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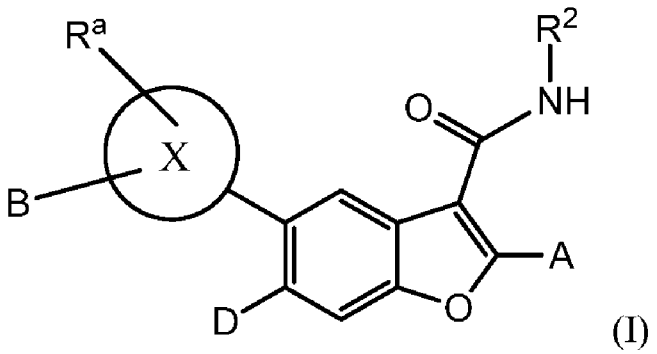
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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF FOR TREATMENT OF HEPATITIS C



(I)

(57) Abstract: Compounds of formula (I) that are useful as hepatitis C virus (HCV) NS5B polymerase inhibitors, the synthesis of such compounds, and the use of such compounds for inhibiting HCV NS5B polymerase activity, for treating or preventing HCV infections and for inhibiting HCV viral replication and/or viral production in a cell-based system are disclosed.

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HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF FOR TREATMENT OF HEPATITIS C

FIELD OF THE INVENTION

The present disclosure relates to compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS5B (non-structural protein 5B) polymerase, compositions comprising such compounds, the use of such compounds for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection, methods for inhibiting the function of the NS5B polymerase, and methods for inhibiting HCV viral replication and/or viral production.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Current treatments for HCV infection include immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin.

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3, amino acid residues 1-180), a helicase (NS3, full length), an NS3 protease cofactor (NS4A), a membrane protein (NS4B), a zinc metalloprotein (NS5A) and an RNA-dependent RNA polymerase (NS5B).

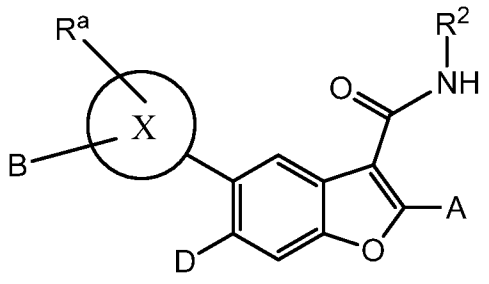
One identified target for therapeutic intervention is HCV NS5B polymerase. Sven-Erik Behrens *et al.*, *Identification and properties of the RNA-dependent RNA polymerase of heptatitis C virus*, 15(1) EMBO J. 12-22 (1996). Antagonists of NS5B activity are inhibitors of HCV replication. Steven S. Carroll *et al.*, *Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs*, 278(14) J. BIOL. CHEM. 11979-84 (2003).

There is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection. Specifically, there is a need to develop compounds that inhibit HCV viral replication and that would be useful for treating HCV-infected patients.

SUMMARY OF THE INVENTION

The present disclosure relates to novel compounds of formula I and pharmaceutically acceptable salts thereof. These compounds are useful, either as compounds or their pharmaceutically acceptable salts (when appropriate), in the inhibition of HCV (hepatitis C virus) NS5B (non-structural 5B) polymerase, the prevention or treatment of one or more of the symptoms of HCV infection, the inhibition of HCV viral replication and/or HCV viral production, and/or as pharmaceutical composition ingredients. As pharmaceutical composition ingredients, these compounds and their salts may be the primary active therapeutic agent, and, when appropriate, may be combined with other therapeutic agents including but not limited to other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines, as well as the present Standard of Care treatment options for HCV.

In one aspect, the present invention relates to a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is a 5 or 6-membered saturated monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from N and O;

A is fluorophenyl;

B is
a) hydrogen;
b) $-C(O)CH=C(CH_3)_2$;
c) Ar;
d) –C(O)-Ar;
e) $-C(O)CHR^y$-Ar;
f) $-C(O)CH(NHR^x)$-Ar;
g) $-SO_2(CH_2)_{0-2}$-Ar;

h) $-SO_2$-CH=CH-Ar;

i) –CO-Cyc;

j) $-COCH_2$-Cyc;

k) $-SO_2$-Cyc;

Ar is an aromatic ring system selected from:

(i) 5-6 membered monocyclic ring with 0, 1, or 2 heteroatom ring atoms independently selected from N or O, optionally substituted with 1 or 2 substituents independently selected from fluorophenyl, C_1-C_6 alkyl, and halo; and

(ii) 8-10 membered bicyclic rings with 1, 2 or 3 heteroatom ring atoms selected from N, O and S, optionally substituted with 1, 2 or 3 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CF_3, cyano, oxo, $-NH_2$, and cyclopropylmethyl;

Cyc is C_3-C_6 cycloalkyl optionally substituted with fluorophenyl or pyridine; or 3-oxabicyclo[3.1.0]hexane;

D is H or $NR^3SO_2R^4$;

R^2, R^3, and R^4 are independently C_1-C_6 alkyl;

R^a is hydrogen or C_1-C_6 alkyl;

R^x is hydrogen or $C(O)OC(CH_3)_3$; and

R^y is hydrogen, morpholinyl or Ar.

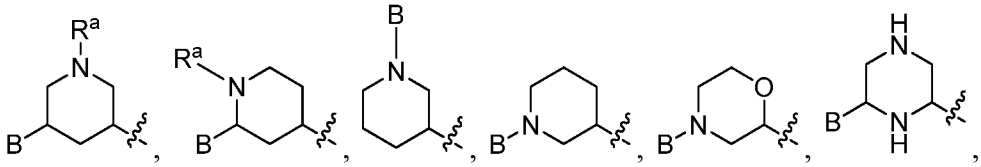
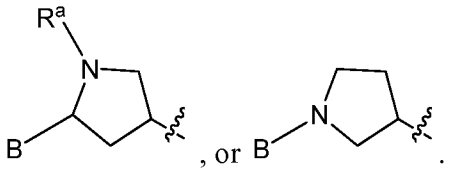
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or reducing the likelihood or severity of HCV infection, methods for inhibiting the activity of the NS5B polymerase, and methods for inhibiting HCV viral replication and/or viral production.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of formula I above, and pharmaceutically acceptable salts thereof. The compounds of formula I are HCV NS5B polymerase inhibitors.

In an aspect of the invention, X is

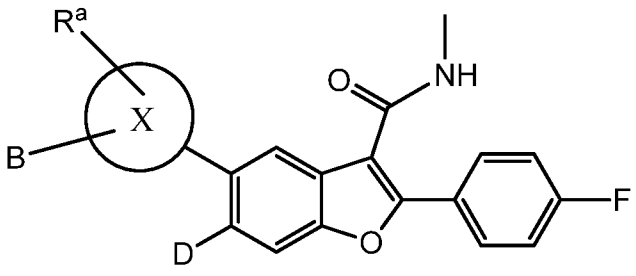



In a first embodiment of the invention, R^2, R^3 and R^4 are methyl, and the other groups are as provided in the general formula above or as in the first aspect.

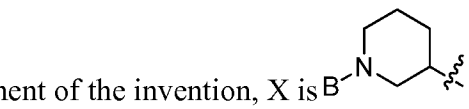
In a second embodiment of the invention, D is $N(CH_3)SO_2CH_3$, and the other groups are as provided in the general formula above, as in the first aspect, or as in the first embodiment.

In a third embodiment of the invention, each halo is F, and the other groups are as provided in the general formula above, as in the first aspect or as in the first or second embodiments.

In a fourth embodiment of the invention, the compound of the invention has the formula

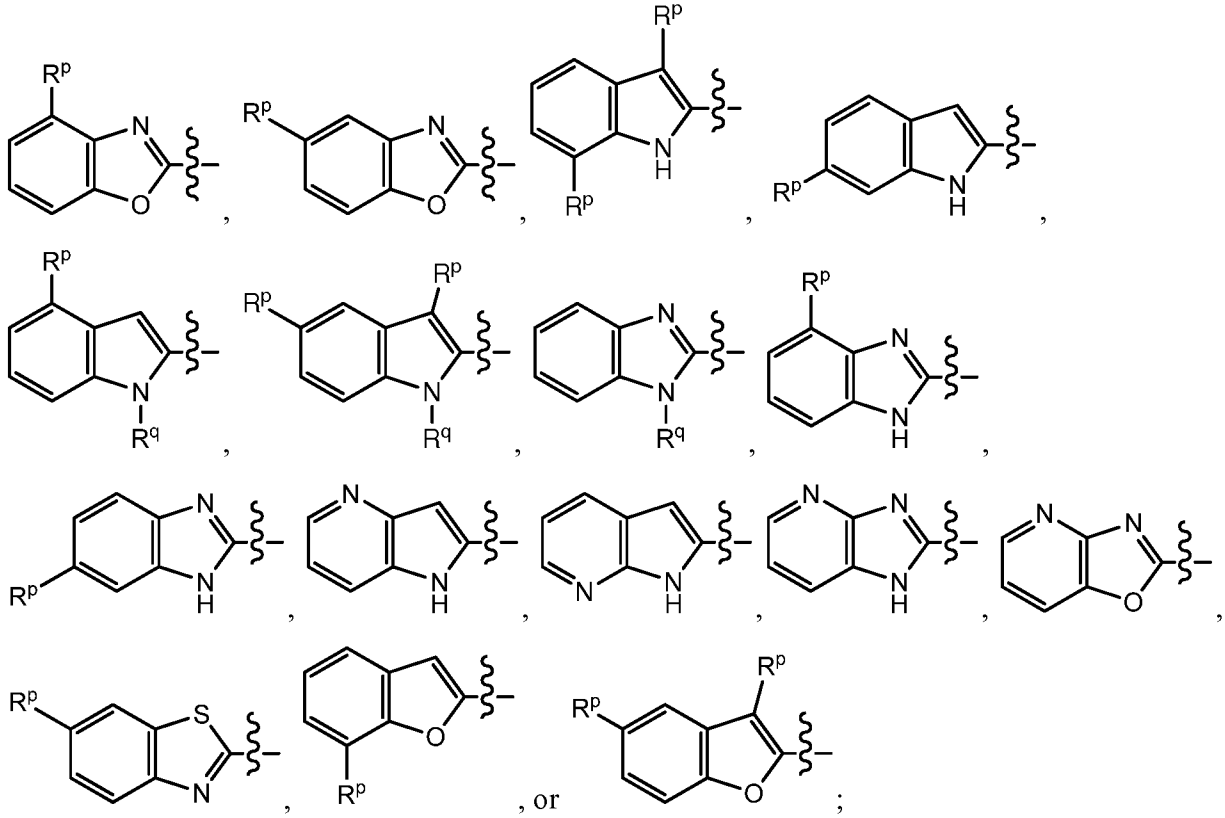

(Ia),

or a pharmaceutically acceptable salt thereof, and the groups are as provided in the general formula above, as in the first aspect or as in the first through third embodiments.

In a fifth embodiment of the invention, X is  , and the other groups are as provided in the general formula above, or as in the first through fourth embodiments.

In a sixth embodiment of the invention, B is Ar, –C(O)-Ar, or –SO_2-Ar; wherein Ar is a 9-membered bicyclic ring with 1, 2, or 3 heteroatom ring atoms selected from N, O and S, optionally substituted with 1, 2 or 3 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, F, CF_3, and cyano, and the other groups are as provided in the general

formula above, as in the first aspect or as in the first through fifth embodiments. In an aspect of this sixth embodiment, Ar is



wherein each R^p is independently selected from hydrogen, methyl, methoxy, F, CF_3, or cyano, and R^q is hydrogen, methyl or ethyl, and the other groups are as provided in the general formula above, as in the first aspect or as in the first through fifth embodiments.

In a seventh embodiment of the invention, B is $–SO_2$-Ar, $–SO_2CH_2$-Ar, $–SO_2CH_2CH_2$-Ar, –C(O)-Ar; or $–C(O)CH_2$-Ar; wherein Ar is phenyl, methylphenyl, fluorophenyl, difluorophenyl, pyridine, or fluoropyridine, and the other groups are as provided in the general formula above, as in the first aspect or as in the first through sixth embodiments.

In certain aspects of the invention, a fluorophenyl is para-fluorophenyl.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1-144 shown below, and pharmaceutically acceptable salts thereof.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 2, 4, 7, 11, 14, 25, 35, 37, 38 and 59 shown below, and pharmaceutically acceptable salts thereof.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of direct inhibitors of HCV, including but not limited to NS3 and NS3/4A protease inhibitors, NS5A inhibitors and HCV NS5B polymerase inhibitors.

(d) A pharmaceutical combination that is (i) a compound of formula I and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of formula I and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS5B activity, or for inhibiting HCV viral replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

(e) The combination of (d), wherein the HCV antiviral agents are one or more antiviral agents selected from the group consisting of direct inhibitors of HCV, including but not limited to NS3 and NS3/4A protease inhibitors, NS5A inhibitors and HCV NS5B polymerase inhibitors.

(f) A use of a compound of formula I in the preparation of a medicament for inhibiting HCV NS5B activity in a subject in need thereof.

(g) A use of a compound of formula I in the preparation of a medicament for preventing and/or treating infection by HCV in a subject in need thereof.

(h) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof, which comprises administering to the subject an effective amount of a compound of formula I.

(i) The method of (h), wherein the compound of formula I is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(j) The method of (i), wherein the HCV antiviral agent is an antiviral selected from the group consisting of direct inhibitors of HCV, including but not limited to NS3 and NS3/4A protease inhibitors, NS5A inhibitors and HCV NS5B polymerase inhibitors.

(k) A method of inhibiting HCV viral replication and/or HCV viral production in a cell-based system, which comprises administering to the subject an effective amount of a compound of formula I in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(l) The method of (k), wherein the HCV antiviral agent is an antiviral selected from the group consisting of direct inhibitors of HCV, including but not limited to NS3 and NS3/4A protease inhibitors, NS5A inhibitors and HCV NS5B polymerase inhibitors.

(m) A method of inhibiting HCV NS5B activity in a subject in need thereof, which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(n) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof, which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

In the embodiments of the compounds and salts provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound or salt and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (n) above are understood to include all embodiments of the compounds and/or salts, including such embodiments as result from combinations of embodiments.

Additional embodiments of the invention include the pharmaceutical compositions, combinations, uses and methods set forth in (a) through (n) above, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-

classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inhibiting HCV NS5B activity, or (b) inhibiting HCV viral replication, or (c) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection, or (d) use in medicine. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure is understood to predominate.

As used herein, the term "administration" and variants thereof (*e.g.*, "administering" a compound) in reference to a compound of the invention mean providing the compound to the individual in need of treatment. When a compound of the invention is provided in combination with one or more other active agents (*e.g.*, antiviral agents useful for treating HCV infection), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt and other agents.

As used herein, the term “alkoxy” refers to an “alkyl-O-” group. Alkoxy groups may be substituted as indicated.

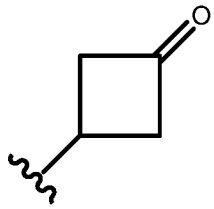
The term “alkyl” refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from about 1 to about 3 carbon atoms (C_1-C_3 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched.

The term "aryl" (or "aromatic ring system") refers to aromatic mono- and poly-carbocyclic ring systems wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. As used herein, the term aryl includes aromatic mono- and poly-carbocyclic ring systems that include from 0 to 4 heteroatoms (non-carbon atoms) that are independently chosen from N, O and S. Aromatic ring systems also includes ring systems where an aromatic ring is fused to a saturated ring. Suitable aryl groups include phenyl, naphthyl, biphenylenyl, pyridinyl, pyrimidinyl and pyrrolyl, as well as those discussed below. Aryl ring systems may include, where appropriate, an indication of the variable to which a particular ring atom is attached. Unless otherwise indicated, substituents to the aryl ring systems can be attached to any ring atom, provided that such attachment results in formation of a stable ring system.

The term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results from combining the specified ingredients.

The term "compound" is intended to encompass chemical agents described by generic formula I in all forms. Such chemical agents can be present in different forms such as hydrates and solvates.

The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The term “cycloalkyl” also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl, bicyclo[3.1.0]hexyl and adamantyl. The term “3 to 7-membered cycloalkyl” refers to a cycloalkyl group having from 3 to 7 ring carbon atoms. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group (also referred to herein as a “cycloalkanoyl” group) includes, but is not limited to, cyclobutanoyl:



The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of one or more symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for reduction of the severity or likelihood of one or more symptoms of the disease or condition. In another embodiment, the effective amount is a "therapeutically effective amount" for inhibition of HCV viral replication and/or HCV viral production. The term also includes herein the amount of active compound sufficient to inhibit HCV NS5B activity and thereby elicit the response being sought (*i.e.*, an "inhibition effective amount"). When the active compound (*i.e.*, active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$. The term "C_1-C_6 haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

The term "halogen" (or "halo") refers to atoms of fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic and

has 9 or 10 ring atoms. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term “heteroaryl” also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. The term "heteroaryl" also encompasses any fused polycyclic ring system containing at least one ring heteroatom selected from N, O and S, wherein at least one ring of the fused polycyclic ring system is aromatic. For example, the term "9 to 10-membered bicyclic heteroaryl" encompasses a non-aromatic 5 membered heterocyclic ring that is fused to a benzene or pyridyl ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term “heteroaryl” also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered heteroaryl group fused to a benzene ring.

The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group’s hydrogen atoms has been replaced with an –OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include $–CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ and $-CH_2CH(OH)CH_3$. The term “C_1-C_6 hydroxyalkyl” refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

As used herein, the term “oxo” or “=O” forms a carbonyl moiety with the carbon atom to which it is attached.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term “preventing,” as used herein with respect to an HCV viral infection or HCV-virus related disorder, refers to reducing the likelihood of HCV infection.

The term "subject" (alternatively referred to herein as "patient"), as used herein,

refers to an animal, preferably a mammal, most preferably a human.

The term “substituted” means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom provided such substitution is chemically allowed and results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

In the compounds of formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H or D). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "1 to 3 heteroatoms" means the ring can contain 1, 2, or 3 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. The oxidized forms of the heteroatoms N and S are also included within the scope of the present invention.

When any variable (for example, R^1 or R^3) occurs more than one time in any constituent or in formula I or in any other formula depicting and describing compounds of the

invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

Certain of the compounds of the present invention can exist as tautomers. For the purposes of the present invention a reference to a compound of formula I is a reference to the compound *per se*, or to any one of its tautomers *per se*, or to mixtures of two or more tautomers.

The compounds of the present inventions are useful in the inhibition of HCV replication (*e.g.*, HCV NS5B activity), the treatment of HCV infection and/or reduction of the likelihood or severity of symptoms of HCV infection. For example, the compounds of this invention are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for identifying resistant HCV replicon cell lines harboring mutations within NS5B, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to the HCV replicase.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt that possesses the effectiveness of the parent compound and that is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof

can include alkali metal salts (*e.g.*, sodium or potassium salts), alkaline earth metal salts (*e.g.*, calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates ("mesylates"), naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

For the purposes of inhibiting HCV NS5B polymerase, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection and inhibiting HCV viral replication and/or HCV viral production, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the

agent's site of action. They can be administered by one or more conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered by one or more of the following: orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation (such as in a spray form), or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (*e.g.*, suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (*e.g.*, powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as solubility aids. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition (ed. A. R. Gennaro, Mack Publishing Co., 1990).

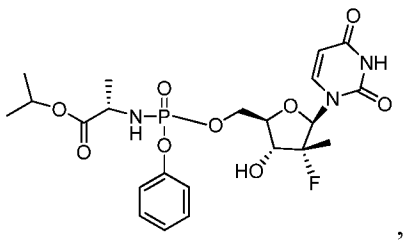
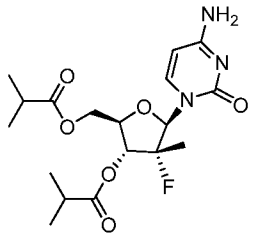
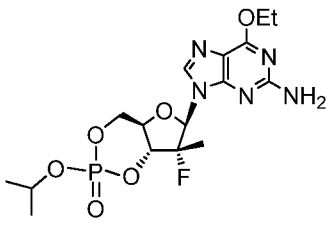
The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (*e.g.*, human) body weight per day in a single dose or in divided doses. One dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 mg of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any

particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, HCV viral genotype, viral resistance, and the host undergoing therapy.

