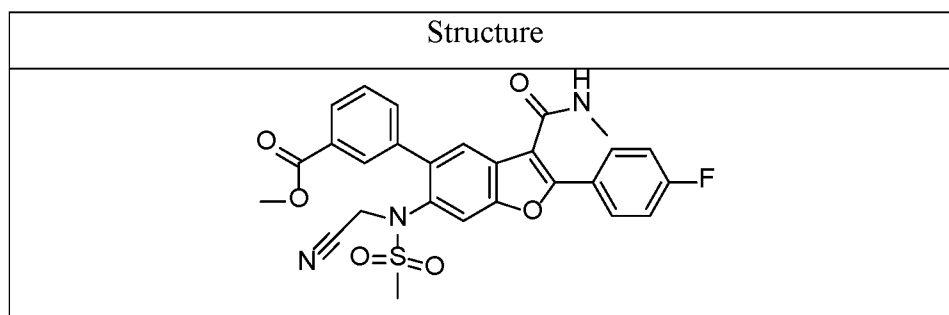
R^3 is $NR^{201}R^{202}$;

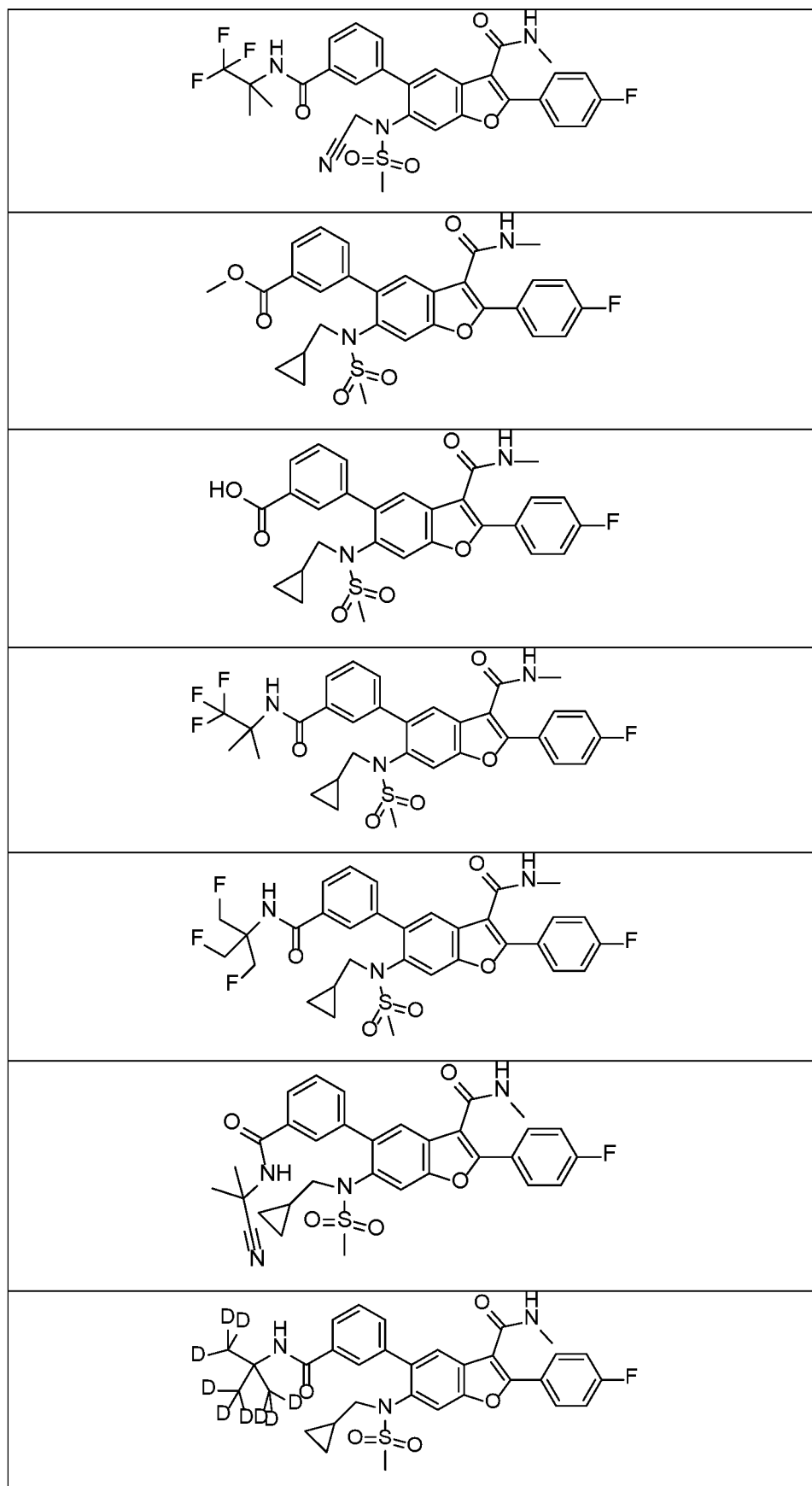
R^{201} is SO_2CH_3 ;

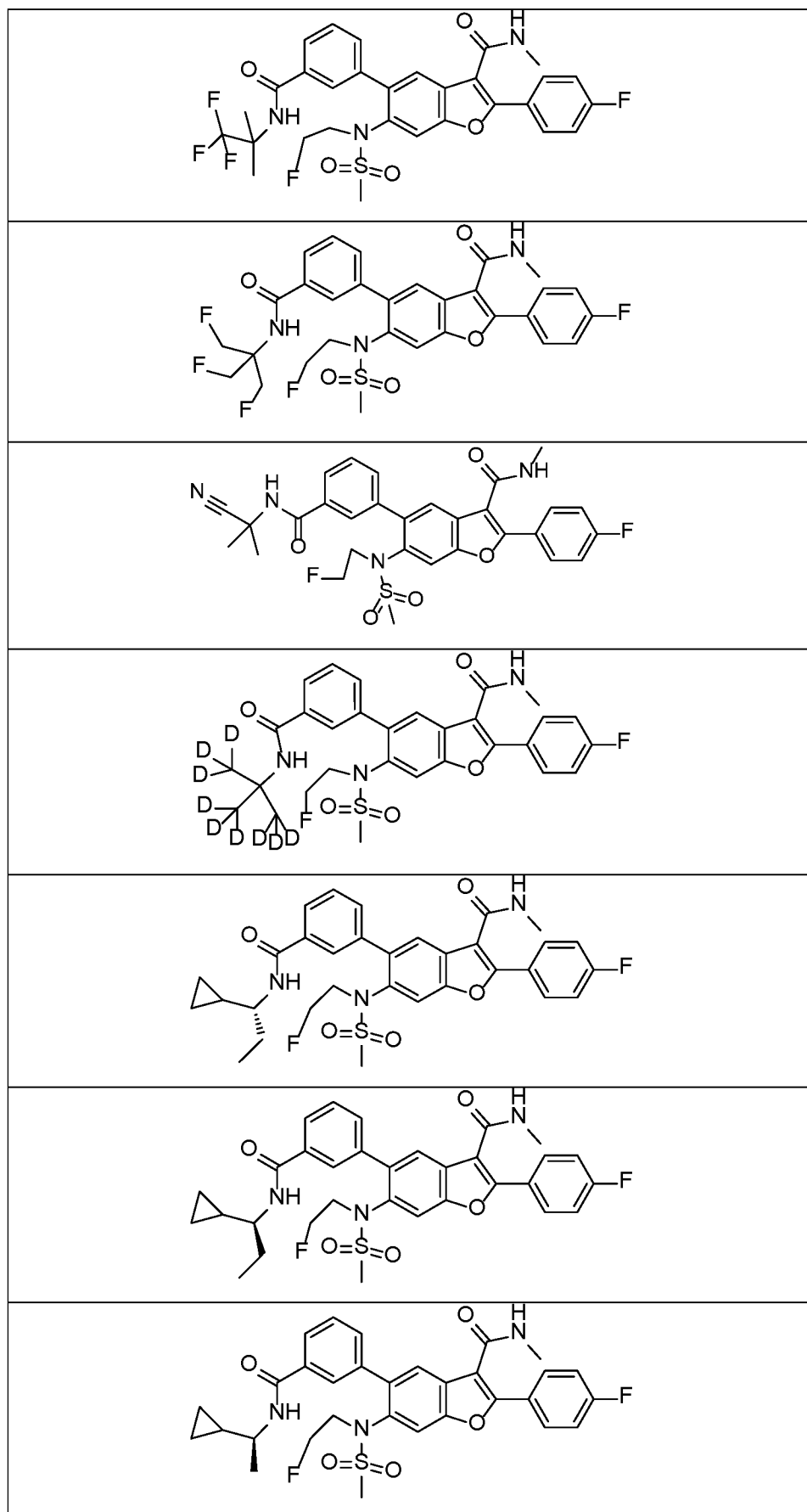
R^{202} is $-CH_3CN$, $-CH_3$ cyclopropyl, $-(CH_2)_2F$, $-(CH_2)_3F$, $-NH(CH_2)_3F$, $-CHF_2$, $-CH_2CHF_2$, $-CH_2CH=CHF_2$, $-(CH_2)_2CF_3$;