As noted above, the present invention also relates to a method of inhibiting HCV NS5B activity, inhibiting HCV viral replication and/or HCV viral production, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such agents are described in detail below.

HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, VP-19744 (Wyeth/ViroPharma), PSI-7851 (Pharmasset), RG7128 (Roche/Pharmasset), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), PSI-879 (Pharmasset), PSI-661 (Pharmasset), PF-868554/filibuvir (Pfizer), VCH-759/VX-759 (ViroChem Pharma/Vertex), HCV-371 (Wyeth/VirroPharma), HCV-796 (Wyeth/ViroPharma), IDX-184 (Idenix), IDX-375 (Idenix), NM-283 (Idenix/Novartis), GL-60667 (Genelabs), JTK-109 (Japan Tobacco), PSI-6130 (Pharmasset), R1479 (Roche), R-1626 (Roche), R-7128 (Roche), MK-0608 (Isis/Merck), INX-8014 (Inhibitex), INX-8018 (Inhibitex), INX-189 (Inhibitex), GS 9190 (Gilead), A-848837 (Abbott), ABT-333 (Abbott), ABT-072 (Abbott), A-837093 (Abbott), BI-207127 (Boehringer-Ingelheim), BILB-1941 (Boehringer-Ingelheim), MK-3281 (Merck), VCH-222/VX-222 (ViroChem/Vertex), VCH-916 (ViroChem), VCH-716(ViroChem), GSK-71185 (Glaxo SmithKline), ANA598 (Anadys), GSK-625433 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Other HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in International Publication Nos. WO 08/082484, WO 08/082488, WO 08/083351, WO 08/136815, WO 09/032116, WO 09/032123, WO 09/032124 and WO 09/032125; and the following compounds:


,

and


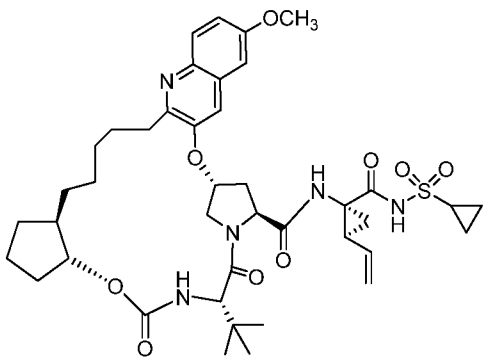
and pharmaceutically acceptable salts thereof.

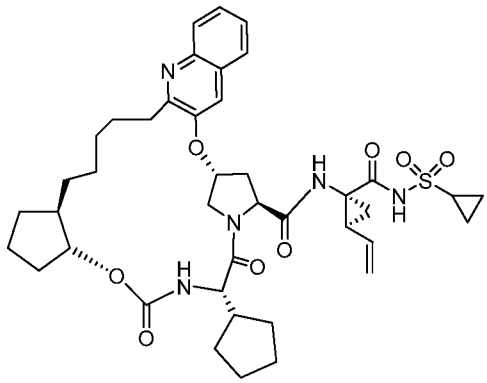
Interferons useful in the present compositions and methods include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and petroleum etherG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a petroleum etherG molecule. Illustrative petroleum etherG-interferon alpha conjugates include interferon alpha-2a (Roferon™, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (*e.g.*, as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (*e.g.*, as sold under the trade name petroleum etherG-Intron™ from Schering-Plough Corporation), interferon alpha-2b-XL (*e.g.*, as sold under the trade name petroleum etherG-Intron™), interferon alpha-2c (Berofor Alpha™, Boehringer Ingelheim, Ingelheim, Germany), petroleum etherG-interferon lambda (Bristol-Myers Squibb and ZymoGenetics), interferon alfa-2b alpha fusion polypeptides, interferon fused with the human blood protein albumin (Albuferon™, Human Genome Sciences), Omega Interferon (Intarcia), Locteron controlled release interferon (Biolex/OctoPlus), Biomed-510 (omega interferon), Peg-IL-29 (ZymoGenetics), Locteron CR (Octoplus), R-7025 (Roche), IFN-α-2b-XL (Flamel Technologies), belerofon (Nautilus) and consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, Amgen, Thousand Oaks, California).

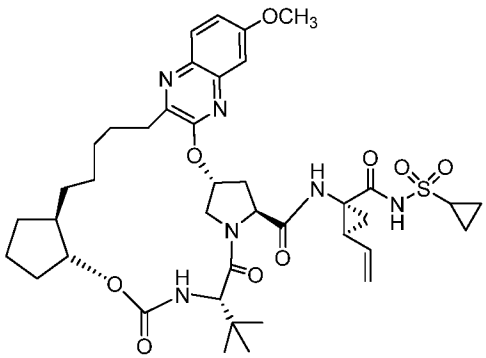
Examples of viral protease inhbitors useful in the present compositions and methods include, but are not limited to, an HCV protease inhibitor. Examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, VX-950 (Telaprevir, Vertex), VX-500 (Vertex), VX-813 (Vertex), VBY-376 (Virobay), BI-201335 (Boehringer Ingelheim), TMC-435 (Medivir/Tibotec), ABT-450 (Abbott/Enanta), TMC-435350 (Medivir), RG7227 (Danoprevir, InterMune/Roche), EA-058 (Abbott/Enanta), EA-063 (Abbott/Enanta), GS-

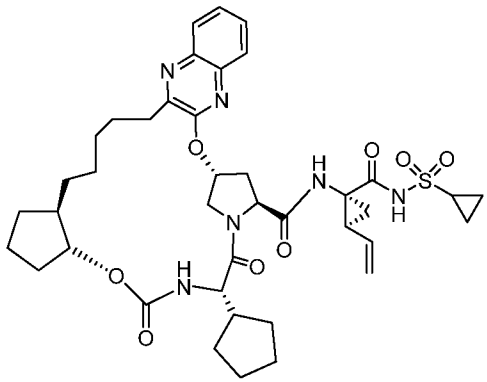
9256 (Gilead), IDX-320 (Idenix), ACH-1625 (Achillion), ACH-2684 (Achillion), GS-9132 (Gilead/Achillion), ACH-1095 (Gilead/Achillon), IDX-136 (Idenix), IDX-316 (Idenix), ITMN-8356 (InterMune), ITMN-8347 (InterMune), ITMN-8096 (InterMune), ITMN-7587 (InterMune), BMS-650032 (Bristol-Myers Squibb), VX-985 (Vertex) and PHX1766 (Phenomix).

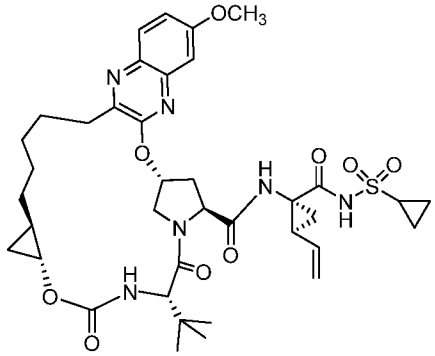
Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, the following compounds:

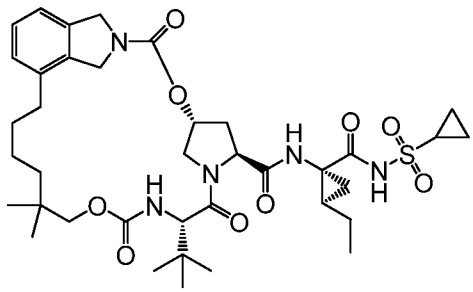


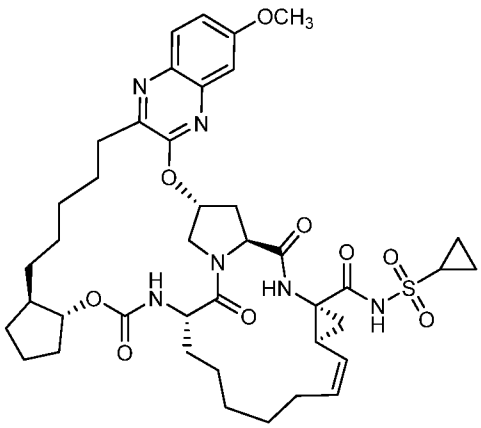


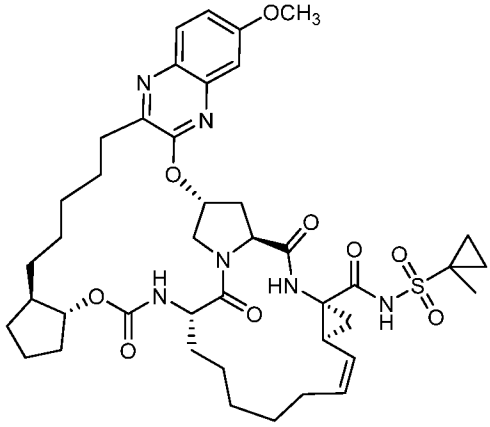


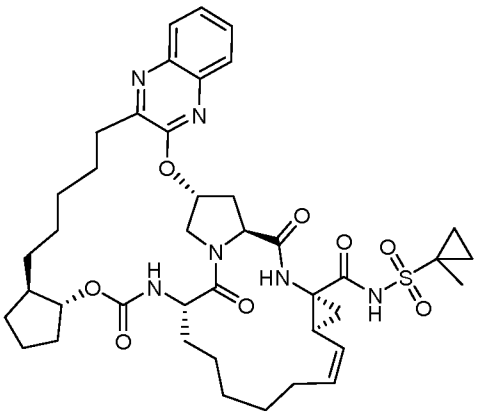


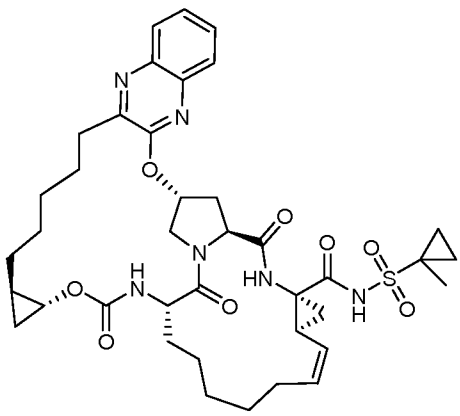


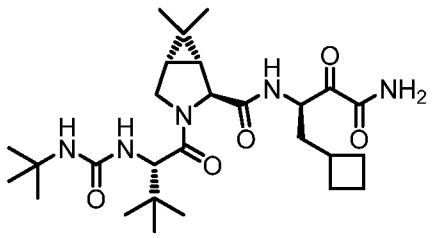


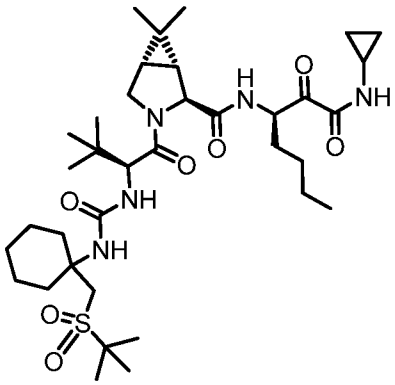


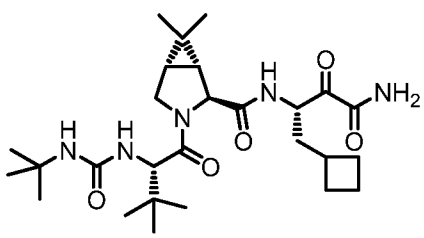


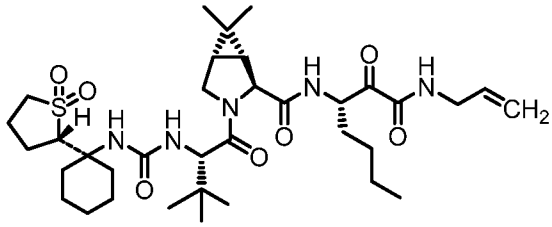


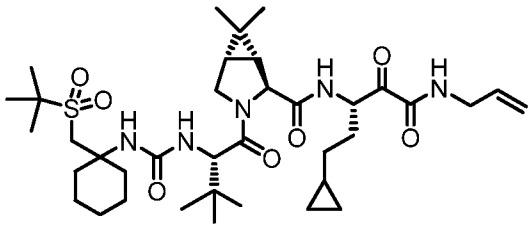


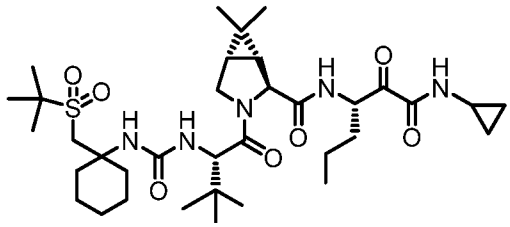


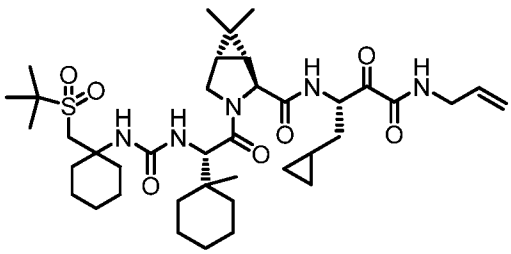


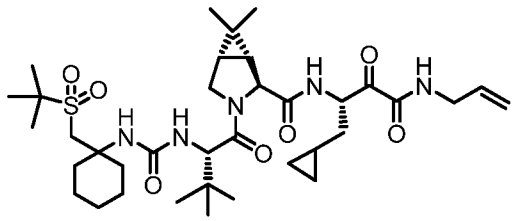


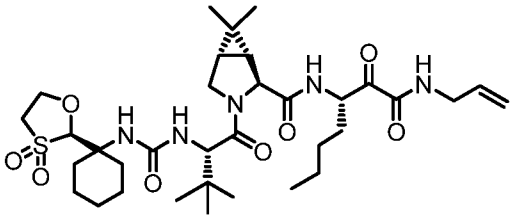


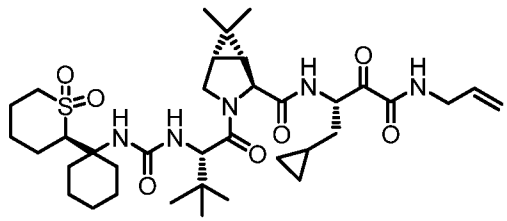


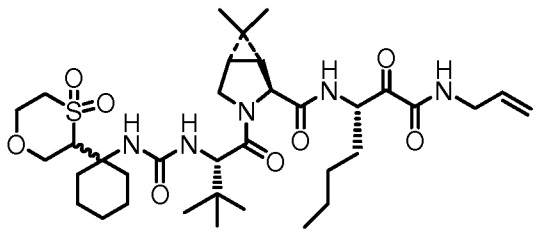


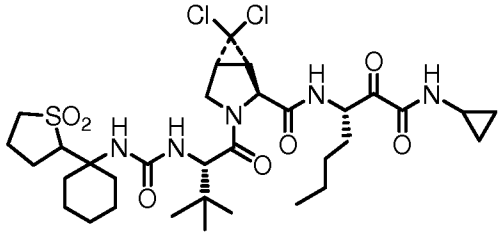


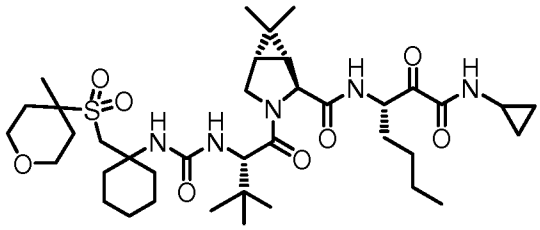


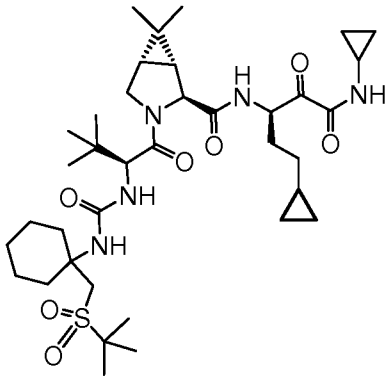


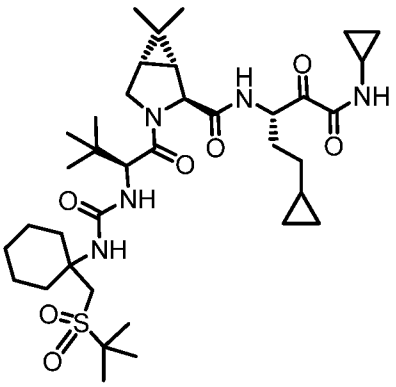


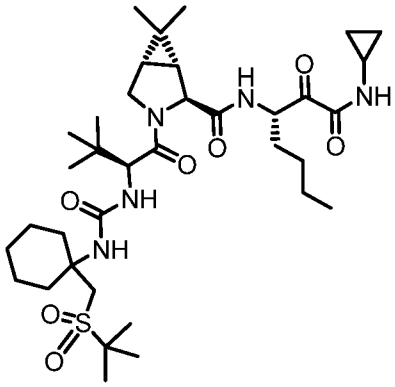


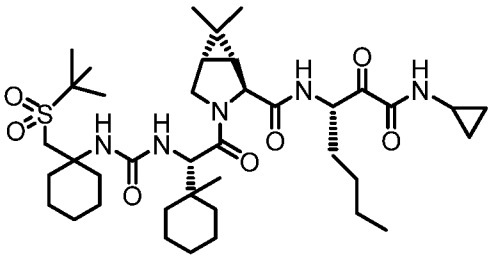


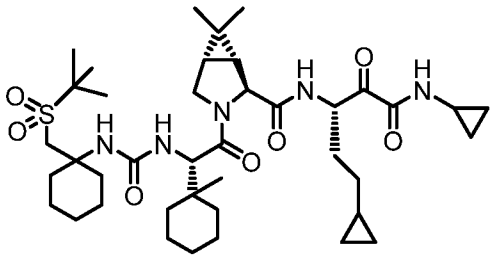


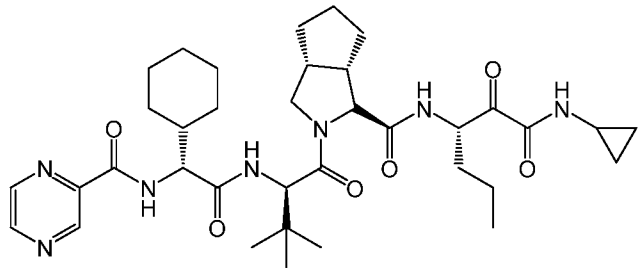








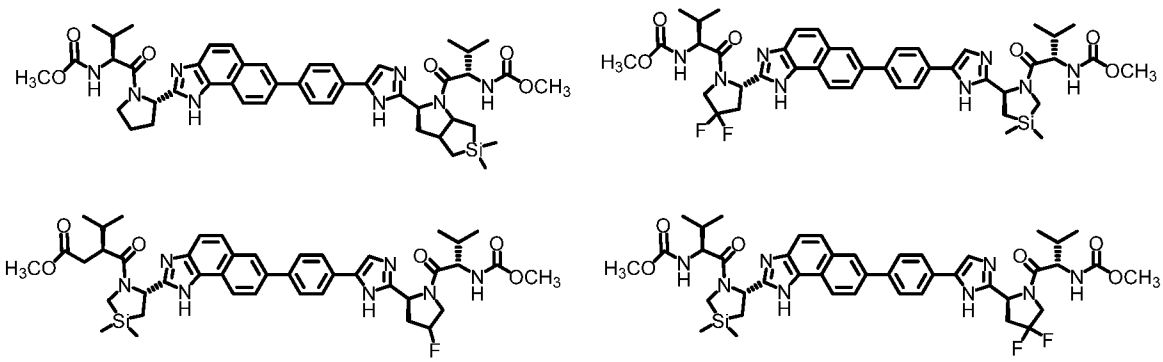


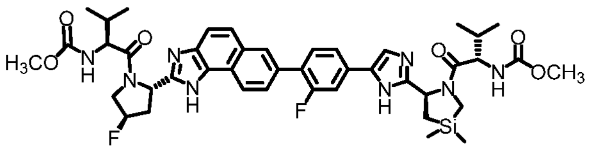
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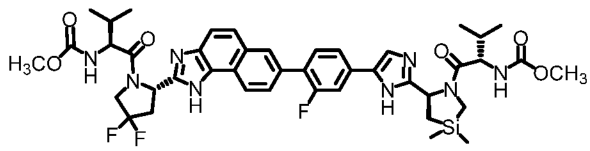
and pharmaceutically acceptable salts thereof.

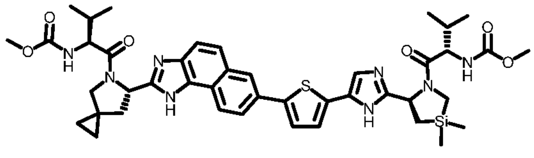
Viral replication inhibitors useful in the present compositions and methods include, but are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase inhibitors, NS5A inhibitors, NS5B inhibitors, ribavirin, AZD-2836 (Astra Zeneca), viramidine, A-831 (Arrow Therapeutics), EDP-239 (Enanta), ACH-2928 (Achillion), GS-5885 (Gilead); an antisense agent or a therapeutic vaccine.

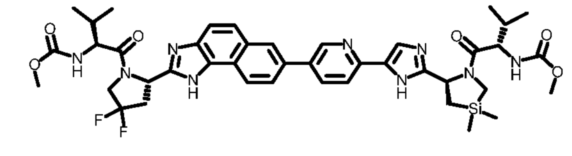
HCV NS5A inhibitors useful in the present compositions and methods include, but are not limited to, ACH-2928 (Achilon), A-832 (Arrow Therpeutics), AZD-7295 (Astra Zeneca/Arrow), GS-5885 (Gilead), PPI-461 (Presidio), PPI-1301 (Presidio), BMS-824383 (Bristol-Myers Squibb) and BMS-790052 (Bristol-Myers Squibb). Additional HCV NS5A inhibitors useful as second additional therapeutic agents in the present compositions and methods include, but are not limited to those disclosed in International Publication No. WO 2010/111483 and the following compounds:

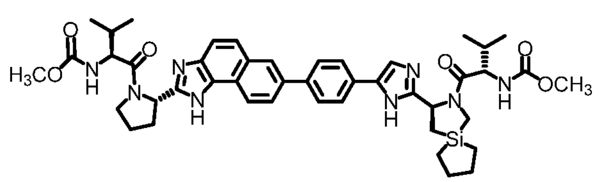


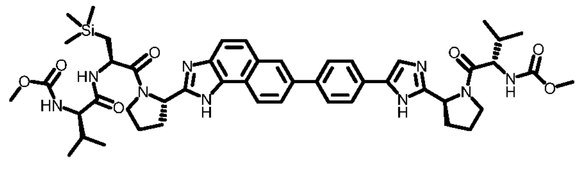


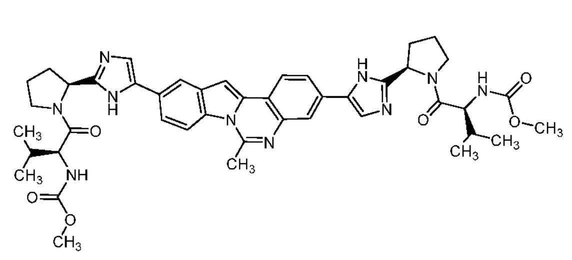


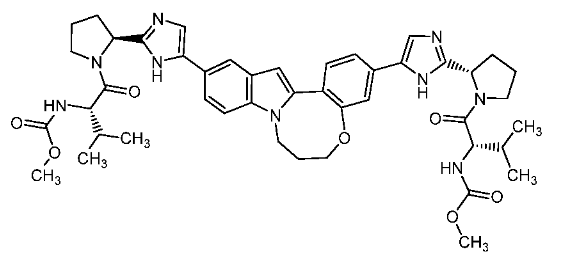


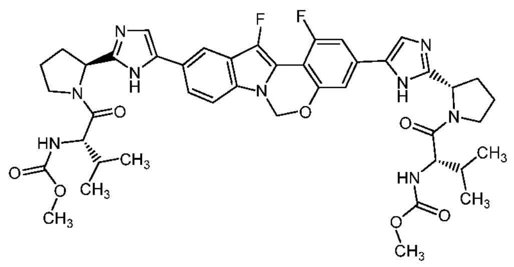


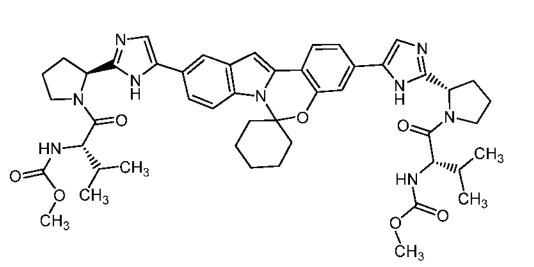


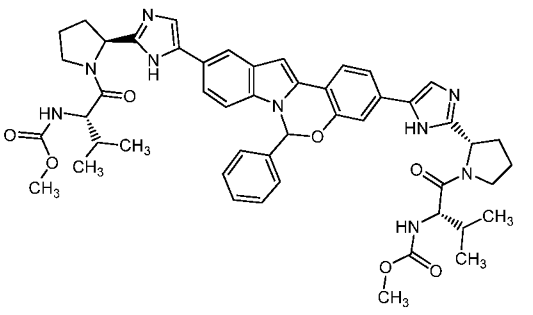


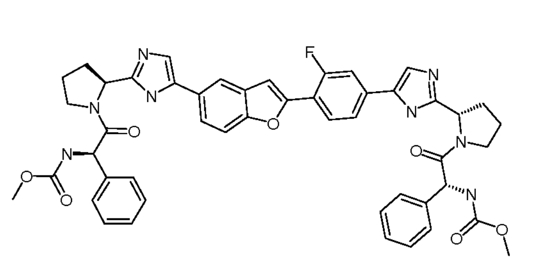


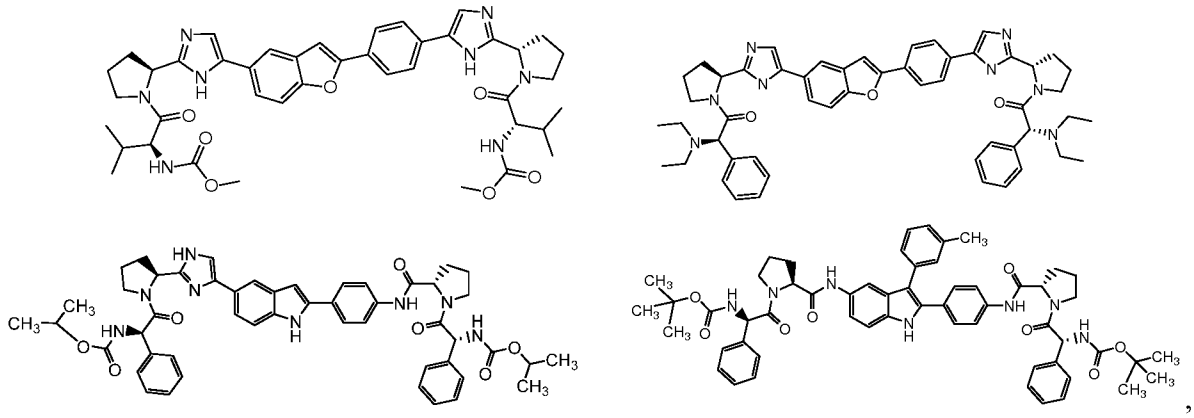


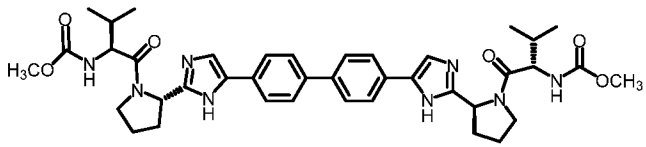












and

and pharmaceutically acceptable salts thereof.

HCV replicase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Publication No. US20090081636.

When administering a combination therapy of the invention to a patient, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). A compound of the invention and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

The HCV NS5B inhibitory activity of the present compounds may be tested using assays known in the art. The HCV NS5B polymerase inhibitors described herein have activities in a genotype 1b replicon assay as described in the Examples. The assay is performed by incubating a replicon harboring cell-line in the presence of inhibitor for a set period of time and measuring the effect of the inhibitor on HCV replicon replication either directly by quantifying replicon RNA level, or indirectly by measuring enzymatic activity of a co-encoded reporter enzyme such as luciferase or β-lactamase. By performing a series of such measurements at different inhibitor concentrations, the

effective inhibitory concentration of the inhibitor (EC_{50} or EC_{90}) is determined. *See* Jan M. Vrolijk *et al.*, *A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C*, 110 J. VIROLOGICAL METHODS 201 (2003). Such assays may also be run in an automated format for high through-put screening. *See* Paul Zuck *et al.*, *A cell-based β-lactamase reporter gene assay for the identification of inhibitors of hepatitis C virus replication*, 334 ANALYTICAL BIOCHEMISTRY 344 (2004).

The present invention also includes processes for making compounds of formula I. The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice.

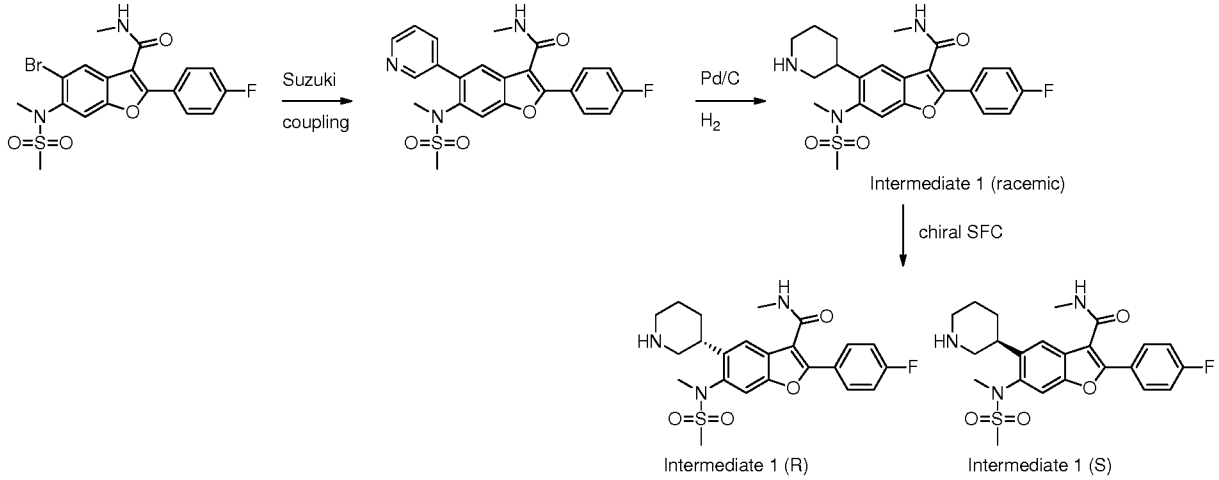
General Schemes

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1-2 below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis. All stereoisomers and tautomeric forms of the compounds are contemplated.

Some commercially available starting materials and intermediates used for the synthesis of the Compounds of Formula (I) are available. These starting materials and intermediates are available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ). Such starting materials and intermediates compounds are used as received.

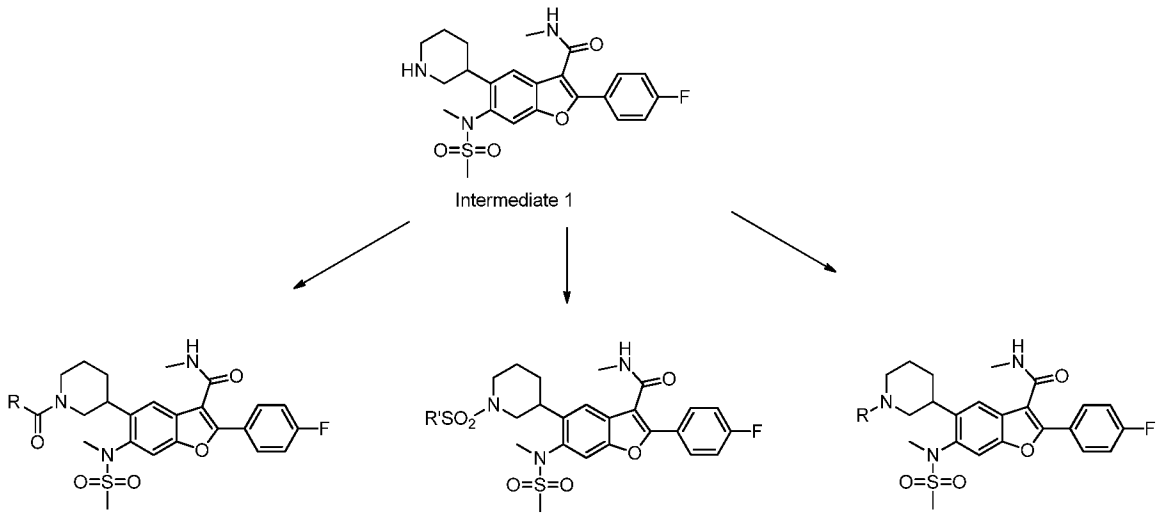
Scheme 1 shows methods useful for making a key intermediate (Intermediate 1) and its two individual enantiomers. Other intermediates with structures similar to Intermediate 1 were prepared as described in the experimental section.

Scheme 1



Scheme 2 shows methods useful for converting Intermediate 1 to amides, sulfonamide, or N-aryl compounds. In some cases, Intermediate 1 was used as an individual enantiomer (R or S); in other cases, Intermediate 1 was used as a racemate. In the latter case, the final compounds were separated into single compounds by chiral SFC.

Scheme 2



List of Abbreviations

a.q. Aqueous

Boc	t-butyloxycarbonyl
Boc_2O	Di-tert-butyl-dicarbonate
$B(O^iPr)_3$	Triisopropyl borate
$(Bpin)_2$	Bis(pinacolato)diboron
n-BuLi	n-butyllithium
$CDCl_3$	Trichloro(^{2}H)methane or deuterio-trichloromethane
CO_2	Carbon dioxide
DCM, CH_2Cl_2	Dichloromethane
DEA	Diethanolamine
DIEA	N,N-Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (also EDC)
Et	Ethyl
Et_3N	Triethylamine
EtOAc, EA	Ethyl acetate
EtOH, CH_3CH_2OH	Ethanol
HATU	(Dimethylamino)-N,N-dimethyl(3H-[1,2,3]triazolo[4,5-b]pyridin-3 yloxy)methaniminium hexafluorophosphate
HCHO	Formaledehyde
HCl	Hydrochloric acid
H_2	Hydrogen gas or atmosphere
HCOOH	Formic acid
H_2O	Water
H_2SO_4	Sulfuric acid
HOAc, CH_3COOH	Acetic acid
HOBT, HOBt	1-Hydroxy benzotriazole
^{1}H-NMR	Proton Nuclear Magnetic Resonance

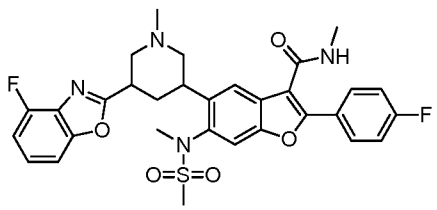
HPLC	High Performance Liquid Chromatography
ISCO	In situ chemical oxidation
K_2CO_3	Potassium carbonate
KOAc	Potassium acetate
K_3PO_4	Potassium Phosphate
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LiOH	Lithium hydroxide
MeCN, CH_3CN	Acetonitrile
MeI, CH_3I	Methyl iodide
MeOD	Methan(^{2}H)ol
MeOH, CH_3OH	Methanol
MS	Mass spectroscopy
Ms	Methanesulfonyl (or mesyl) group
MsCl	Methanesulfonyl chloride
N_2	Nitrogen gas or atmosphere
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate (anhydrous)
NCS	N-Chlorosuccinimide
NH_4Cl	Ammonium chloride
NMO	N-Methylmorpholine-N-Oxide
OsO_4	Osmium tetroxide
PCC	Pyridinium Chlorochromate
Pd	Palladium
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride
$Pd(dtbpf)Cl_2$	1,1′-bis(di-*tert*-butylphosphino)ferrocene-dichloropalladium(II)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)

PE	Petroleum ether
Ph	Phenyl
Pt	Platinum
PtO_2	Platinum (IV) oxide
PTSA	p-Toluenesulfonic acid
RT	Room temperature, approximately 25°C
sat	saturated
SFC	Supercritical fluid chromatography
SO_2	Sulfur dioxide
$SOCl_2$	Thionyl chloride
T_3P	Propylphosphonic Anhydride
TCDI	N,N'-Thiocarbonyldiimidazole
TEA	Triethylamine
TF_2NPh	N-phenyltrifluoromethanesulphonimide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TsOH	p-Toluenesulfonic acid
TLC	Thin layer chromatography

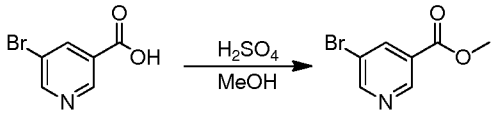
EXAMPLES

In the examples below, some enantiomer pairs are identified by consecutive example numbers without identifying which enantiomer corresponds to which example number. The example numbers correspond to a specific peak number which was tested for activity.

Example 1: 5-(5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpiperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-carboxamide

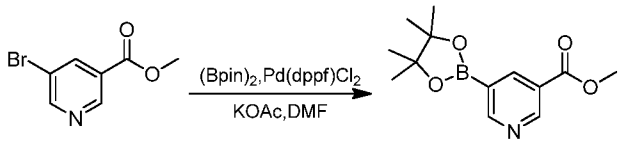


Step 1 - Synthesis of methyl 5-bromonicotinate



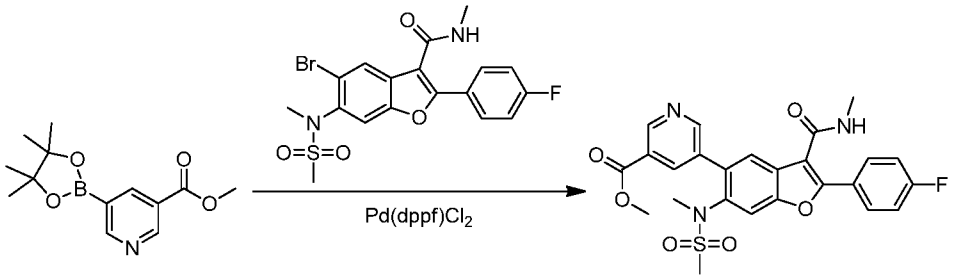
To cooled methanol (20 mL, 0°C) was added dropwise concentrated H_2SO_4 (2 mL). To the resulting clear solution was added 5-bromonicotinic acid (2 g, 10 mmol) and the mixture was refluxed for 3 h. After being cooled to room temperature, the solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated $NaHCO_3$ (a.q.), dried over Na_2SO_4 and concentrated to give methyl 5-bromonicotinate (1.5 g, yield: 71%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.10 (d, J = 1.6 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H), 8.41 (t, J = 2.4 Hz, 1H), 3.94 (s, 3H). MS $(M+H)^+$: 216 / 218.