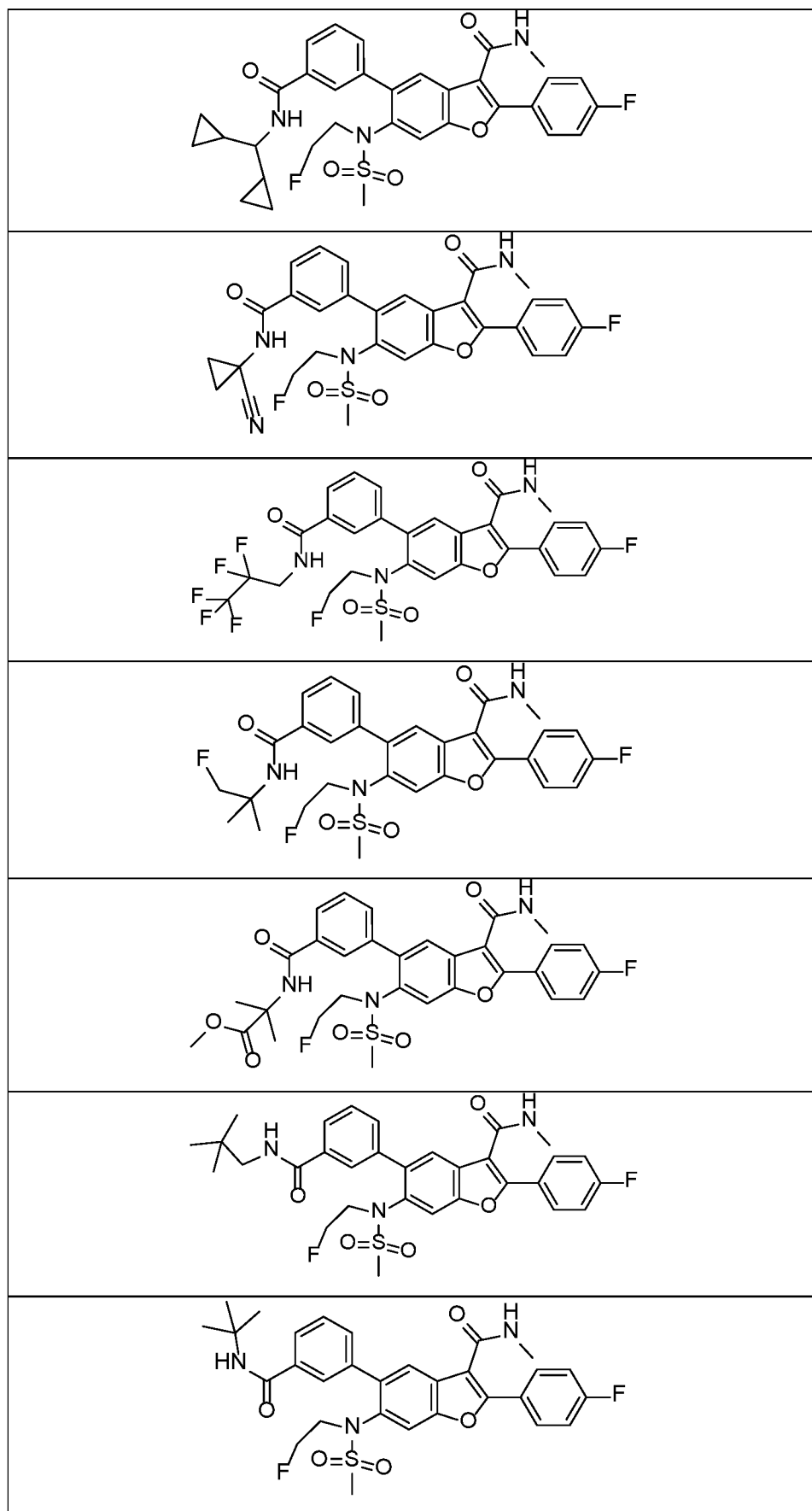
and/or a pharmaceutically acceptable salt or stereoisomer thereof.