Step 2 - Synthesis of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate



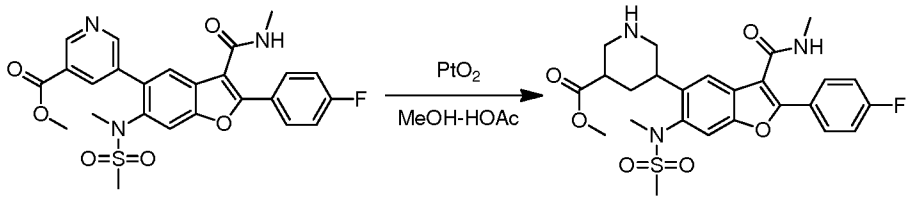
To a solution of methyl 5-bromonicotinate (1 g, 4.6 mmol), KOAc (920 mg, 9.2 mmol) and $(Bpin)_2$ (1.7 g, 6.9 mmol) in DMF (10 mL) was added Pd(dppf)Cl_2 under N_2, and the resulting reaction mixture was stirred for 4 h at 80°C. After the reaction mixture was concentrated, the residue was dissolved in DCM, then filtered, evaporated and the residue was purified by flash chromatography (PE / EtOAc = 4 / 1) to give the product of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (800 mg, yield: 66%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.21 (d, J = 2.4 Hz, 1H), 9.03 (d, J = 2.0 Hz, 1H), 8.61 (t, J = 2.0 Hz, 1H), 3.90 (s, 3H), 1.31 (s, 12H). MS $(M+H)^+$: 264.

Step 3 - Synthesis of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)nicotinate



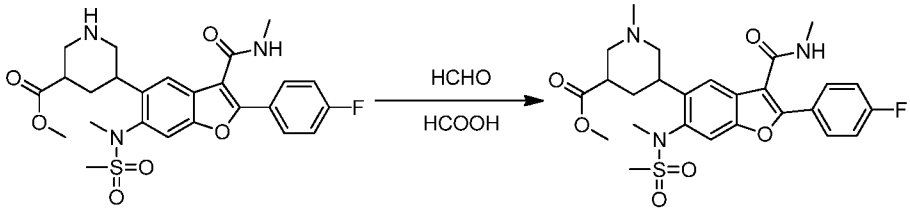
To a solution of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (1.1 g, 2.4 mmol), 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-carboxamide (763 mg, 2.9 mmol) (prepared according to International Patent Application Publication No. WO 2011106992) and $K_3PO_4 \cdot 3H_2O$ (1.3 g, 4.8 mmol) in DMF (20 mL) was added $Pd(dppf)Cl_2$ under N_2, and the resulting reaction mixture was stirred for 3 h at 90°C. After the reaction mixture was concentrated, the residue was dissolved in DCM, then filtered, evaporated and the residue was purified by column chromatography (PE / EtOAc = 4 / 1 to 1 / 1) to give the product of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)nicotinate (1 g, yield: 83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, J = 1.2 Hz, 1H), 8.00 (d, J = 1.6 Hz, 1H), 8.40 (s, 1H), 7.83~7.87 (m, 3H), 7.59 (s, 1H), 7.16 (t, J = 8.4 Hz, 2H), 5.76 (d, J = 4.0 Hz, 1H), 3.92 (s, 3H), 3.15 (s, 3H), 2.92 (d, J = 4.8 Hz, 3H), 2.69 (s, 3H). MS $(M+H)^+$: 512.

Step 4 - Synthesis of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)piperidine-3-carboxylate



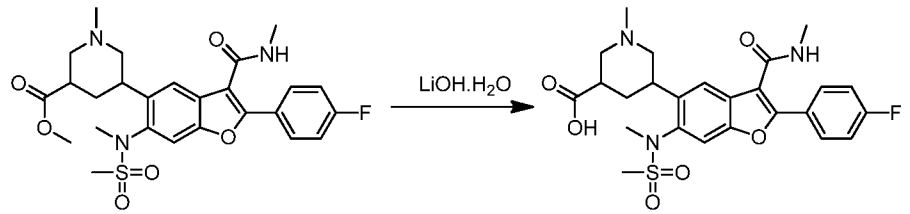
To a solution of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)nicotinate (650 mg, 1.27 mmol) in MeOH : CH_3COOH = 4 : 1 (100 mL) was added PtO_2, and the resulting reaction mixture was stirred at 35°C under H_2 at 35 Psi overnight. After being filtered, evaporated, diluted with water and basified with saturated $NaHCO_3$ (a.q.), the resulting mixture was extracted with DCM, and then the organic layer was dried, concentrated and purified by column chromatography (DCM / MeOH = 20 / 1) to give methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)piperidine-3-carboxylate (600 mg, yield: 91%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 2H), 7.70~7.73 (m, 1H), 7.36~7.39 (m, 1H), 7.11~7.15 (m, 2H), 6.03 (d, J = 5.6 Hz, 1H), 3.77~3.80 (m, 3H), 3.61~3.64 (m, 3H), 3.17~3.20 (m, 6H), 3.04 (s, 2H), 2.93~2.97 (m, 7H). MS $(M+H)^+$: 518.

Step 5 - Synthesis of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxylate



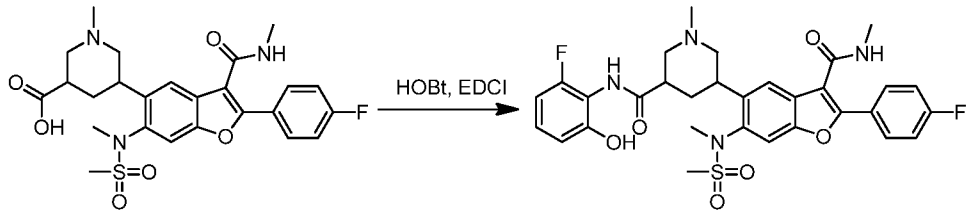
A solution of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidine-3-carboxylate (400 mg, 0.8 mmol) in HCHO (4 mL) and HCOOH (4 mL) was heated to reflux for 1 h. After being concentrated, diluted with water and basified with saturated $NaHCO_3$ (aq), the mixture was extracted with DCM, and then the organic layer was dried, concentrated and purified by column chromatography (DCM / MeOH = 50 / 1) to give methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxylate (380 mg, yield: 92%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.78~7.81 (m, 1H), 7.73 (s, 2H), 7.50~7.59 (m, 1H), 7.15 (d, J = 8.8 Hz, 2H), 5.72~5.87 (m, 1H), 3.95~3.98 (m, 1H), 3.61~3.78 (m, 4H), 3.47~3.49 (m, 1H), 3.16~3.42 (m, 6H), 3.08 (s, 1H), 3.00 (s, 1H), 2.78~2.90 (m, 3H), 2.35~2.65 (m, 5H), 2.26~2.28 (m, 1H). MS $(M+H)^+$: 532.

Step 6 - Synthesis of 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)-1-methylpiperidine-3-carboxylic acid



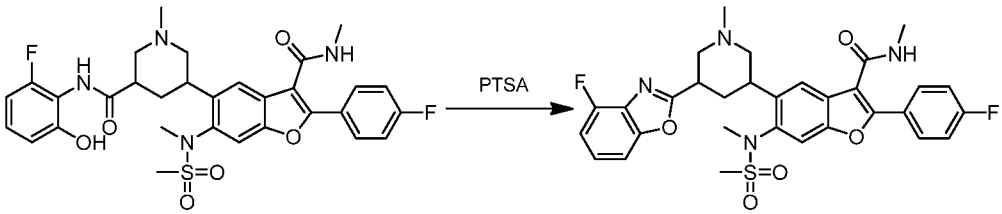
A solution of methyl 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxylate (450 mg, 0.85 mmol) and $LiOH{\cdot}H_2O$ (178 mg, 4.3 mmol) in 1,4-dioxane : H_2O = 5 : 1 (18 mL) was heated to reflux and stirred for 1 h. Then the reaction mixture was cooled and diluted with water, followed by adjusting the solution to pH = 2~3. The resulting precipitate was collected by filtration, washed with water and dried to give 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxylic acid (400 mg, yield: 91%), which was used for the next step without further purification. MS $(M+H)^+$: 518.

Step 7 - Synthesis of N-(2-fluoro-6-hydroxyphenyl)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxamide



A solution of 5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxylic acid (100 mg, 0.2 mmol), HOBT (54 mg, 0.4 mmol) and EDCl·HCl (77 mg, 0.4 mmol) in DMF (5 mL) was stirred at room temperature for 1.5 hours. 2-amino-3-fluorophenol (76 mg, 0.6 mmol) was then added and the reaction continued to stir at room temperature overnight. The reaction was then poured into water, then extracted with DCM, washed with $NaHCO_3$, and dried over Na_2SO_4. After being concentrated, the residue was purified by column chromatography (DCM / MeOH = 20 / 1) to give pure N-(2-fluoro-6-hydroxyphenyl)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxamide (80 mg, yield: 66%), which was used for the next step without further purification. MS $(M+H)^+$: 627.

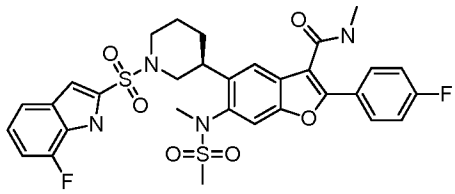
Step 8 - Synthesis of 5-(5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpiperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Example 1)



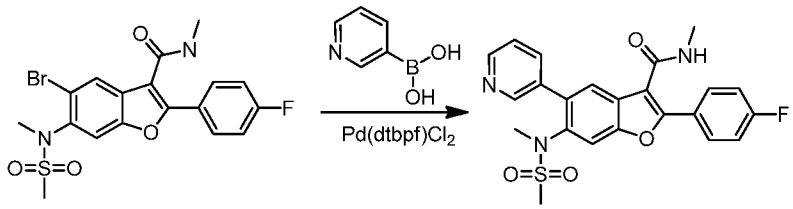
A solution of N-(2-fluoro-6-hydroxyphenyl)-5-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpiperidine-3-carboxamide (70 mg, 0.11 mmol) and PTSA (11 mg, 0.06 mmol) in toluene (30 mL) was heated to reflux for 24 hours. After being concentrated, diluted with water and extracted with DCM, the organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified (DCM / CH_3OH = 10 / 1) to give pure 5-(5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpiperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-

carboxamide (20 mg, yield: 29%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.0 Hz, 3H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.20~7.24 (m, 2H), 7.10~7.14 (m, 2H), 6.94~6.98 (m, 1H), 5.77 (s, 1H), 3.60~3.68 (m, 1H), 3.24~3.47 (m, 2H), 3.08~3.11 (m, 3H), 2.80~3.02 (m, 7H), 2.29~2.55 (m, 1H), 2.17~2.26 (m, 3H), 1.91~1.94 (m, 3H). MS $(M+H)^+$: 609.

Example 2: (*S*)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

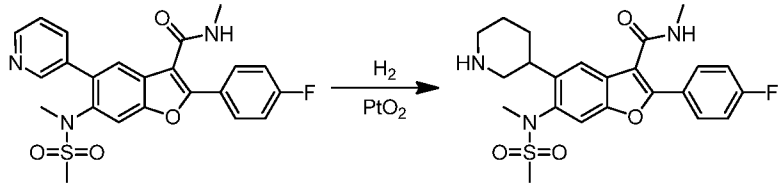


Step 1 - Synthesis of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(pyridin-3-yl)benzofuran-3-carboxamide



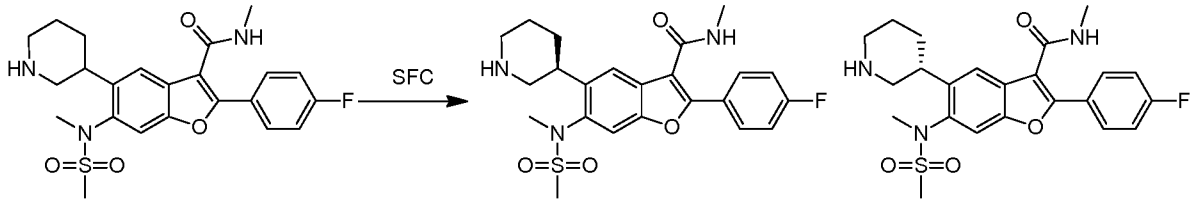
A mixture of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethyl sulfonamido)benzofuran-3-carboxamide (1.5 g, 3.29 mmol), pyridine-3-boronicacid (0.810 g, 6.59 mmol), potassium phosphate tribasic (5.59 g, 13.18 mmol) and 1,1'-bis(di-tert-butyosphosphino)ferrocene palladium dichloride (0.215 g, 0.329 mmol) was suspended in DMF (15 ml) and heated at 120°C for 30 min. The reaction mixture was filtered and concentrated under vacuum, applied onto ISCO with normal phase and eluted with EtOAc/Hexane 30-100%. This resulted in 1.2 g (80 %) of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(pyridin-3-yl)benzofuran-3-carboxamide as a white solid. LC-MS (ES, m/z) $C_{23}H_{20}FN_3O_4S$: 453; Found: 454 $[M+H]^+$.

Step 2 - Synthesis of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide



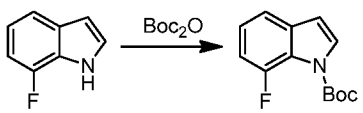
To a solution of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(pyridin-3-yl)benzofuran-3-carboxamide (1 g, 2.205 mmol) in MeOH (5 mL) and hydrochloric acid (37%, 0.5 ml) was added platinum(IV) oxide (20 mg, 0.088 mmol). The mixture was shaken under H_2 (45 Psi) for 2.5 hours. The reaction mixture was filtered and concentrated under vacuum. This resulted in 1.01 g (100%) of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethyl sulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide as a white solid. LC-MS (ES, m/z) $C_{23}H_{26}FN_3O_4S$: 459; Found: 460 $[M+H]^+$.

Step 3 - Synthesis of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide and (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide



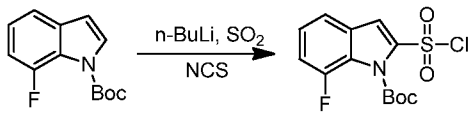
2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (2.7 g, 5.88 mmol) was dissolved in DCM, applied onto IC 30 x 250 mm column and eluted with 35% MeOH (0.2% DEA)/CO_2 (100 bar, 35°C). This resulted in 0.9 g (33.3 %) of (*S*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide as a white solid. LC-MS (ES, m/z) $C_{23}H_{26}FN_3O_4S$: 459; Found: 460 $[M+H]^+$, and 1 g (37 %) of (*R*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide as a white solid. LC-MS (ES, m/z) $C_{23}H_{26}FN_3O_4S$: 459; Found: 460 $[M+H]^+$. The absolute configurations were determined by vibrational circular dichroism spectroscopy.

Step 4 - Synthesis of tert-butyl 7-fluoro-1H-indole-1-carboxylate



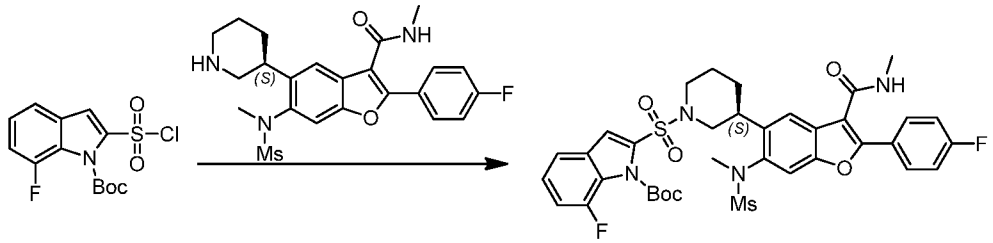
A mixture of 7-fluoro-1H-indole (3 g, 22.2 mmol), DIEA (8.6 g, 66.6 mmol) and DMAP (50 mg) in DCM (50 mL) was stirred at RT under N_2 atmosphere. Then $(Boc)_2O$ (5.81 g, 26.6 mmol) was added, and the reaction mixture was stirred at RT for 16 h. The mixture was diluted with water, extracted with EtOAc, concentrated in vacuum and dried over Na_2SO_4. The residue was purified by column chromatography (PE : EA = 20 : 1) to afford the desired product tert-butyl 7-fluoro-1H-indole-1-carboxylate (4 g, yield: 77%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.16~7.17 (m, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.59 (s, 1H), 1.66 (s, 9H). MS $(M+H)^+$: 236.

Step 5 - Synthesis of tert-butyl 2-(chlorosulfonyl)-7-fluoro-1H-indole-1-carboxylate



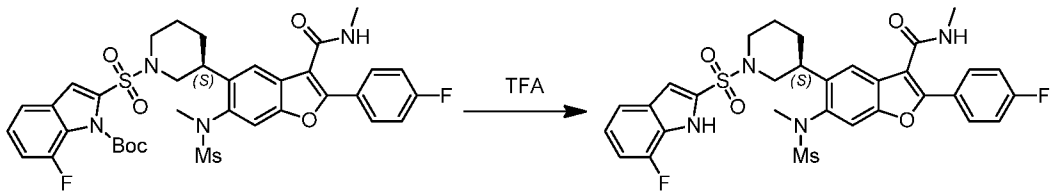
To a mixture of tert-butyl 7-fluoro-1H-indole-1-carboxylate (500 mg, 2.03 mmol) in THF (10 mL) was added n-BuLi (1 mL, 2.5 mmol) under N_2 atmosphere at -78°C. The mixture was stirred at -78°C for 1 h. Then SO_2 (g) was bubbled into the mixture for 10 min, and the reaction mixture was allowed to warm to 10°C over 2 h. After being concentrated in vacuum, the mixture was diluted with DCM (20 mL) followed by addition of NCS (460 mg, 3.05 mmol). The reaction was stirred at RT overnight. Water was added and the reaction mixture was extracted with DCM, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE : EA = 20 : 1) to afford the desired product of tert-butyl 2-(chlorosulfonyl)-7-fluoro-1H-indole-1-carboxylate (500 mg, yield: 65%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44~7.51 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 1.63 (s, 9H). MS $(M+H)^+$: 334 / 336.

Step 6 - Synthesis of (S)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate



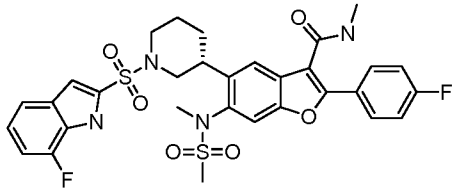
A mixture of tert-butyl 2-(chlorosulfonyl)-7-fluoro-1H-indole-1-carboxylate (64 mg, 0.20 mmol), (*S*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (70 mg, 0.15 mmol) and TEA (45 mg, 0.45 mmol) in DCM (6 mL) was stirred at RT for 6 h under N_2 atmosphere. The mixture was diluted with water, extracted with DCM, dried over Na_2SO_4 and concentrated to give the product (*S*)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate (100 mg, yield: 88%), which was used for the next step without further purification. MS $(M+H)^+$: 757.

Step 7 - Synthesis of (S)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Example 2)

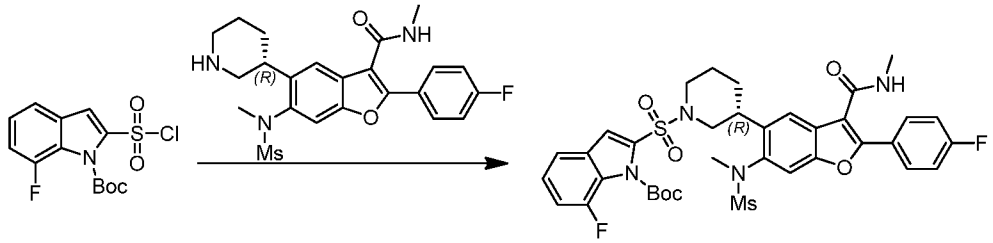


A mixture of (*S*)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate (100 mg, 0.13 mmol) and TFA (1 mL) in CH_2Cl_2 (5 mL) was stirred at RT for 2 h. Then the mixture was concentrated. The residue was purified by prep-HPLC to afford the desired product of (*S*)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (50 mg, yield: 59%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.10~9.55 (m, 1H), 7.77~7.83 (m, 3H), 7.44~7.50 (m, 2H), 7.01~7.17 (m, 5H), 5.76~5.81 (m, 1H), 3.50~4.16(m, 3H), 3.12~3.33 (m, 6H), 2.90~3.02 (m, 3H), 2.50~2.76 (m, 2H),1.73~2.02 (m, 4H). MS $(M+H)^+$: 657.

Example 3: (R)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

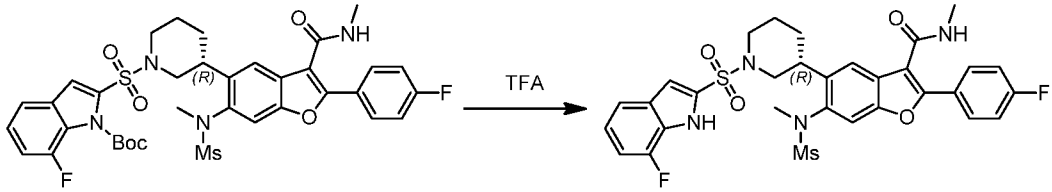


Step 1 - Synthesis of (R)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate



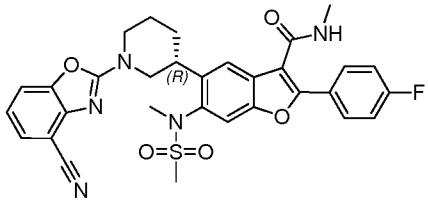
A mixture of tert-butyl 2-(chlorosulfonyl)-7-fluoro-1H-indole-1-carboxylate (64 mg, 0.20 mmol), (*R*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (70 mg, 0.15 mmol) and TEA (45 mg, 0.45 mmol) in DCM (6 mL) was stirred at RT for 6 h under N_2 atmosphere. The mixture was diluted with water, extracted with DCM, dried over Na_2SO_4 and concentrated to give the product (*R*)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate (100 mg, yield: 88%), which was used for the next step without further purification. MS $(M+H)^+$: 757.

Step 2 - Synthesis of (R)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

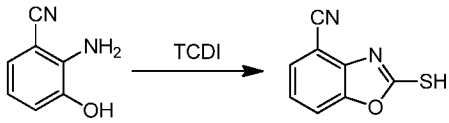


A mixture of (*R*)-tert-butyl 7-fluoro-2-((3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)sulfonyl)-1H-indole-1-carboxylate (100 mg, 0.13 mmol) and TFA (1 mL) in CH_2Cl_2 (5 mL) was stirred at RT for 2 h. Then the mixture was concentrated. The residue was purified by prep-HPLC to afford the desired product of (*R*)-5-(1-((7-fluoro-1H-indol-2-yl)sulfonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (50 mg, yield: 59%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.10~9.55 (m, 1H), 7.77~7.83 (m, 3H), 7.44~7.50 (m, 2H), 7.01~7.17 (m, 5H), 5.76~5.81 (m, 1H), 3.50~4.16(m, 3H), 3.12~3.33 (m, 6H), 2.90~3.02 (m, 3H), 2.50~2.76 (m, 2H),1.73~2.02 (m, 4H). MS $(M+H)^+$: 657.

Example 4: (R)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

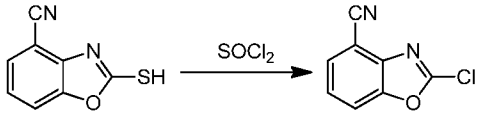


Step 1 - Synthesis of 2-mercaptobenzo[d]oxazole-4-carbonitrile



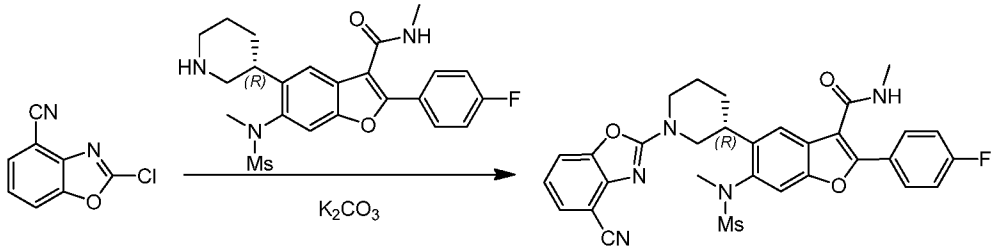
A mixture of 2-amino-3-hydroxybenzonitrile (200 mg, 1.22 mmol), TCDI (260 mg, 1.46 mmol) and in THF (10 mL) was stirred at RT for 6 h under N_2 atmosphere. The mixture was diluted with 1N HCl, extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuum to give the product 2-mercaptobenzo[d]oxazole-4-carbonitrile (200 mg, yield: 80%), which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.45 (t, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 1H). MS $(M+H)^+$: 177.

Step 2 - Synthesis of 2-chlorobenzo[d]oxazole-4-carbonitrile



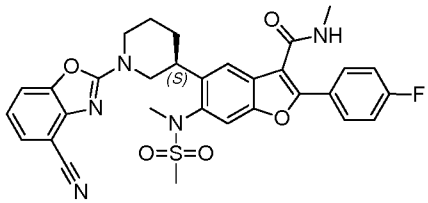
To a mixture of 2-mercaptobenzo[d]oxazole-4-carbonitrile (100 mg, 0.57 mmol) in $SOCl_2$ (2 mL) was added DMF (1 drop). The mixture was heated to 80°C for 20 min. The reaction mixture was concentrated in vacuum, diluted with $NaHCO_3$ (aq), extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (PE : EA = 5 : 1) to give the product of 2-chlorobenzo[d]oxazole-4-carbonitrile (60 mg, yield: 60%). ^{1}H-NMR ($CDCl_3$, 400MHz) δ 7.75 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H). MS $(M+H)^+$: 179 / 181.

Step 3 - Synthesis of (R)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Example 4)

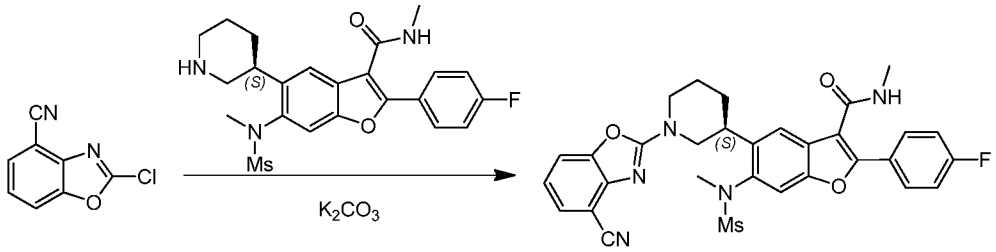


A mixture of 2-chlorobenzo[d]oxazole-4-carbonitrile (33 mg, 0.18 mmol), (*R*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (70 mg, 0.15 mmol) and K_2CO_3 (63 mg, 1.98 mmol) in DMF (5 mL) was stirred at RT overnight under N_2 atmosphere. The mixture was diluted with water, extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to afford the desired product of (*R*)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (50 mg, yield: 56%). ^{1}H-NMR ($CDCl_3$, 400MHz) δ 7.83~7.89 (m, 3H), 7.36~7.62 (m, 3H), 7.18~7.22 (m, 2H), 6.97~6.99 (m, 1H), 5.78 (br s, 1H), 4.39~4.42(m, 2H), 3.22~3.55 (m, 3H), 2.97~3.16 (m, 8H), 1.79~2.23 (m, 5H). MS $(M+H)^+$: 602.

Example 5: (S)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

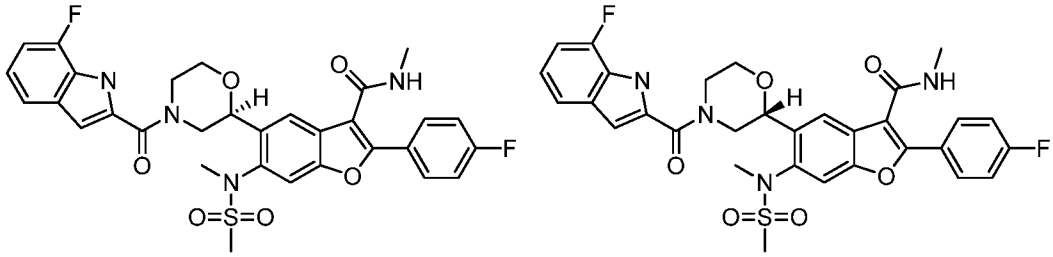


Synthesis of (S)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

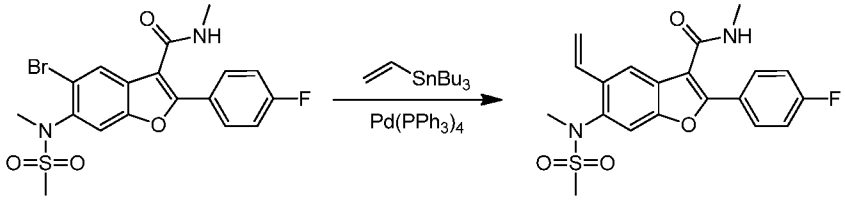


A mixture of 2-chlorobenzo[d]oxazole-4-carbonitrile (33 mg, 0.18 mmol), (*S*)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (70 mg, 0.15 mmol) and K_2CO_3 (63 mg, 1.98 mmol) in DMF (5 mL) was stirred at RT overnight under N_2 atmosphere. The mixture was diluted with water, extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC to afford the desired product of (*S*)-5-(1-(4-cyanobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (50 mg, yield: 56%). ^{1}H-NMR ($CDCl_3$, 400MHz) δ 7.83~7.89 (m, 3H), 7.36~7.62 (m, 3H), 7.18~7.22 (m, 2H), 6.97~6.99 (m, 1H), 5.78 (brs, 1H), 4.39~4.42(m, 2H), 3.22~3.55 (m, 3H), 2.97~3.16 (m, 8H), 1.79~2.23 (m, 5H). MS $(M+H)^+$: 602.

Examples 6 and 7: 5-(4-(7-fluoro-1H-indole-2-carbonyl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)



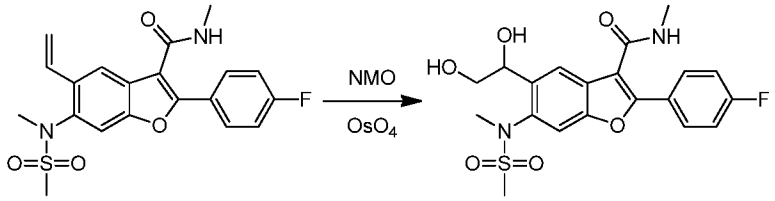
Step 1 - Synthesis of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-vinylbenzofuran-3-carboxamide



A mixture of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethyl sulfonamido)benzofuran-3-carboxamide (10 g, 21.96 mmol), tributyl(vinyl)stannane (14 g, 44.15 mmol) and $Pd(PPh_3)_4$ (2.54 g, 2.20 mmol) in dioxane (150 mL) was stirred at 90°C for 20 hours under N_2 protection. Then the mixture was cooled to room temperature, diluted with EA (100 mL) and filtered through a Celite pad. The combined organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column

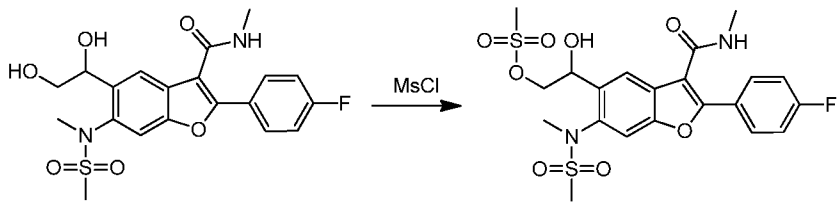
chromatography (PE : EA = 2 :1) to afford the desired product of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-vinylbenzofuran-3-carboxamide (8.8 g, yield: 79.5%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.90 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.51 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 11.2, 17.6 Hz, 1H), 5.84 (d, *J* = 17.6 Hz, 2H), 5.41 (d, *J* = 11.2 Hz, 1H), 3.28 (s, 3H), 2.97~3.04 (m, 6H). MS $(M+H)^+$: 403.

Step 2 - Synthesis of 5-(1,2-dihydroxyethyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



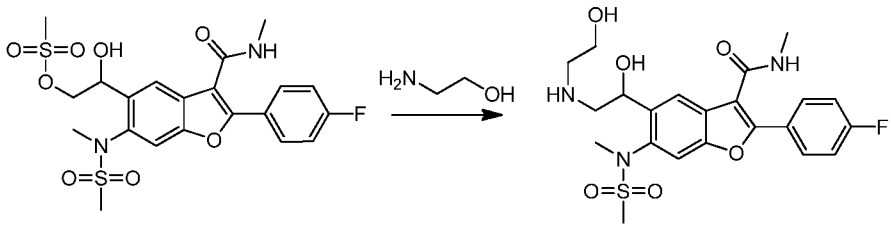
A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-vinylbenzofuran-3-carboxamide (4 g, 9.94 mmol), NMO (3.49 g, 29.81 mmol) and OsO_4 (250 mg, 0.98 mmol) in THF / MeOH / H_2O (20 mL / 20 mL / 5 mL) was stirred at room temperature for 2 hours. Then Na_2SO_3 (5 g, 39.7 mmol) was added, and the reaction mixture was extracted with EA (10 mL * 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM : MeOH = 10 : 1) to afford the product of 5-(1,2-dihydroxyethyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (3.5 g, yield: 80.8%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.98~8.05 (m, 1H), 7.88~7.97 (m, 2H), 7.44 (s, 1H), 7.17 (t, *J* = 8.4 Hz, 2H), 6.15~6.29 (m, 1H), 5.39 (dd, *J* = 3.6, 7.6 Hz, 1H), 5.22 (d, *J* = 4.4 Hz, 1H), 3.91~3.99 (m, 1H), 3.81~3.90 (m, 1H), 3.44~3.79 (m, 2H), 3.25~3.37 (m, 3H), 2.82~3.12 (m, 7H). MS $(M+H)^+$: 436.

Step 3 - Synthesis of 2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)-2-hydroxyethyl methanesulfonate



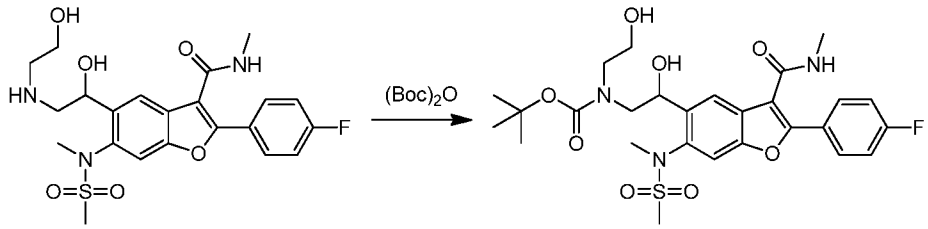
To a solution of 5-(1,2-dihydroxyethyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (3.5 g, 8.02 mmol) in pyridine (30 mL) was added MsCl (1.5 g, 13.09 mmol). The reaction mixture was stirred at room temperature for 2 hours and then the reaction mixture was diluted with water, and then extracted with EA (20 mL * 8). The combined organic layer was washed with brine (150 mL), dried over Na_2SO_4 and concentrated, the residue was purified by silica gel column chromatography (DCM : MeOH = 20 : 1) to afford the product 2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-2-hydroxyethyl methanesulfonate (3.8 g, yield: 92.2%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.03~8.09 (m, 1H), 7.91~8.02 (m, 2H), 7. 40~7.54 (m, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 6.14~5.91 (m, 1H), 5.48~5.68 (m, 1H), 4.39~4.72 (m, 2H), 3.29~3.39 (m, 3H), 2.97~3.15 (m, 9H). MS $(M+H)^+$: 515.

Step 4 - Synthesis of 2-(4-fluorophenyl)-5-(1-hydroxy-2-((2-hydroxyethyl)amino)ethyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



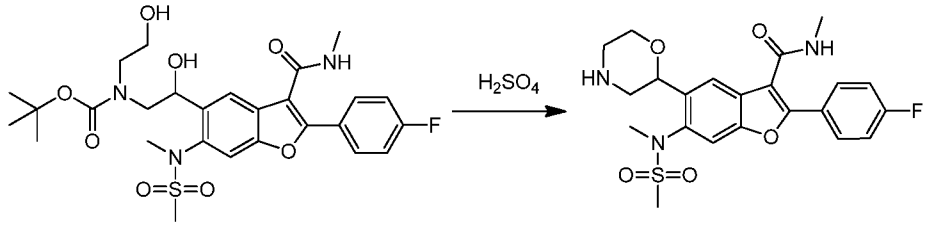
To a solution of 2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-2-hydroxyethyl methanesulfonate (3.8 g, 7.38 mmol) in DMF (20 mL) was added 2-aminoethanol (2.71 g, 44.32 mmol) and K_2CO_3 (3.06 g, 22.16 mmol). The reaction mixture was stirred at 80°C for 40 hours. Then the reaction mixture was concentrated to afford the crude product 2-(4-fluorophenyl)-5-(1-hydroxy-2-((2-hydroxyethyl)amino)ethyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide, which was used for next step without purification. MS $(M+H)^+$: 480.

Step 5 - Synthesis of tert-butyl (2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-2-hydroxyethyl)(2-hydroxyethyl)carbamate



A mixture of 2-(4-fluorophenyl)-5-(1-hydroxy-2-((2-hydroxyethyl)amino)ethyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (crude from previous step) and $(Boc)_2O$ (15 g, 68.7 mmol) in THF (30 mL) was stirred at room temperature for 18 hours under N_2 protection. Then the mixture was quenched with water and extracted with EA (20 mL *5). The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM : MeOH = 20 : 1) to afford the product of tert-butyl (2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-2-hydroxyethyl)(2-hydroxyethyl)carbamate (2.5 g, yield: 58.1% for 2 steps). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71~8.14 (m, 3H), 7.41 (d, *J* = 15.6 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 2H), 5.95~6.33 (m, 1H), 5.35~5.64 (m, 1H), 3.59~3.95 (m, 4H), 3.50 (d, *J* = 12.4 Hz, 1H), 3.26~3.43 (m, 4H), 3.15 (br. s., 1H), 2.94~3.10 (m, 5H), 1.39~1.54 (m, 9H). MS $(M+H)^+$: 580.