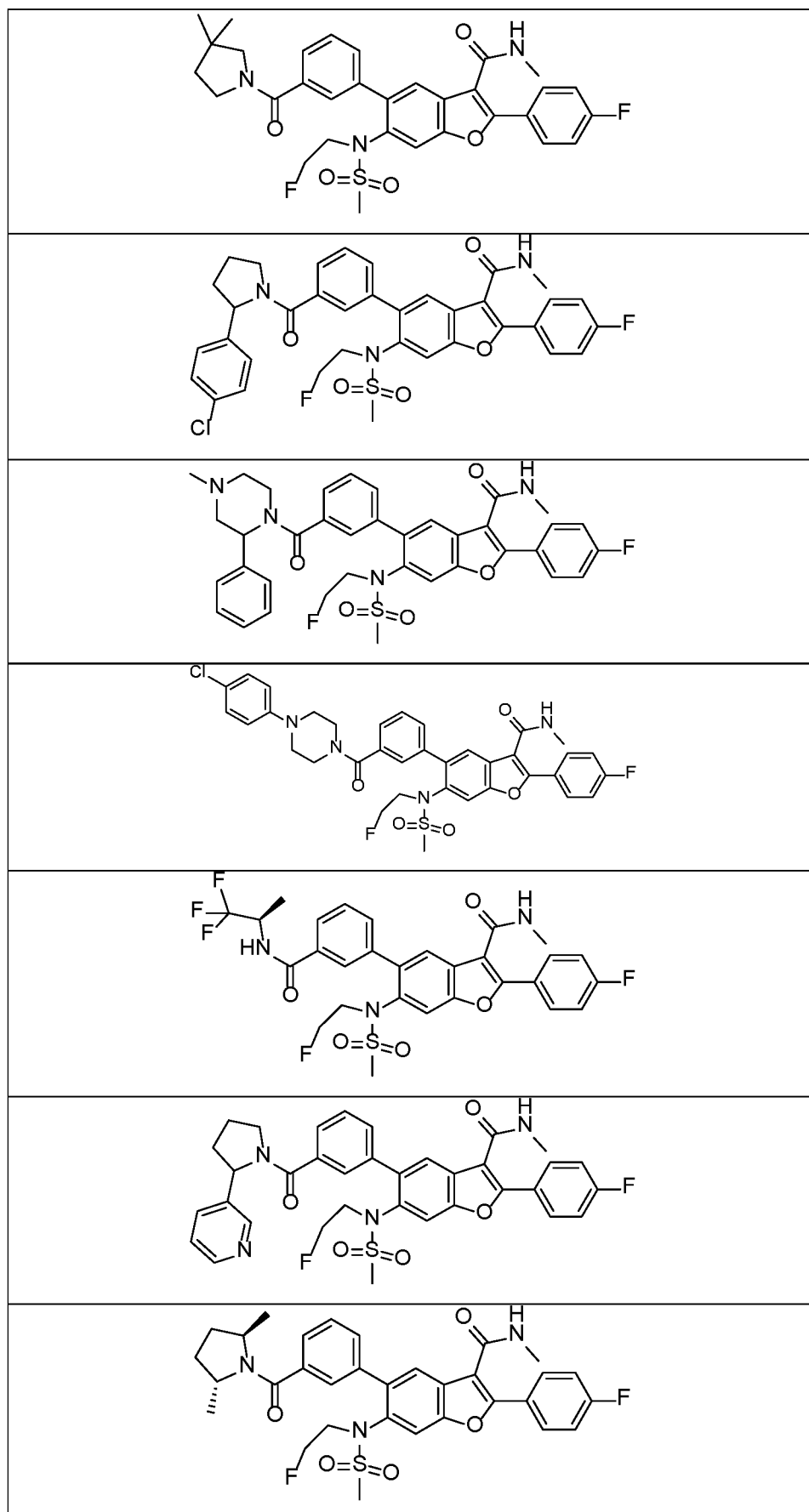
7. A compound of the Formula

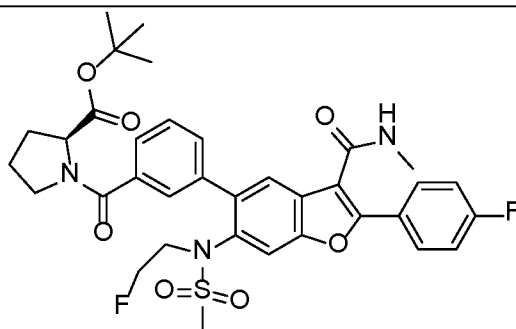
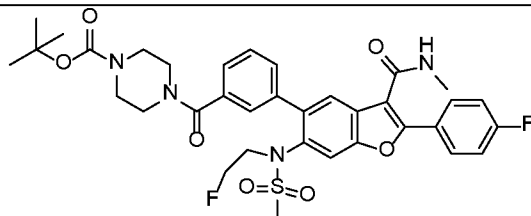
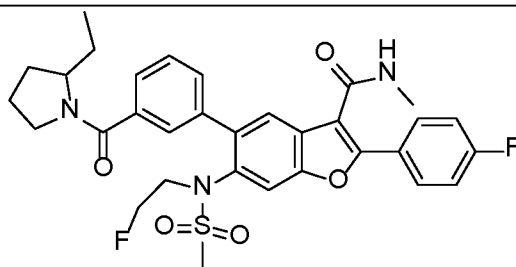
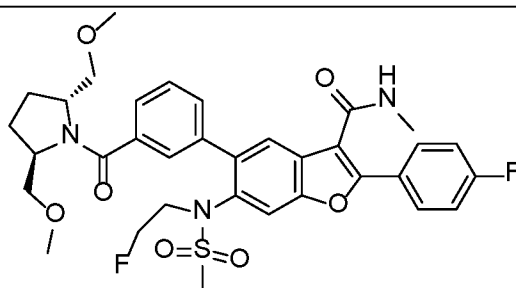
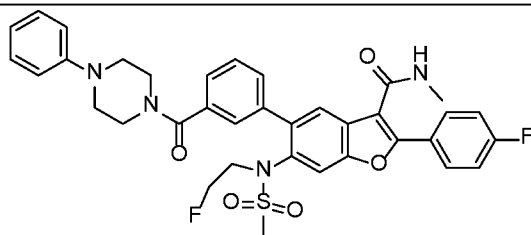
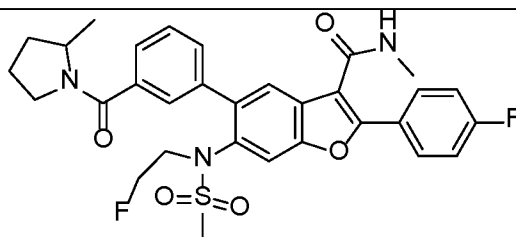