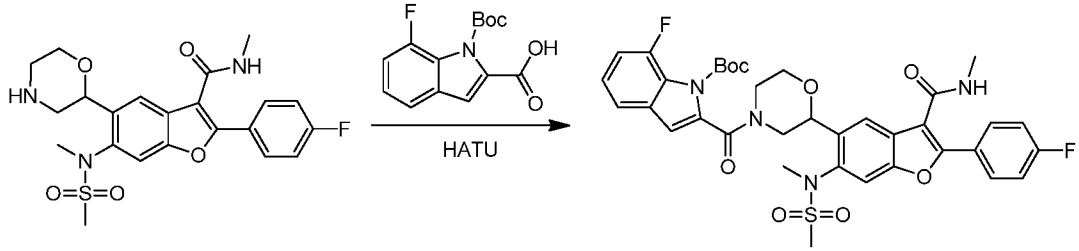
Step 6 - Synthesis of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(morpholin-2-yl)benzofuran-3-carboxamide



Tert-butyl (2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-2-hydroxyethyl)(2-hydroxyethyl)carbamate (700 mg, 1.2 mmol) in 70% H_2SO_4 aqueous (20 mL) was stirred at room temperature for 12 hours under N_2 protection. Then the mixture was quenched with water, adjusted to pH ~8, and extracted with EA (20 mL* 5). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM : MeOH = 20 : 1) to afford the product of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(morpholin-2-

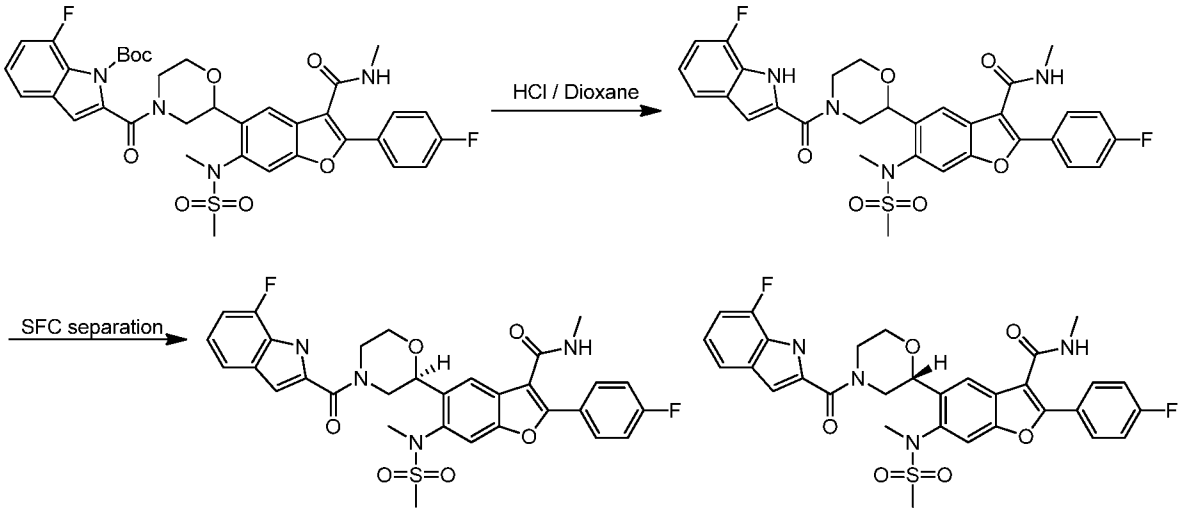
yl)benzofuran-3-carboxamide (350 mg, yield: 62.8%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.01 (br s, 1H), 7.87~7.97 (m, 2H), 7.40~7.55 (m, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 5.85~6.04 (m, 1H), 4.87~5.12 (m, 1H), 3.96~4.10 (m, 1H), 3.76~3.90 (m, 1H), 3.19~3.38 (m, 4H), 2.98~3.15 (m, 8H), 2.76~2.97 (m, 2H). MS $(M+H)^+$: 462.

Step 7 - Synthesis of tert-butyl 7-fluoro-2-(2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)morpholine-4-carbonyl)-1H-indole-1-carboxylate



A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(morpholin-2-yl)benzofuran-3-carboxamide (150 mg, 0.33 mmol), 1-(tert-butoxycarbonyl)-7-fluoro-1H-indole-2-carboxylic acid (91 mg, 0.33 mmol), HATU (371 mg 0.98 mmol) and Et_3N (165 mg 1.6 mmol) in DMF (2 mL) was stirred at RT overnight under N_2 protection. Then the mixture was diluted with H_2O (20 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by prep-TLC (PE : EA= 1 : 1) to give the product of tert-butyl 7-fluoro-2-(2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl) morpholine-4-carbonyl)-1H-indole-1-carboxylate (180 mg, yield: 76%). MS $(M+H)^+$: 723.

Step 8 - Synthesis of 5-(4-(7-fluoro-1H-indole-2-carbonyl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Enantiomers 1 and 2)

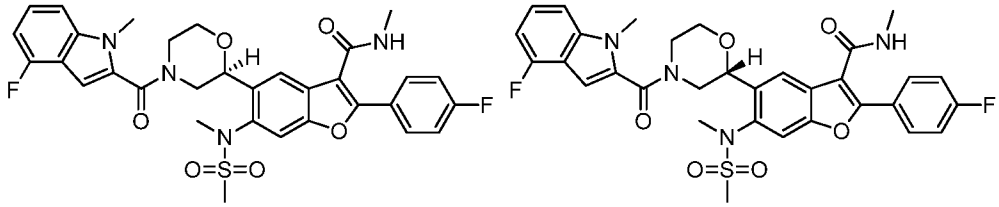


To a solution of tert-butyl 7-fluoro-2-(2-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)morpholine-4-carbonyl)-1H-indole-1-carboxylate (230 mg, 0.32 mmol) in dioxane (2 mL) was added HCl solution in dioxane (5 mL, 4 M) at RT. The mixture was stirred at RT for 5 hours. The mixture was diluted with water and extracted with DCM. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by prep-HPLC and SFC to give two single enantiomers.

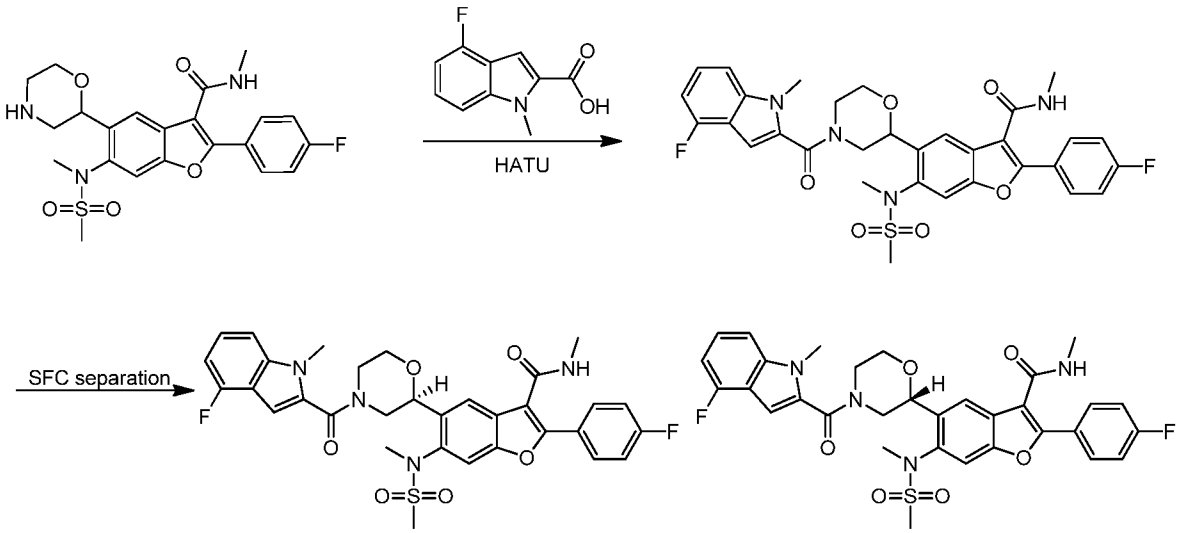
Example 6 (enantiomer 1, peak 1 on SFC, AS-H_S_3_5_40_3ML_8MIN_15CM, HPLC_RT= 5.097 min) (60 mg, yield: 30 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.38 (br s, 1H), 8.10~8.17 (m, 1H), 7.84~7.98 (m, 2H), 7.33~7.57 (m, 2H), 7.15~7.23 (m, 2H), 6.87~7.09 (m, 3H), 5.88 (br s, 1H), 4.87~5.10 (m, 2H), 4.51~4.75 (m, 3H), 4.10~4.25 (m, 1H), 3.80~3.95 (m, 1H), 3.31 (s, 3H), 2.88~3.14 (m, 6 H). MS $(M+H)^+$: 623.

Example 7 (enantiomer 2, peak 2 on SFC, AS-H_S_3_5_40_3ML_8MIN_15CM, HPLC_RT= 5.582 min) (60 mg, yield: 30 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.38 (br s, 1H), 8.10~8.17 (m, 1H), 7.84~7.98 (m, 2H), 7.33~7.57 (m, 2H), 7.15~7.23 (m, 2H), 6.87~7.09 (m, 3H), 5.88 (br s, 1H), 4.87~5.10 (m, 2H), 4.51~4.75 (m, 3H), 4.10~4.25 (m, 1H), 3.80~3.95 (m, 1H), 3.31 (s, 3H), 2.88~3.14 (m, 6 H). MS $(M+H)^+$: 623.

Examples 8 and 9: 5-(4-(4-fluoro-1-methyl-1H-indole-2-carbonyl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)



Synthesis of 5-(4-(4-fluoro-1-methyl-1H-indole-2-carbonyl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 1) and 5-(4-(4-fluoro-1-methyl-1H-indole-2-carbonyl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 2)

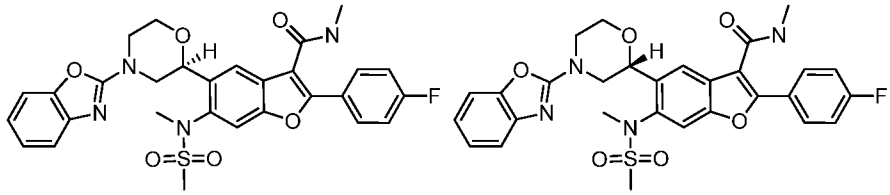


A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(morpholin-2-yl)benzofuran-3-carboxamide (150 mg, 0.33 mmol), 4-fluoro-1-methyl-1H-indole-2-carboxylic acid (63 mg, 0.33 mmol), HATU (371 mg 0.98 mmol) and Et_3N (165 mg 1.6 mmol) in DMF (2 mL) was stirred at RT overnight under N_2 protection. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with DCM, the organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC and SFC to give two single enantiomers.

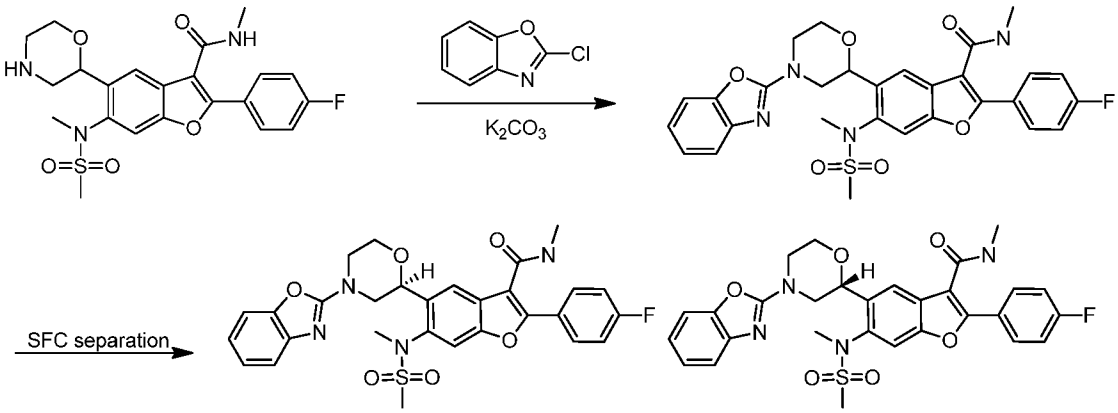
Example 8 (enantiomer 1, peak 1 on SFC, AS-H_S_3_5_40_2.5ML_6MIN_25CM, HPLC_RT= 2.40 min) (80 mg, yield: 38 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.02~8.13 (m, 1H), 7.84~7.96 (m, 2H), 7.30~7.55 (m, 1H), 7.09~7.22 (m, 4 H), 6.64~6.86 (m, 2H), 5.97 (br s, 1H), 4.89~5.27 (m, 1H), 4.03~4.76 (m, 3H), 3.78~3.97 (m, 4H), 3.29 (s, 3H), 2.64~3.09 (m, 8H). MS $(M+H)^+$: 637.

Example 9 (enantiomer 2, peak 2 on SFC, AS-H_S_3_5_40_2.5ML_6MIN_25CM, HPLC_RT= 3.07 min) (80 mg, yield: 38 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.02~8.13 (m, 1H), 7.84~7.96 (m, 2H), 7.30~7.55 (m, 1H), 7.09~7.22 (m, 4 H), 6.64~6.86 (m, 2H), 5.97 (br s, 1H), 4.89~5.27 (m, 1H), 4.03~4.76 (m, 3H), 3.78~3.97 (m, 4H), 3.29 (s, 3H), 2.64~3.09 (m, 8H). MS $(M+H)^+$: 637.

Examples 10 and 11: 5-(4-(benzo[d]oxazol-2-yl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)



Synthesis of 5-(4-(benzo[d]oxazol-2-yl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide and 5-(4-(benzo[d]oxazol-2-yl)morpholin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



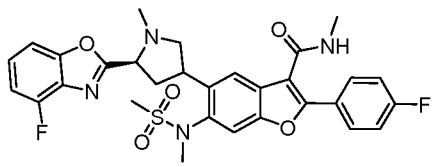
A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(morpholin-2-yl)benzofuran-3-carboxamide (229 mg, 0.50 mmol), 2-chlorobenzo[d]oxazole (91 mg, 0.595 mmol) and K_2CO_3 (206 mg 1.49 mmol) in DMF (5 mL) was stirred at RT for 4 h under N_2 protection. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC and SFC to give two single enantiomers.

Example 10 (enantiomer 1, peak 1 on SFC, OJ-H_3UM_5_5_40_4ML_3MIN, HPLC_RT= 1.385 min) (100 mg, yield: 34 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.09 (br s, 1H), 7.88~7.97 (m, 2H), 7.53

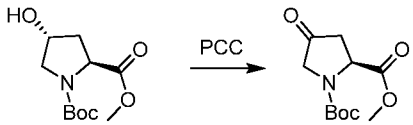
(s, 1H), 7.32~7.40 (m, 1H), 7.24~7.31 (m, 1H), 7.13~7.23 (m, 3H), 7.04 (q, *J* =7.6 Hz, 1H), 5.95 (br s, 1H), 4.99~5.26 (m, 1H), 4.07~4.29 (m, 3 H), 3.85~4.03 (m, 1 H), 3.36~3.52 (m, 2H), 3.17 (s, 3H), 2.96~3.07 (m, 6H). MS $(M+H)^+$: 579.

Example 11 (enantiomer 2, peak 2 on SFC, OJ-H_3UM_5_5_40_4ML_3MIN, HPLC_RT= 1.765 min) (100 mg, yield: 34 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.09 (br s, 1H), 7.88~7.97 (m, 2H), 7.53 (s, 1H), 7.32~7.40 (m, 1H), 7.24~7.31 (m, 1H), 7.13~7.23 (m, 3H), 7.04 (q, *J* =7.6 Hz, 1H), 5.95 (br s, 1H), 4.99~5.26 (m, 1H), 4.07~4.29 (m, 3 H), 3.85~4.03 (m, 1 H), 3.36~3.52 (m, 2H), 3.17 (s, 3H), 2.96~3.07 (m, 6H). MS $(M+H)^+$: 579.

Example 12: 5-((5S)-5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

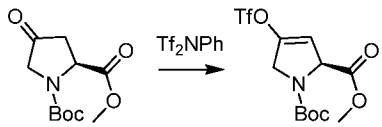


Step 1 - Synthesis of (S)-1-tert-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate



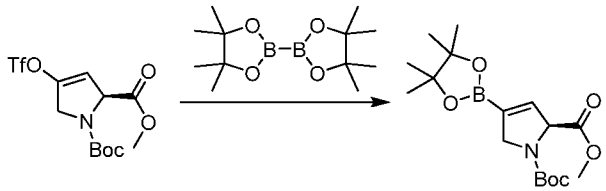
PCC (52.9 g, 244.63 mmol) was added into a solution of (2*S*,4*R*)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (10 g, 81.54 mmol) in DCM (300 mL) under N_2 and the mixture was stirred for 48 hours. After being filtered and concentrated, the residue was purified by column chromatography eluted with PE : EtOAc = 4 : 1 to afford (*S*)-1-tert-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (11 g, yield: 55.5%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.67~4.79 (m, 1H), 3.86 (d, *J* = 12.0 Hz, 2H), 3.73 (s, 3H), 2.90~2.93 (m, 1H), 2.56 (d, *J* = 20.0 Hz, 1H), 1.45 (s, 9H). MS $(M+H)^+$: 244.

Step 2 - Synthesis of (S)-1-tert-butyl 2-methyl 4-(trifluoromethylsulfonyloxy)-1H-pyrrole-1,2(2H,5H)-dicarboxylate



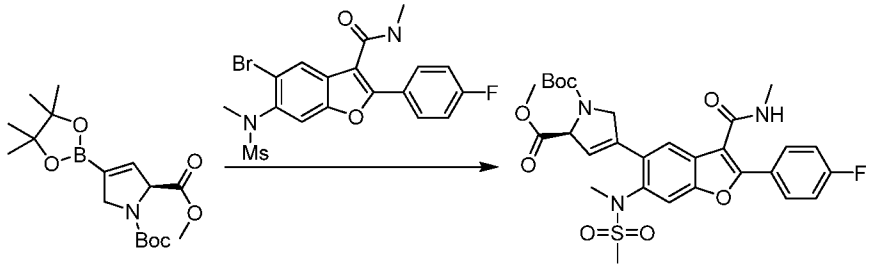
LiHMDS (1.51 g, 9.04 mmol) was added into a solution of (*S*)-1-tert-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (2 g, 8.22 mmol) in dry THF (20 mL) under N_2 dropwise at -78°C and the mixture was stirred for 0.5 hours. 1,1,1-trifluoro-N-phenyl -N-(trifluoromethylsulfonyl)methanesulfonamide (3.23 g, 9.04 mmol) in dry THF (20 mL) was added into the reaction mixture under N_2 dropwise at -78°C and stirred for 2 hours. Then the reaction mixture was stirred at RT for 12 hours. After being diluted with NH_4Cl (a.q.) and extracted with EtOAc (200 mL* 3), the orgranics were washed with brine and dried over Na_2SO_4. After being filtered and concentrated in vacuo, the residue was purified by column chromatography and eluted with PE : EtOAc = 20 : 1 to afford (*S*)-1-tert-butyl 2-methyl 4-(trifluoromethylsulfonyloxy)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (1.1 g, yield: 35.5%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.69~5.74 (m, 1H), 4.99~5.08 (m, 1H), 4.23~4.41 (m, 2H), 3.75 (s, 3H), 1.47 (s, 9H). MS $(M+H)^+$: 376.

Step 3 - Synthesis of (S)-1-tert-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate



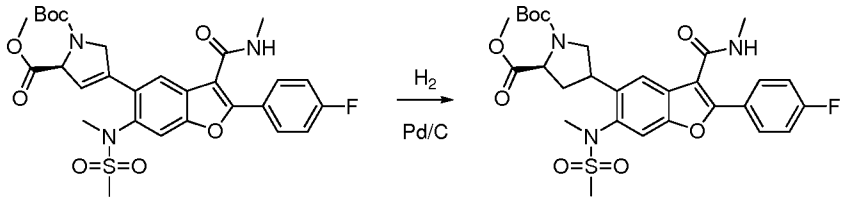
To a degassed solution of (*S*)-1-tert-butyl 2-methyl 4-(trifluoromethylsulfonyloxy) -1H-pyrrole-1,2(2H,5H)-dicarboxylate (200 mg, 0. 53 mmol) and bis(pinacolato)diboron (148 mg, 0.58 mmol) in dry dioxane (3 mL) was added $Pd(dppf)Cl_2$ (1 mg) and KOAc (162 mg, 165 mmol) under N_2. The mixture was heated to100°C and then stirred overnight. The reaction mixture was cooled to RT and filtered. The filtrate was diluted with EtOAc (50 mL), washed with H_2O, brine, dried over Na_2SO_4. After being concentrated, the residue was purified by prep-TLC (PE: EtOAc = 1 : 1) to afford (*S*)-1-tert-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (160 mg, yield: 85%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.27~6.33 (m, 1H), 5.07~5.10 (m, 1H), 4.26~4.32 (m, 2H), 3.69 (s, 3H), 1.42 (s, 9H), 1.21 (s, 12H). MS $(M+H)^+$: 354.

Step 4 - Synthesis of (S)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate



To a degassed solution of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (120 mg, 0.26 mmol) and (*S*)-1-tert-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (102 mg, 0.29 mmol) in dry dioxane (3 mL) was added Pd(dppf)Cl_2 (2 mg) and K_3PO_4 (112 mg, 1.05 mmol) under N_2. The mixture was heated to 100°C and then stirred overnight. The reaction mixture was cooled to RT and filtered. The filtrate was diluted with EtOAc (50 mL), washed with H_2O, brine, and dried over Na_2SO_4. After being concentrated, the residue was purified by prep-HPLC (PE : EtOAc = 1 : 2) to give the product of (*S*)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (50 mg, yield: 31.6%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.86~7.92 (m, 2H), 7.77~7.81 (m, 1H), 7.55 (s, 1H), 7.17~7.22 (m, 2H), 6.04~6.06 (m, 2H), 5.12~5.21 (m, 1H), 4.57~4.67 (m, 2H), 3.78 (s, 3H), 3.25 (s, 3H), 3.00~3.02 (m, 6H), 1.23 (s, 9H). MS $(M+H)^+$: 602.

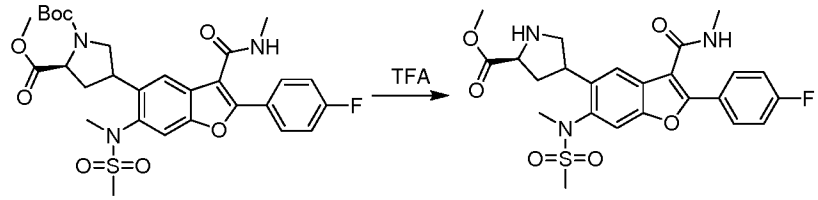
Step 5 - Synthesis of (2S)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)pyrrolidine-1,2-dicarboxylate



To a solution of (*S*)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1H-pyrrole-1,2(2H,5H)-dicarboxylate (460 mg, 0.76 mmol) in MeOH (10 mL), Pd/C (200 mg) was added and the resulting reaction mixture was stirred under 40 psi of H_2 atmosphere for 24 h at 25°C. Then the reaction mixture was filtered, and the filtrate was evaporated to give the crude product of (2*S*)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-

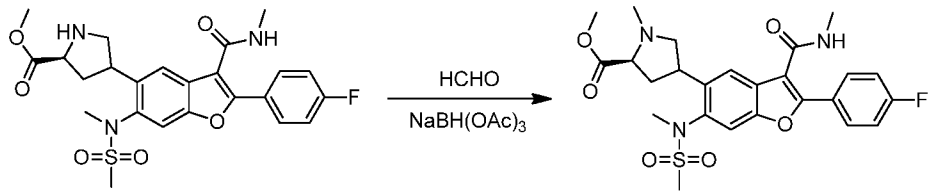
yl)pyrrolidine-1,2-dicarboxylate (400 mg, yield: 86.7%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.61~7.94 (m, 3H), 7.36~7.47 (m, 1H), 7.10~7.14 (m, 2H), 5.88~6.13 (m, 1H), 4.28~4.35 (m, 1H), 3.91~4.01 (m, 2H), 3.66~3.72 (m, 4H), 3.37~3.50 (m, 1H), 3.19~3.32 (m, 2H), 2.94~2.98 (m, 6H), 2.57~2.78 (m, 1H), 1.88~2.14 (m, 1H), 1.39 (s, 9H). MS $(M+H)^+$: 604.

Step 6 - Synthesis of (2S)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)pyrrolidine-2-carboxylate



TFA (0.5 mL) was added into a solution of (2*S*)-1-tert-butyl 2-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)pyrrolidine-1,2-dicarboxylate (200 mg, 0.33 mmol) in DCM (5 mL) under N_2 dropwise at 0°C and stirred for 6 hours. After being diluted with $NaHCO_3$ (a.q.) and extracted with EtOAc (50 mL * 3), the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give the desired product of (2*S*)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)pyrrolidine-2-carboxylate (150 mg, yield: 89.8%). MS $(M+H)^+$: 504.

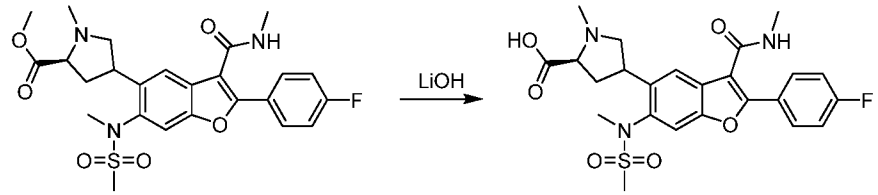
Step 7 - Synthesis of (2S)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylate



A solution of (2*S*)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)pyrrolidine-2-carboxylate (50 mg, 0.09 mmol), CH_3CO_2Na (8 mg, 0.09 mmol) and HCHO (8 mg, 0.09 mmol) in MeOH (5 mL) was stirred at RT for 1 h under N_2. Then TEA (3 drops) and $NaBH(OAc)_3$ (105 mg, 0.5 mmol) were added to the mixture. After being stirred for 12 h, the mixture was diluted with water and extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to

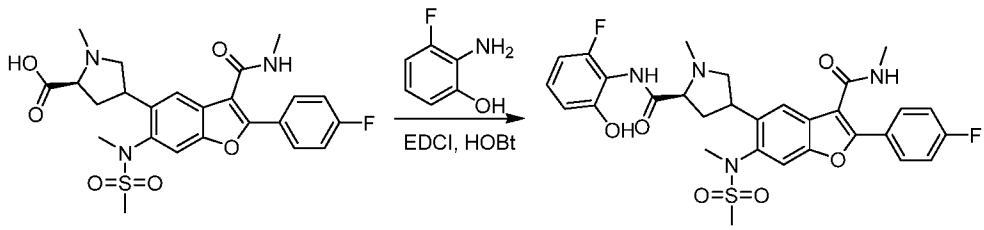
give (2*S*)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylate (40 mg, yield: 78.4%). MS $(M+H)^+$: 518.

Step 8 - Synthesis of (2S)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethyl sulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylic acid



To a solution of (2*S*)-methyl 4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylate (100 mg, 0.19 mmol) in dioxane (5 mL) and water (3 mL), $LiOH{\cdot}H_2O$ (82 mg, 1.93 mmol) was added, and the mixture was stirred overnight at 20°C. After being concentrated, H_2O was added, the mixture was extracted with ether, and the aqueous phase was acidified by 1 N HCl. Then the mixture was extracted by EtOAc (50 mL*3), and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dried to give the desired product of (2*S*)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylic acid (90 mg, yield: 91.8%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.91~7.95 (m, 2H), 7.83~7.86 (m, 2H), 7.22~7.26 (m, 2H), 4.45~4.52 (m, 1H), 4.00~4.12 (m, 1H), 3.65~3.73 (m, 2H), 3.46~3.57 (m, 1H), 3.28~3.34 (m, 3H), 3.07 (d, J = 8.0 Hz, 3H), 2.96~3.01 (m, 6H), 2.18~2.30 (m, 1H). MS $(M+H)^+$: 504.

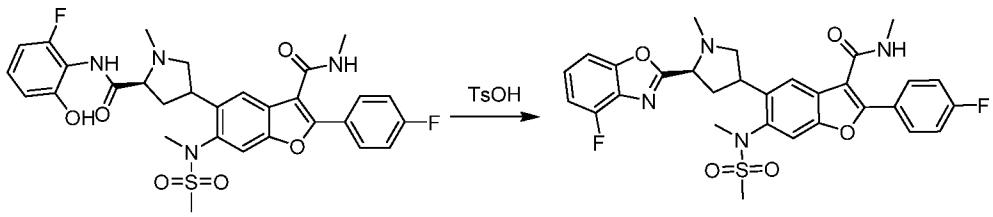
Step 9 - Synthesis of (2S)-N-(2-fluoro-6-hydroxyphenyl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxamide



(2*S*)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)-1-methylpyrrolidine-2-carboxylic acid (57 mg, 0.11 mmol), HOBT (17 mg, 0.12

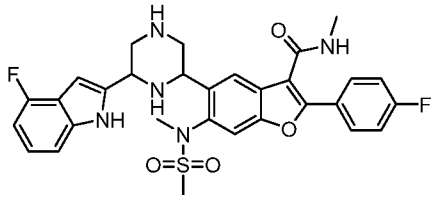
mmol), EDCI (33 mg, 0.16 mmol) and TEA (35 mg, 0.33 mmol) were dissolved in dry DMF (3 mL). The resulting solution was stirred for 30 minutes. Then 2-amino-3-fluorophenol (22 mg, 0.16 mmol) was added to the mixture. The mixture was stirred at 20°C overnight. Then H_2O was added, and the reaction mixture filtered to give the crude solid. The crude product was purified by prep-TLC (DCM : MeOH = 20 : 1) to give (2*S*)-N-(2-fluoro-6-hydroxyphenyl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxamide (30 mg, yield: 43.4 %), which was used for the next step without further purification. MS $(M+H)^+$: 613.

Step 10 - Synthesis of 5-((5S)-5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Example 12)

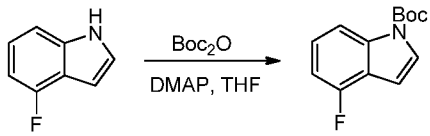


4-methylbenzene sulfonic acid (10 mg, 0.05 mmol) was added to a solution of (2*S*)-N-(2-fluoro-6-hydroxyphenyl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyrrolidine-2-carboxamide (30 mg, 0.05 mmol) in toluene (1 mL) under N_2. The mixture was stirred at reflux overnight. After being concentrated in vacuo, the residue was purified by prep-HPLC to give the product of 5-((5*S*)-5-(4-fluorobenzo[d]oxazol-2-yl)-1-methylpyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (20 mg, yield: 68.9%). ^{1}H-NMR (MeOD, 400 MHz) δ 7.87~7.99 (m, 4H), 7.49~7.58 (m, 2H), 7.22~7.29 (m, 3H), 5.25~5.41 (m, 1H), 4.54~4.72 (m, 1H), 3.95~4.22 (m, 1H), 3.61~3.92 (m, 1H), 3.21~3.38 (m, 6H), 3.10~3.17 (m, 4H), 3.08~2.87 (m, 3H), 2.70~2.80 (m, 1H). MS $(M+H)^+$: 595.

Example 13: 5-(6-(4-fluoro-1H-indol-2-yl)piperazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-carboxamide

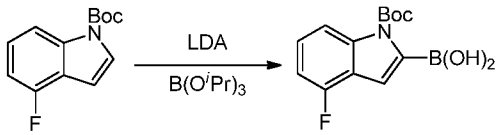


Step 1 - Synthesis of tert-butyl 4-fluoro-1H-indole-1-carboxylate



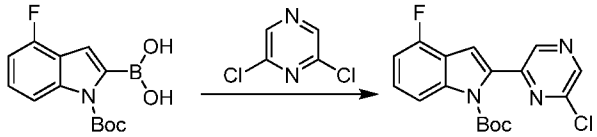
To a solution of 4-fluoro-1H-indole (150 g, 1.11mol) and DMAP (4.5 g, 3%wt) in THF (2.5 L) was added $(Boc)_2O$ (255 g, 1.16 mol) dropwise. The mixture was stirred at room temperature overnight. The organic solvent was removed in vacuum, and the residue was purified by column chromatography (PE) to give tert-butyl 4-fluoro-1H-indole-1-carboxylate (250 g, yield: 96%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 3.6 Hz, 1H), 7.23 (m, 1H), 6.90 (m, 1H), 6.66 (d, J = 3.6 Hz, 1H), 1.67 (s, 9H). MS $(M+H)^+$: 236.

Step 2 - Synthesis of (1-(tert-butoxycarbonyl)-4-fluoro-1H-indol-2-yl)boronic acid



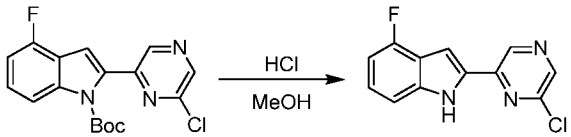
To a solution of diisopropylamine (175 mL, 1.25 mol) in THF (800 mL) at 0°C was added n-BuLi (500 mL, 1.25 mol) dropwise. The mixture was stirred at 0°C for 40 minutes. Then the mixture was cooled to -78 °C. Tert-butyl 4-fluoro-1H-indole-1-carboxylate (118 g, 0.50 mol) in THF (300 mL) was added dropwise, followed by triisopropyl borate (231 mL, 1.00 mol). The mixture was stirred at -78 °C for another 40 min. The reaction was monitored by HPLC. When the reaction was completed, the reaction was quenched with NH_4Cl (sat. 500 mL). Then the mixture was adjusted to pH = 6 with 1 N HCl, extracted with EtOAc (2000 mL) and the combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated. The obtained solid was recrystallized with EtOAc and PE to give (1-(tert-butoxycarbonyl)-4-fluoro-1H-indol-2-yl)boronic acid (93 g, yield: 64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.44 (s, 2H), 7.24 (m, 1H), 6.90 (m, 1H), 1.66 (s, 9H). MS $(M+H)^+$: 280.

Step 3 - Synthesis of tert-butyl 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole-1-carboxylate



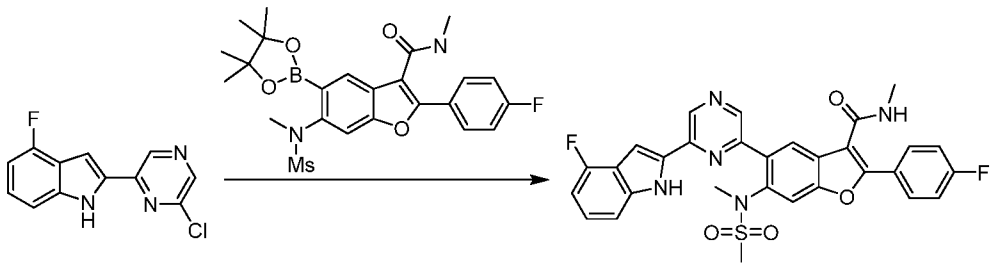
$Pd(dppf)Cl_2$ (53 mg, 0.072 mmol) was added to a mixture of 1-(tert-butoxycarbonyl)-4-fluoro-1H-indol-2-ylboronic acid (200 mg, 0.717 mmol), 2,6-dichloropyrazine (106 mg, 0.717 mmol) and K_3PO_4 (572 mg, 2.151 mmol) in DMF (2 mL) under N_2. The mixture was stirred at 80°C overnight under N_2. The mixture was then diluted with water (40 mL) and extracted with EA (25 mL * 3). The organic layer was washed with brine (30 mL * 3), dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE : EA = 8 : 1) to afford the desired product of tert-butyl 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole-1-carboxylate (150 mg, yield: 60.2 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.65 (s, 1H), 8.50 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.24~7.30 (m, 1H), 6.88~6.94 (m, 2H), 1.35 (s, 9H). MS $(M+H)^+$: 348 / 350.

Step 4 - Synthesis of 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole



A mixture of tert-butyl 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole-1-carboxylate (150 mg, 0.432 mmol) in HCl / CH_3OH (10 mL) was stirred at RT for 2 hours. The mixture was then concentrated to afford the product of 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole (100 mg, yield: 93.4 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.33 (s, 1H), 8.92 (s, 1H), 8.37 (s, 1H), 7.13~7.17 (m, 3H), 6.73~6.78 (m, 1H). MS $(M+H)^+$: 248 / 250.

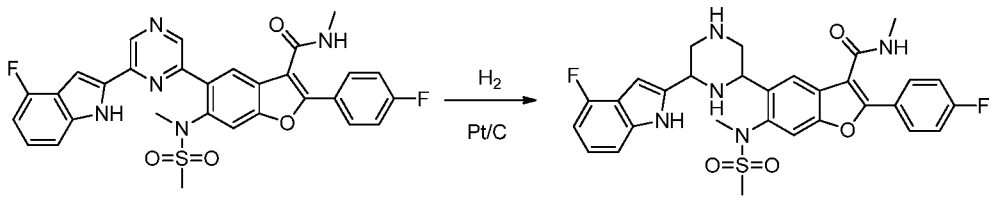
Step 5 - Synthesis of 5-(6-(4-fluoro-1H-indol-2-yl)pyrazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



$Pd_2(dba)_3$ (10 mg, 0.011 mmol) and X-Phos (10 mg, 0.022 mmol) were added to a mixture of 2-(6-chloropyrazin-2-yl)-4-fluoro-1H-indole (58 mg, 0.241 mmol), 2-(4-fluorophenyl)-

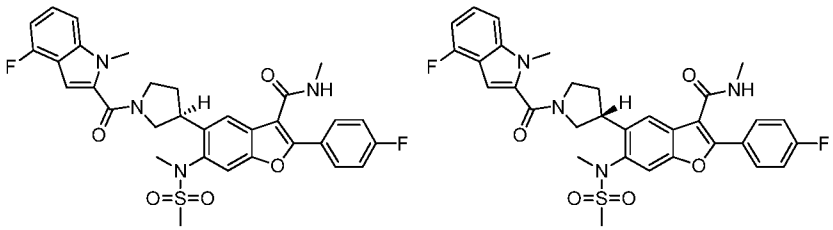
N-methyl-6-(N-methylmethylsulfonamido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide (121 mg, 0.241 mmol) and K_3PO_4 (175 mg, 0.657 mmol) in dioxane / H_2O (1.6 mL / 0.4 mL) under N_2. The mixture was stirred at 110°C overnight. The mixture was then diluted with water (3 mL) and extracted with EtOAc (20 mL * 3). The organic layer was washed with brine (30 mL * 3), dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE : EA = 1 : 1.5) to afford the desired product of 5-(6-(4-fluoro-1H-indol-2-yl)pyrazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (80 mg, yield: 56.7 %). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 12.03 (s, 1H), 9.29 (s, 1H), 8.72 (s, 1H), 8.52 (d, J = 4.4 Hz, 1H), 8.16 (s, 1H), 7.98~8.03 (m, 3H), 7.38~7.46 (m, 3H), 7.32 (d, J = 8.4 Hz, 1H), 7.09~7.14 (m, 1H), 6.78~6.82 (m, 1H), 3.33 (s, 3H), 2.97 (s, 3H), 2.80 (d, J = 5.2 Hz, 3H). MS $(M+H)^+$: 588.

Step 6 - Synthesis of 5-(6-(4-fluoro-1H-indol-2-yl)piperazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

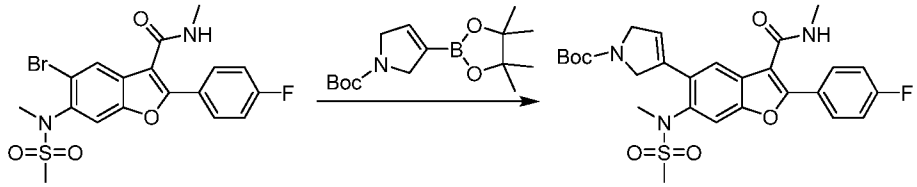


A mixture of 5-(6-(4-fluoro-1H-indol-2-yl)pyrazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (30 mg, 0.051 mmol) and HCl / CH_3OH (20 mL) was concentrated in vacuum. The residue was then dissolved in CH_3OH (10 mL) and Pt/C (20 mg) was added to the solution. The mixture was stirred at 30°C under H_2 (35 Psi) for 24 hours. The mixture was then filtered through Celite. The filtrate was concentrated and purified by prep-HPLC to afford 5-(6-(4-fluoro-1H-indol-2-yl)piperazin-2-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-carboxamide (15 mg, yield: 50.0 %). ^{1}H-NMR (Methanol-d4, 400 MHz) δ 8.35 (d, J = 11.2 Hz, 1H), 7.94~7.98 (m, 3H), 7.28~7.32 (m, 2H), 7.21~7.24 (m, 1H), 7.07~7.13 (m, 1H), 6.66~6.75 (m, 2H), 5.07~5.16 (m, 1H), 4.67~4.81 (m, 1H), 3.70~3.89 (m, 2H), 3.52~3.60 (m, 2H), 3.57 (s, 3H), 3.14 (d, J = 18.0 Hz, 3H), 3.00 (s, 3H). MS $(M+H)^+$: 594.