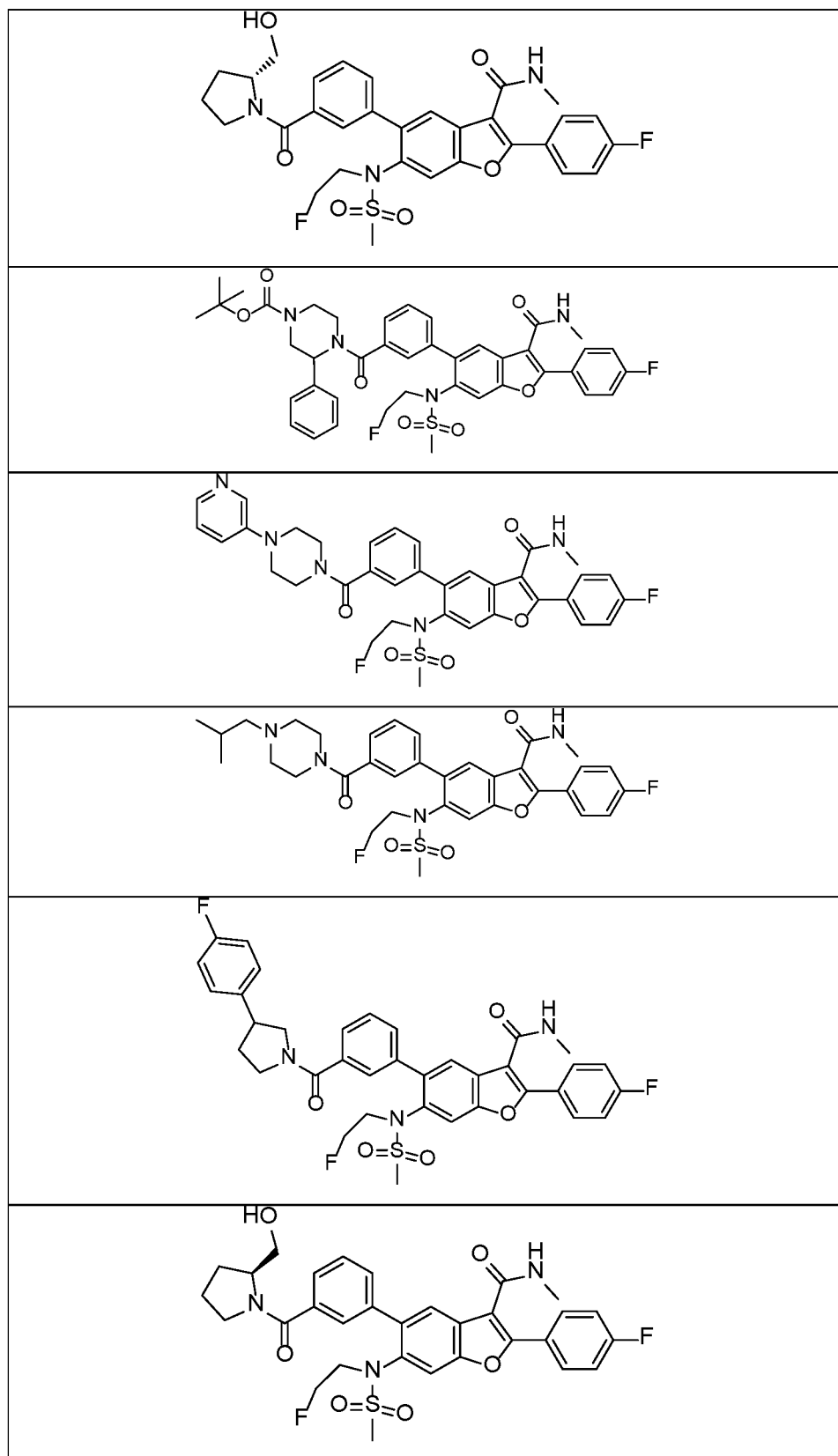


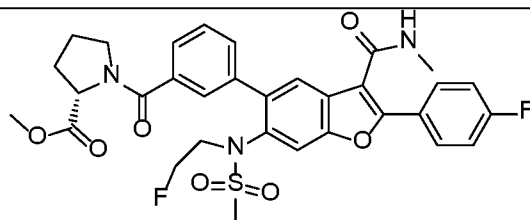
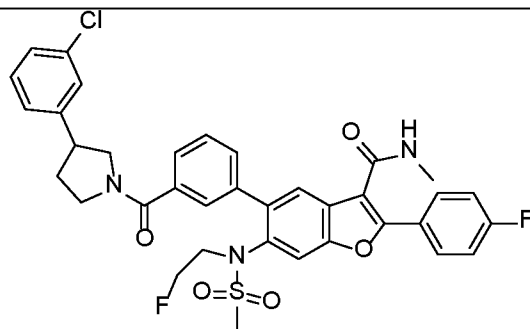
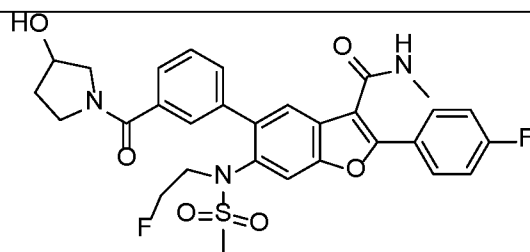
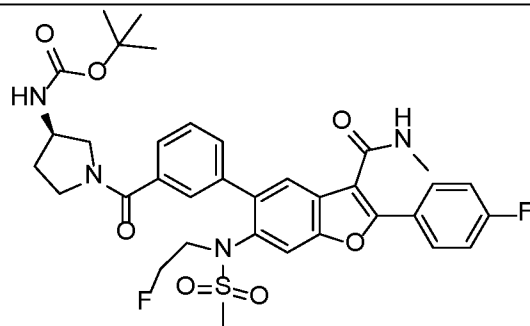
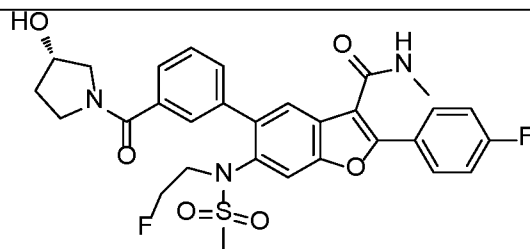
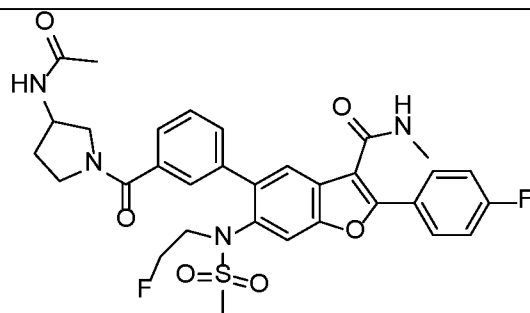


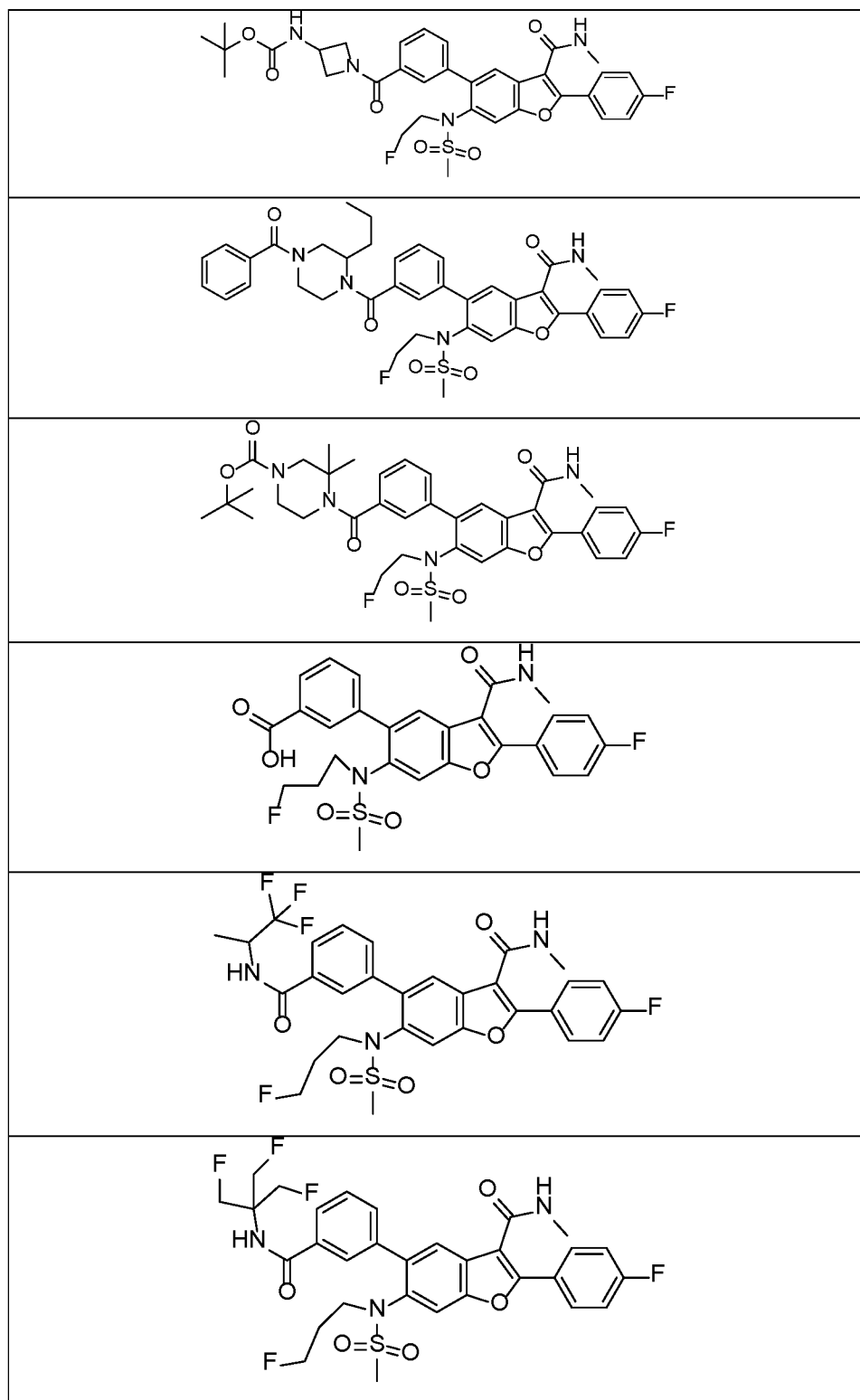


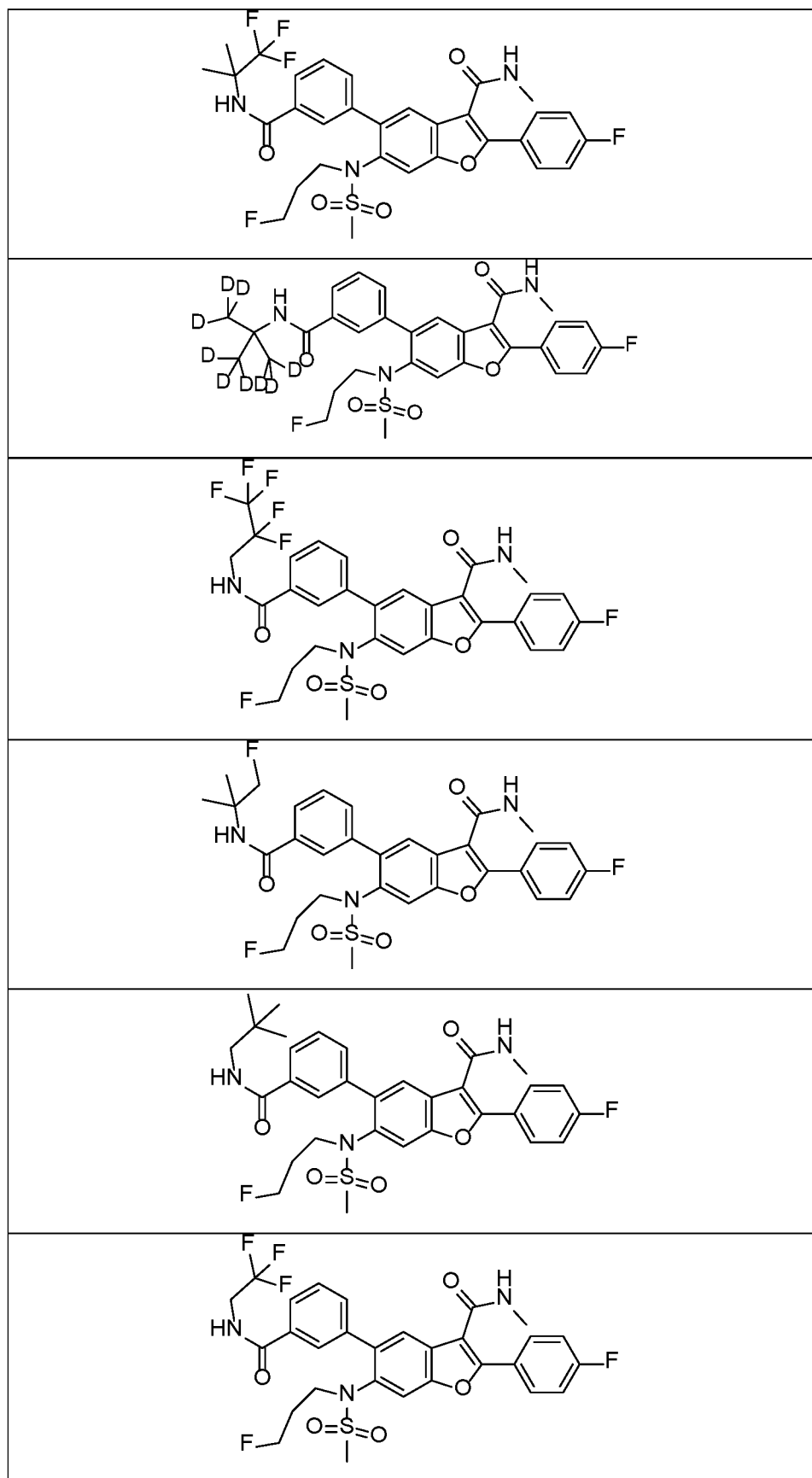


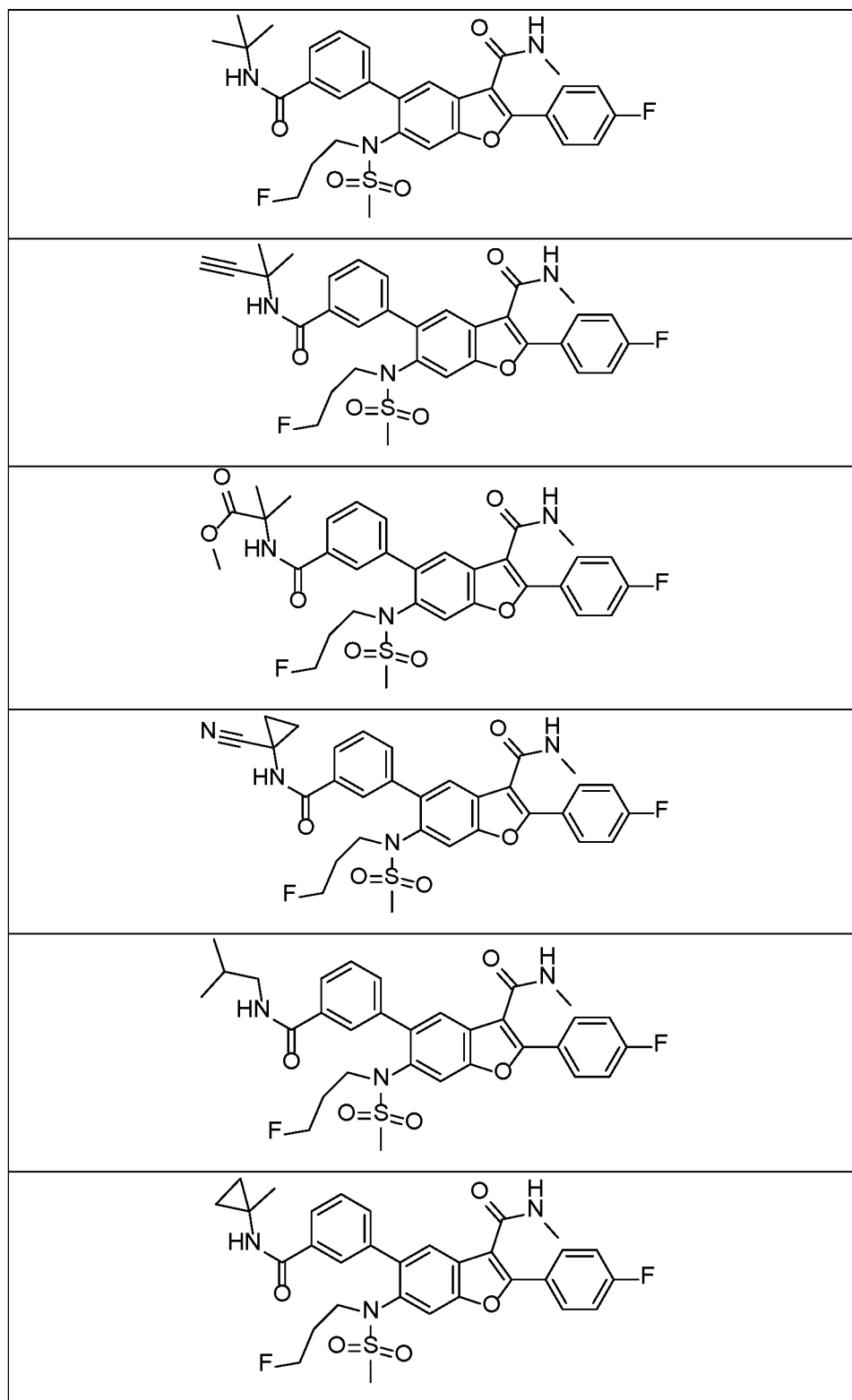


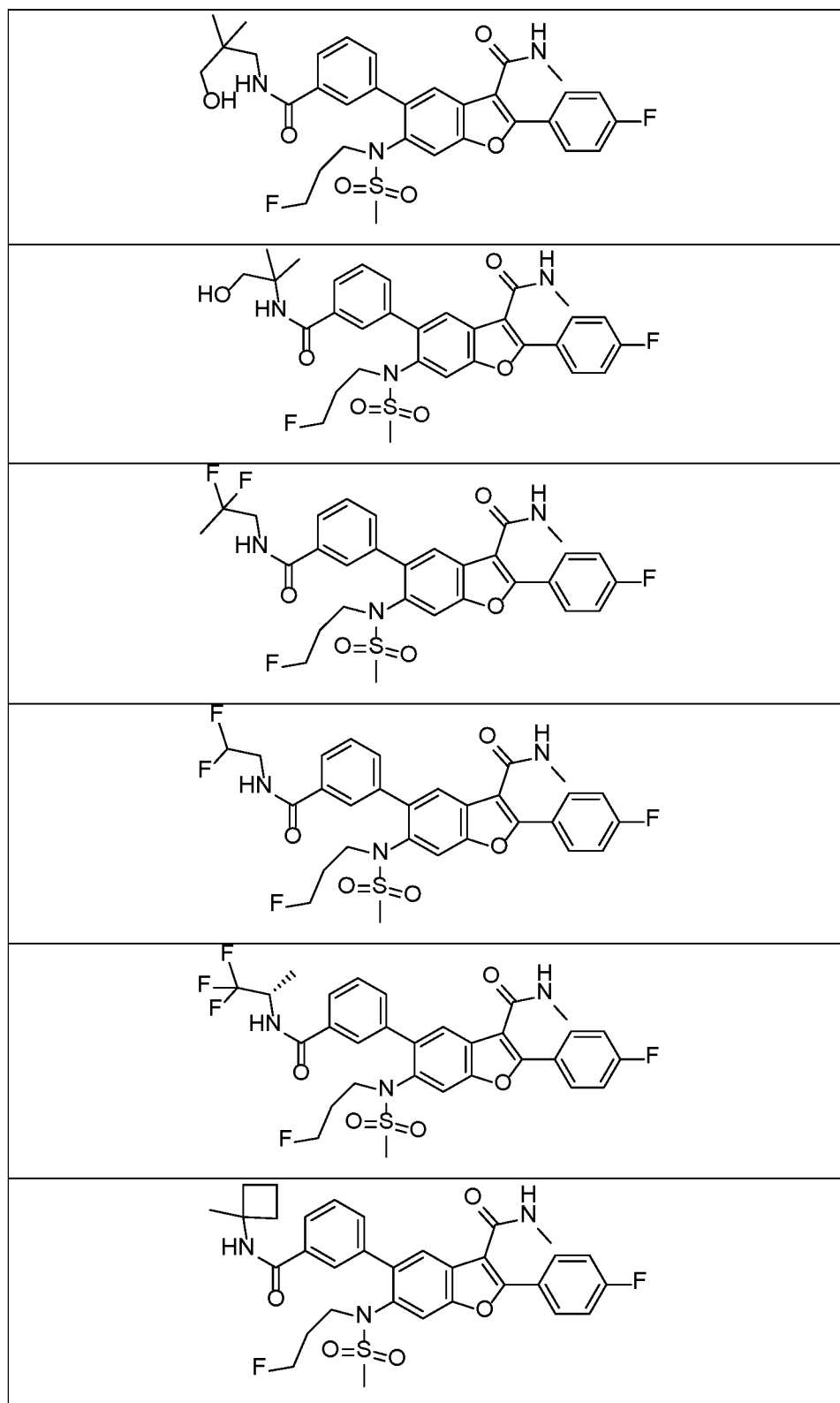


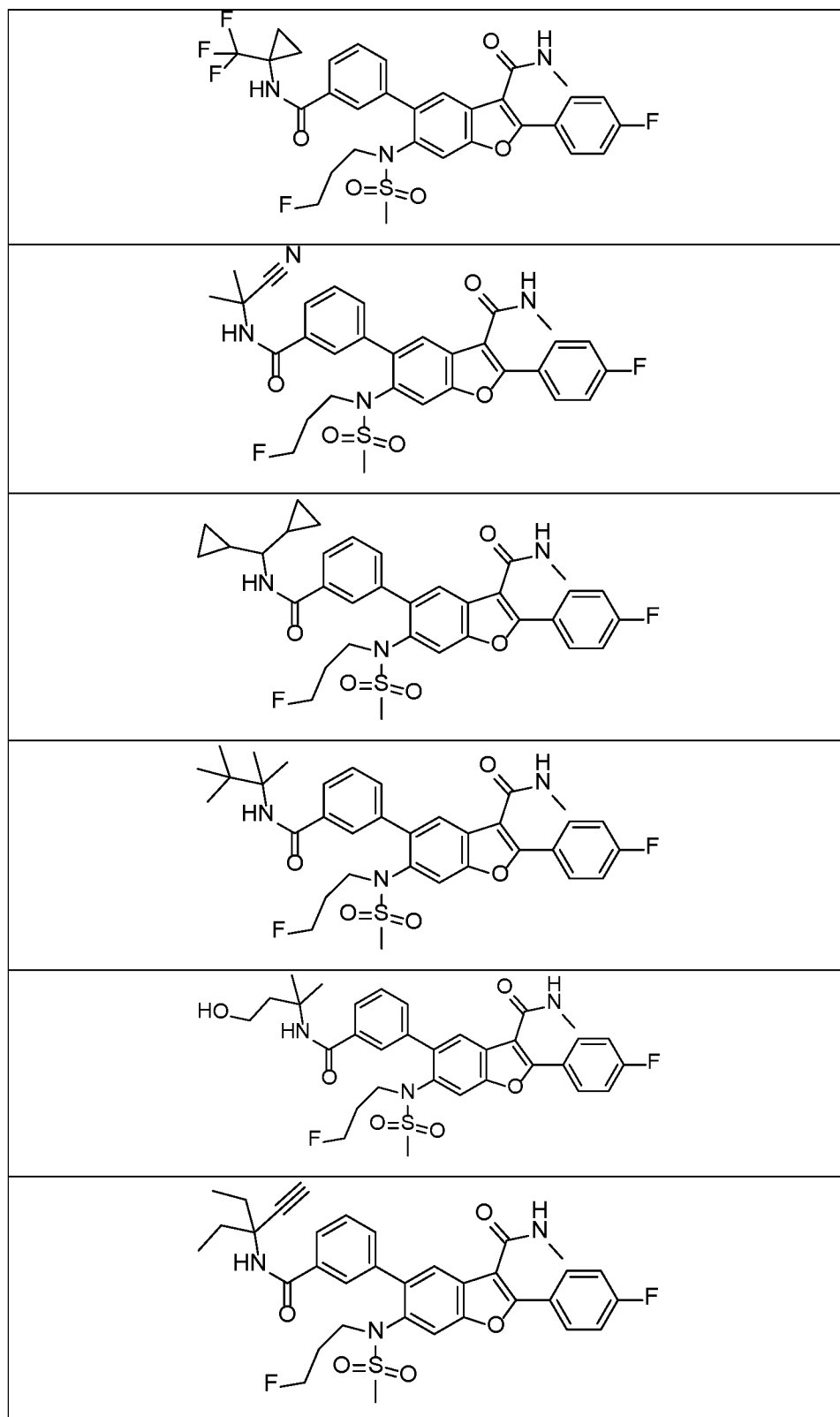


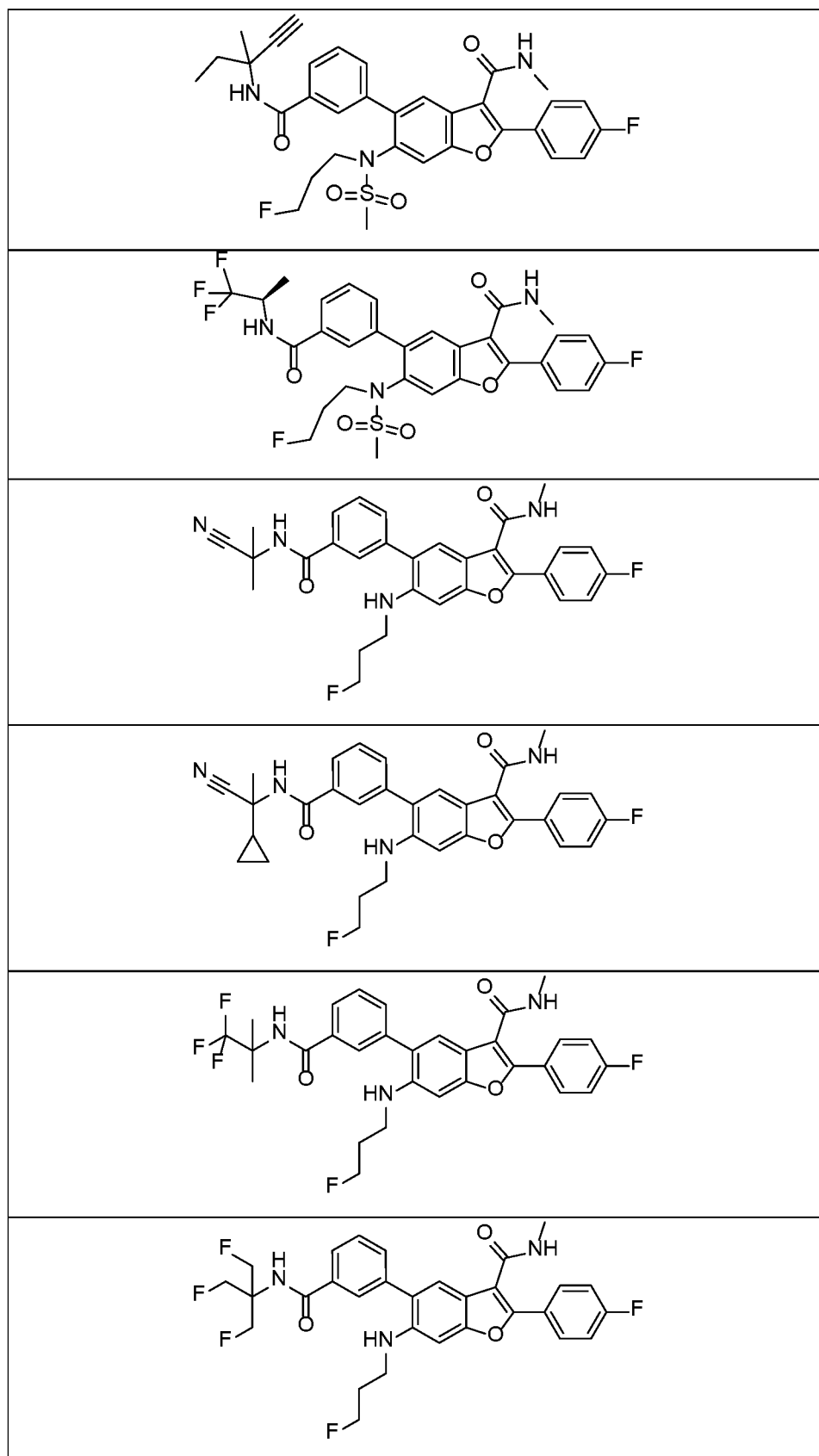


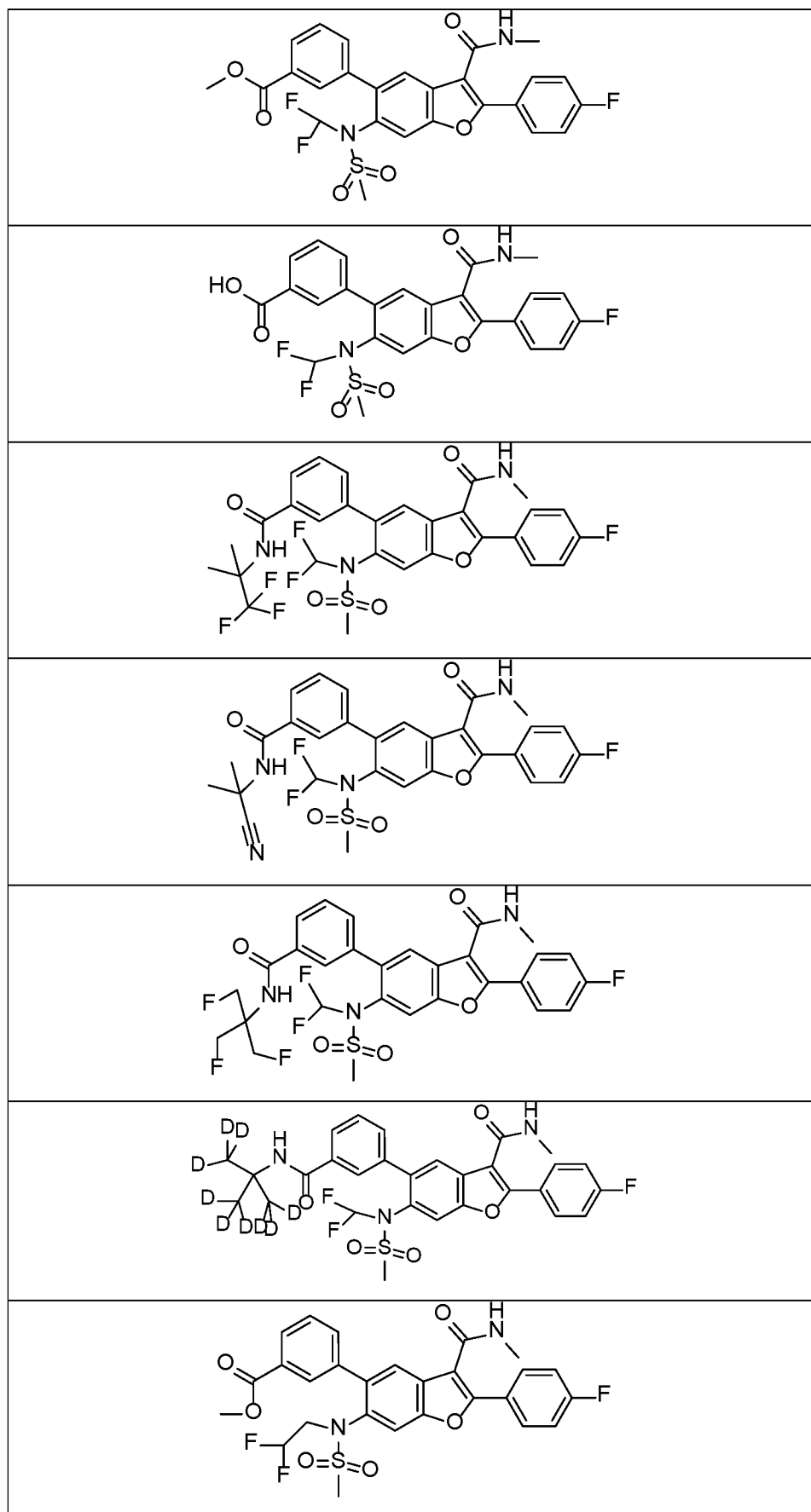


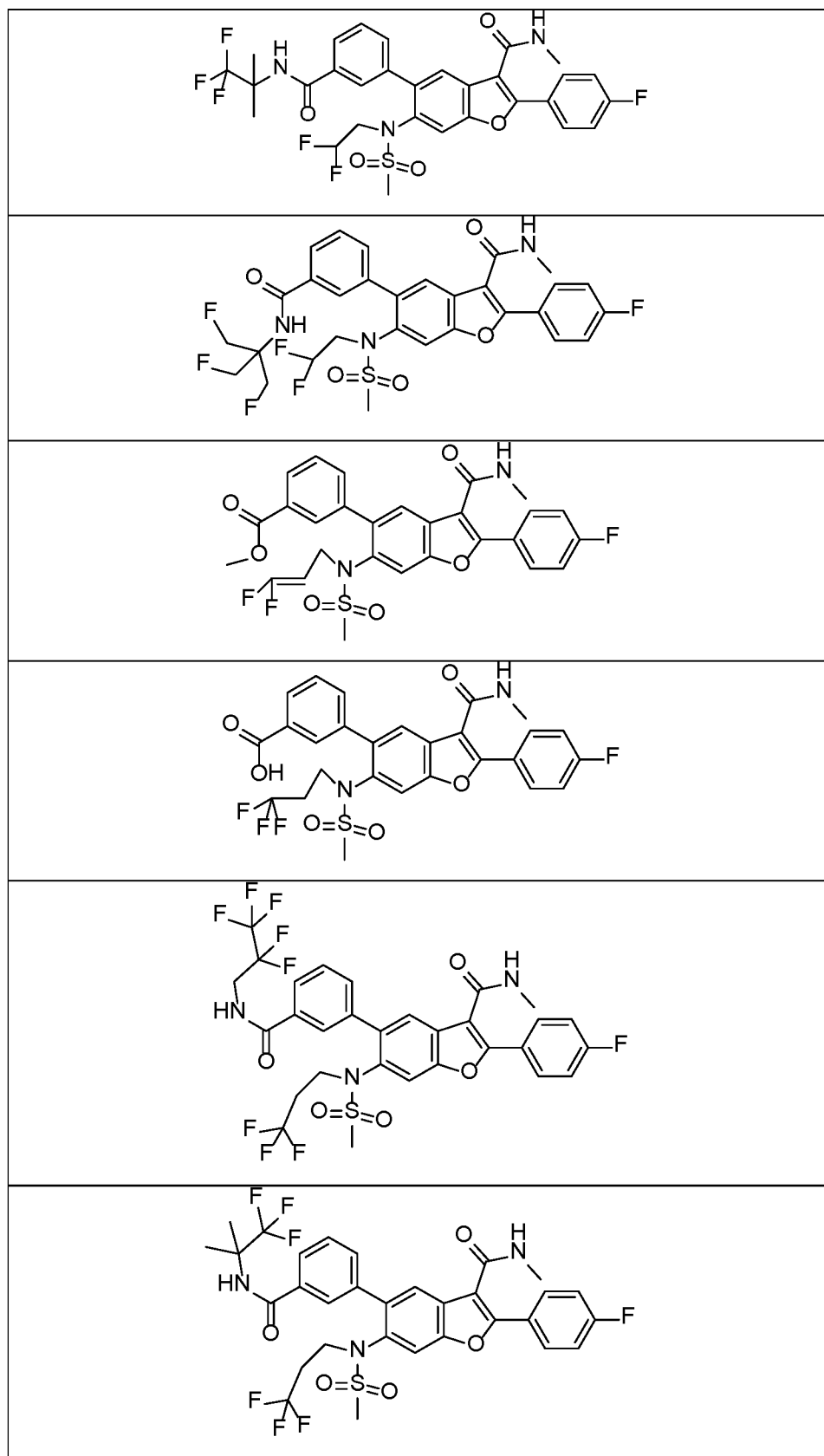


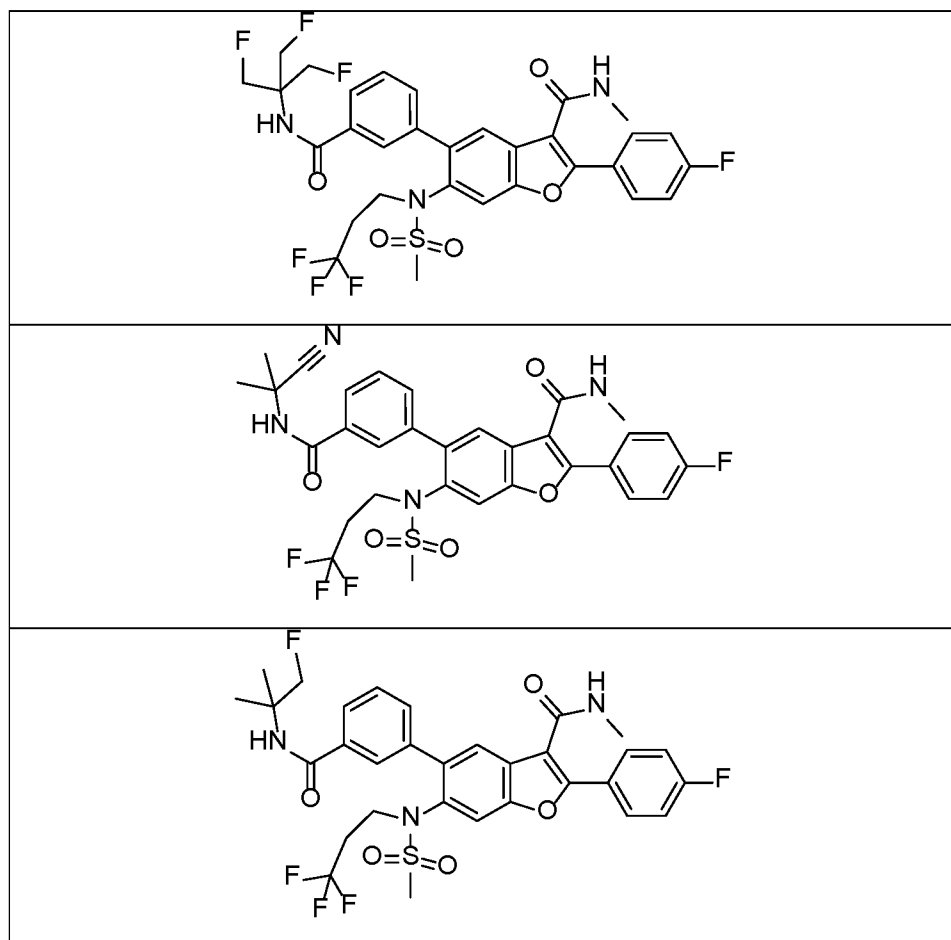












and/or a pharmaceutically acceptable salt or stereoisomer thereof.

8. A pharmaceutical composition comprising one or more compounds according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
9. A composition comprising one or more compounds of claim 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
10. A method of treating hepatitis C infection comprising administering to a patient a therapeutically effective amount of one or more compounds according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/018151

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/04 C07D405/12 C07D307/84 A61K31/343 A61P1/16
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/112191 A1 (SQUIBB BRISTOL MYERS CO [US]; YEUNG KAP-SUN [US]; PARCELLA KYLE E [US]) 15 September 2011 (2011-09-15) page 1, paragraph 1 page 2, lines 8, 9, paragraph 2 page 3; compound I page 14, lines 1, 4, paragraph 3 page 15, paragraphs 1, 2 Schemes 1-4; page 18 - page 21 in particular pages 40, 41, 51, 86-88, 132; page 29 - page 151 page 153, paragraph 2 claims 1-3 -----	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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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

12 May 2016

Date of mailing of the international search report

20/05/2016

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Authorized officer

Hoepfner, Wolfgang

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/018151

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011112191 A1	15-09-2011	CN 102906080 A	30-01-2013
		EP 2545042 A1	16-01-2013
		JP 2013522192 A	13-06-2013
		WO 2011112191 A1	15-09-2011