Examples 14 and 15: 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

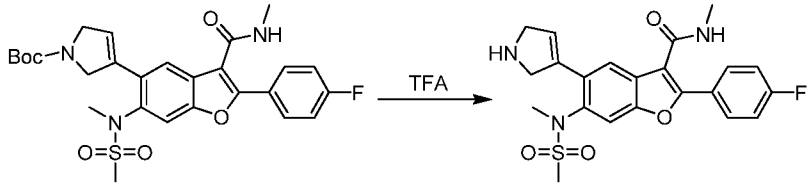


Step 1 - Synthesis of tert-butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate



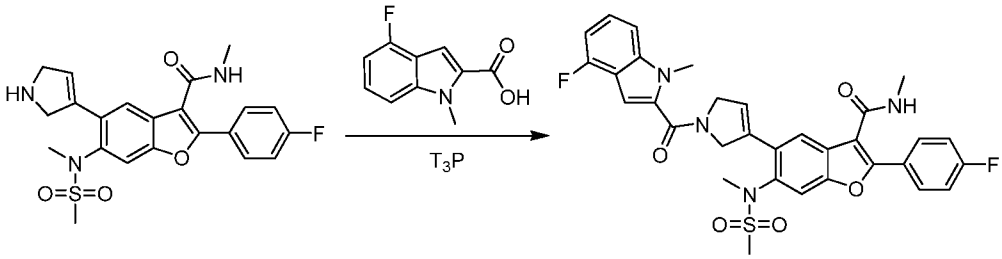
To a solution of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethyl sulfonamido)benzofuran-3-carboxamide (100 mg, 0.22 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylae (65 mg, 0.22 mmol) and K_2CO_3 (61 mg, 0.44 mmol) in 1,4-dioxane (5 mL) and H_2O (0.2 mL) was added $Pd(dppf)Cl_2$ (15 mg) under nitrogen. The reaction mixture was heated at 100°C for 2 h. The mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford the product of tert-butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido) benzofuran-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (80 mg, yield: 67%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.85~7.92 (m, 2H), 7.75~7.79 (m, 1H), 7.52 (s, 1H), 7.15~7.19 (m, 2H), 6.05~6.18 (m, 1H), 5.75~5.80 (m, 1H), 4.50~4.54 (m, 2H), 4.29~4.33 (m, 2H), 3.25 (s, 3H), 3.00 (d, J = 4.0 Hz, 6H), 1.48 (s, 9H). MS $(M+H)^+$: 544.

Step 2 - Synthesis of 5-(2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



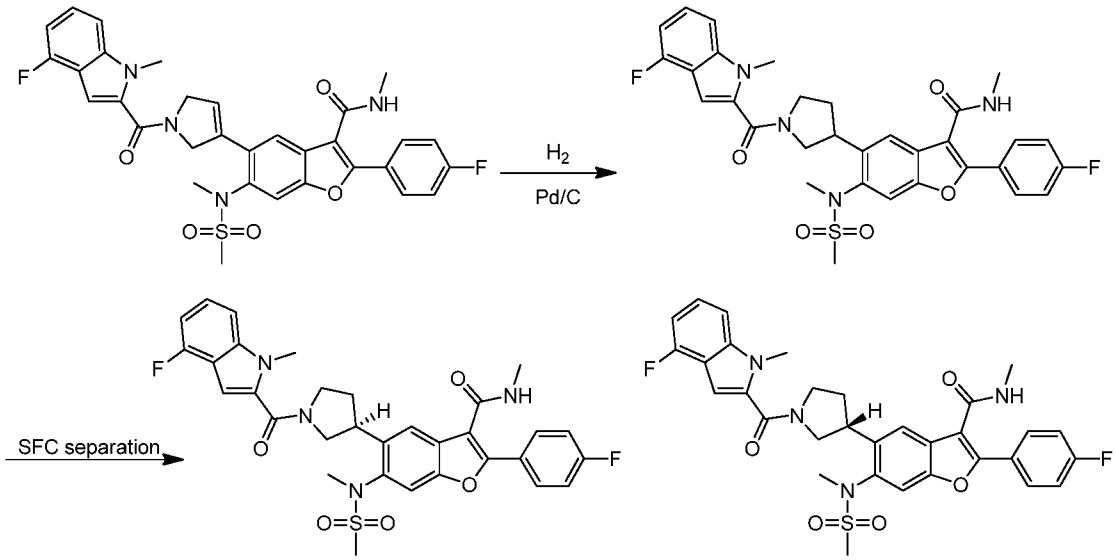
To a solution of tert-butyl 3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (100 mg, 0.18 mmol) in DCM (5 mL) was added TFA (1 mL) under N_2 protection at 0°C. The mixture was stirred at room temperature for 2 h. After being concentrated, the residue was purified by prep-HPLC to give the product of 5-(2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (50 mg, yield: 62%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.87~7.92 (m, 2H), 7.76 (s, 1H), 7.51 (s, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 5.82 (brs, 1H), 4.17 (s, 2H), 3.96 (s, 2H), 3.25 (s, 3H), 2.98~3.00 (m, 6H). MS $(M+H)^+$: 444.

Step 3 - Synthesis of 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



To a solution of 5-(2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (70 mg, 0.16 mmol), 4-fluoro-1-methyl-1H-indole-2-carboxylic acid (30.5 mg, 0.16 mmol) in THF (5 mL) was added Et_3N (48 mg, 0.47 mmol) and T_3P (152 mg, 0.24 mmol) at 0°C under nitrogen. After being stirred at 0°C for 30 minutes and RT overnight, the reaction mixture was quenched with H_2O, extracted with EA, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by prep-HPLC to give 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (34 mg, yield: 35%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.75~7.84 (m, 3H), 7.43~7.48 (m, 1H), 7.08~7.19 (m, 4H), 6.87~6.92 (m, 1H), 6.70~6.76 (m, 1H), 6.22~6.24 (m, 1H), 5.72~5.78 (m, 1H), 4.89 (brs, 2H), 4.63~4.68 (m, 2H), 3.93 (s, 3H), 3.22~3.27 (m, 3H), 2.90~2.97 (m, 6H). MS $(M+H)^+$: 619.

Step 4 - Synthesis of (R) 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide and (S) 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

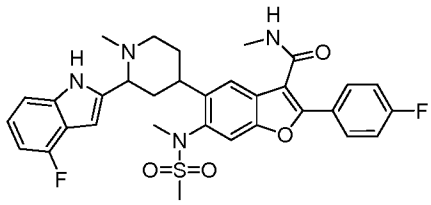


To a degassed solution of 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido) benzofuran-3-carboxamide (150 mg, 0.24 mmol) in EtOH (20 mL) was added Pd/C (30 mg) under N_2, then the mixture was stirred at RT under H_2 balloon for 10 hours. The reaction mixture was filtrated and the filtrate was concentrated. The residue was purified by SFC to give two single enantiomers.

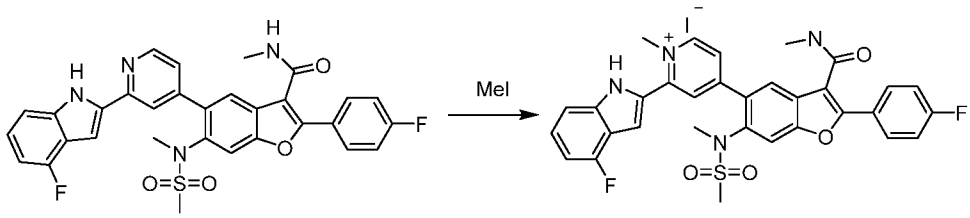
Exanple 14 (enantiomer 1, peak 1 on SFC, OD-H_3UM_3_5_40_4ML_3MIN, HPLC_RT= 1.879 min) (50 mg, yield: 34 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.82~7.88 (m, 2H), 7.42~7.46 (m, 1H), 7.15~7.23 (m, 4H), 6.75~6.89 (m, 2H), 5.80~5.82 (m, 1H), 3.81~4.15 (m, 9H), 3.33~3.37 (m, 2H), 2.96~3.05 (m, 6H), 2.46~2.71 (m, 2H). MS $(M+H)^+$: 621.

Example 15 (enantiomer 2, peak 2 on SFC, OD-H_3UM_3_5_40_4ML_3MIN, HPLC_RT= 2.164 min) (50 mg, yield: 34 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.82~7.88 (m, 2H), 7.42~7.46 (m, 1H), 7.15~7.23 (m, 4H), 6.75~6.89 (m, 2H), 5.80~5.82 (m, 1H), 3.81~4.15 (m, 9H), 3.33~3.37 (m, 2H), 2.96~3.05 (m, 6H), 2.46~2.71 (m, 2H). MS $(M+H)^+$: 621.

Example 16: 5-(2-(4-fluoro-1H-indol-2-yl)-1-methylpiperidin-4-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

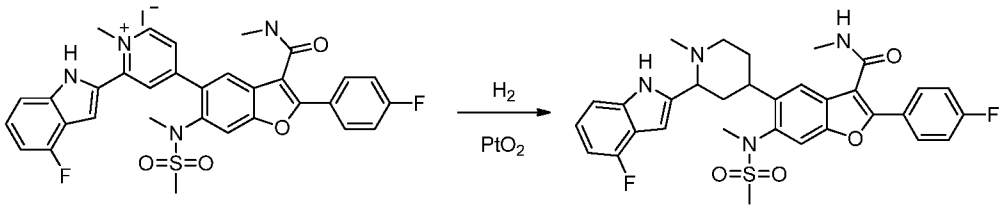


Step 1 - Synthesis of 2-(4-fluoro-1H-indol-2-yl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyridinium iodide



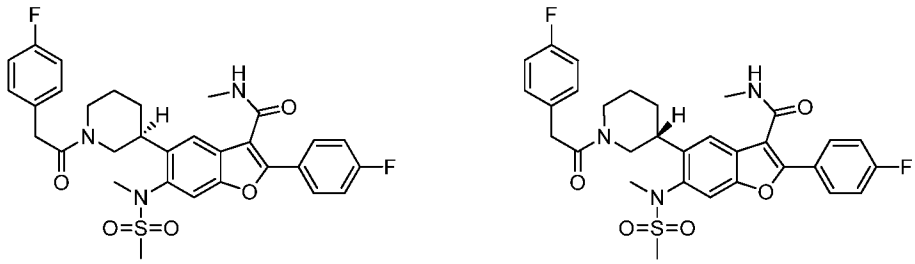
A mixture of 5-(2-(4-fluoro-1H-indol-2-yl)pyridin-4-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (100 mg, 0.17 mmol, prepared from 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-carboxamide according to previous patent) and CH_3I (50 mg, 0.35 mmol) in DMF (2 mL) was stirred at 80°C overnight. The mixture was concentrated to afford a crude product of 2-(4-fluoro-1H-indol-2-yl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyridinium iodide (110 mg, yield: 89 %), which was used in the next step without further purification. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 12.47 (br s, 1H), 9.14 (d, J = 6.4 Hz, 1H), 8.55 (d, J = 4.0 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.91~7.98 (m, 3H), 7.39-7.48 (m, 4H), 7.26~7.35 (m, 1H), 6.95 (t, J = 9.2 Hz, 1H), 4.51 (s, 3H), 3.08 (br s, 3H), 2.87 (s, 3H), 2.82 (d, J = 4.0 Hz, 3H). MS $(M+H)^+$: 601.

Step 2 - Synthesis of 5-(2-(4-fluoro-1H-indol-2-yl)-1-methylpiperidin-4-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



A mixture of 2-(4-fluoro-1H-indol-2-yl)-4-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)-1-methylpyridinium iodide (50 mg, 0.07 mmol) and PtO_2 (30 mg) in CH_3OH (10 mL) was stirred at 50°C for 2 days under H_2 (50 Psi). The mixture was filtered through Celite and concentrated, and the residue was purified by prep-TLC (DCM : MeOH = 10 : 1) to give 5-(2-(4-fluoro-1H-indol-2-yl)-1-methylpiperidin-4-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (20 mg, yield: 48 %). ^{1}H-NMR (MeOD, 400 MHz) δ 7.93 (dd, *J* = 7.6, 5.5 Hz, 2H), 7.77~7.86 (m, 2H), 7.22~7.32 (m, 3H), 7.10~7.18 (m, 1H), 6.84 (s, 1H), 6.70~6.79 (m, 1H), 4.50~4.68 (m, 1H), 3.76~3.93 (m, 2H), 3.41~3.56 (m, 1H), 3.35 (d, *J* = 17.6 Hz, 3H), 3.11 (d, *J* = 10.8 Hz, 3H), 3.00 (s, 3H), 2.74 (s, 3H), 2.12~2.70 (m, 4H). MS $(M+H)^+$: 607.

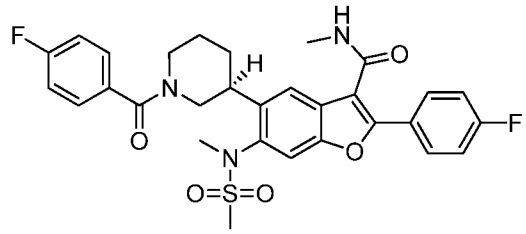
Examples 17 and 18: 2-(4-fluorophenyl)-5-(1-(2-(4-fluorophenyl)acetyl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

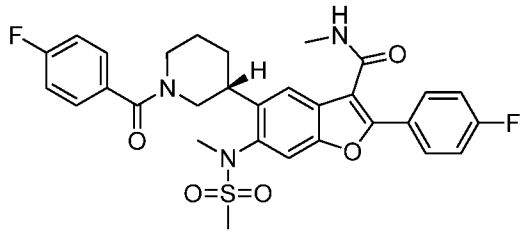


Synthesis of 2-(4-fluorophenyl)-5-(1-(2-(4-fluorophenyl)acetyl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.202 mmol), 4-fluorophenylacetic acid (62.2 mg, 0.403 mmol), DMAP (1.232 mg, 10.08 μmol), N,N-diisopropylethylamine (130 mg, 1.008 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (62.6 mg, 0.403 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a AD-H, 2x25 cm, 35% MeOH/CO_2 to afford Example 17 (Enantiomer 1, peak 1 on SFC, HPLC_RT=3.43 min) as white solid 30 mg (50%) (LC-MS (ES, m/z) $C_{31}H_{31}F_2N_3O_5S$: 595; Found: 596 $[M+H]^+$) and Example 18 (Enantiomer 2, peak 2 on SFC, HPLC_RT=5.05 min) as white solid 33 mg (55%) (LC-MS (ES, m/z) $C_{31}H_{31}F_2N_3O_5S$: 595; Found: 596 $[M+H]^+$).

Examples 19 and 20: 5-(1-(4-fluorobenzoyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

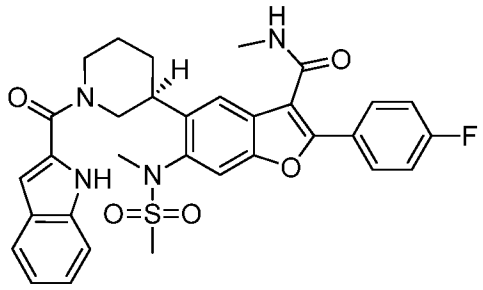
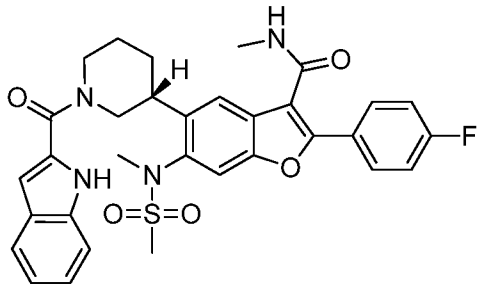




Synthesis of 5-(1-(4-fluorobenzoyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Enantiomer 1) and (S)-5-(1-(4-fluorobenzoyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (Enantiomer 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.202 mmol), 4-fluorobenzoic acid (56.5 mg, 0.403 mmol), DMAP (1.232 mg, 10.08 μmol), N,N-diisopropylethylamine (130 mg, 1.008 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (62.6 mg, 0.403 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 3x25 cm, 40% EtOH(0.1%$NH_3.H_2O$)/CO_2 to afford Example 19 (Enantiomer 1, peak 1 on SFC, HPLC_RT=2.26 min) as white solid 36 mg (59%) (LC-MS (ES, m/z) $C_{30}H_{29}F_2N_3O_5S$: 581; Found: 582 $[M+H]^+$) and Example 20 (Enantiomer 2, peak 2 on SFC, HPLC_RT=2.73 min) as white solid 38 mg (62.2%) (LC-MS (ES, m/z) $C_{30}H_{29}F_2N_3O_5S$: 581; Found: 582 $[M+H]^+$)

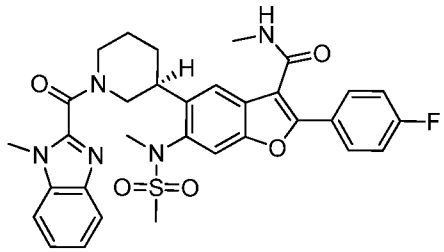
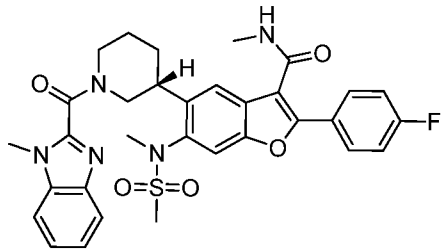
Example 21 and 22: 5-(1-(1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enatiomers 1 and 2)

Synthesis of 5-(1-(1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.202 mmol), 1H-indole-2-carboxylic acid (65 mg, 0.403 mmol), DMAP (1.232 mg, 10.08 μmol), N,N-diisopropylethylamine (130 mg, 1.008 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (62.6 mg, 0.403 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 3x25 cm, 40% MeOH(0.1%$NH_3.H_2O$)/CO_2 to afford Example 21 (Enantiomer 1, peak 1 on SFC, HPLC_RT=4.15 min) as white solid 41 mg (67.3%) (LC-MS (ES, m/z) $C_{32}H_{31}FN_4O_5S$: 602; Found: 603 $[M+H]^+$) and Example 22 (Enantiomer 2, peak 2 on SFC, HPLC_RT=5.49 min) as white solid 38 mg (62.4%) (LC-MS (ES, m/z) $C_{32}H_{31}FN_4O_5S$: 602; Found: 603 $[M+H]^+$).

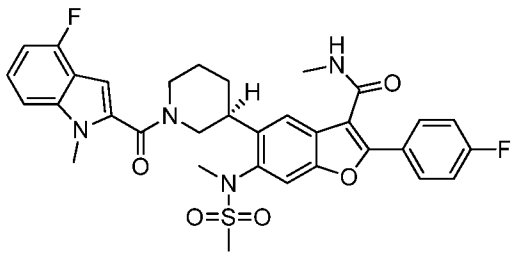
Examples 23 and 24: 2-(4-fluorophenyl)-N-methyl-5-(1-(1-methyl-1H-benzo[d]imidazole-2-carbonyl)piperidin-3-yl)-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

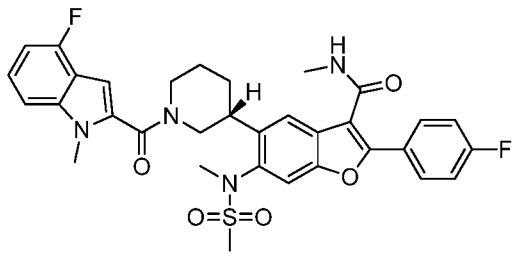



Synthesis of 2-(4-fluorophenyl)-N-methyl-5-(1-(1-methyl-1H-benzo[d]imidazole-2-carbonyl)piperidin-3-yl)-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.161 mmol), 1-methyl-1H-benzo[d]imidazole-2-carboxylic acid (56.8 mg, 0.323 mmol), DMAP (0.985 mg, 8.06 μmol), N,N-diisopropylethylamine (104 mg, 0.806 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (50.1 mg, 0.323 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 4.6x25 cm, 5-40% MeOH(0.05%DEA)/CO_2 to afford Example 23 (Enantiomer 1, peak 1 on SFC, HPLC_RT=8.39 min) as white solid 65 mg (96%) (LC-MS (ES, m/z) $C_{33}H_{32}F_2N_4O_5S$: 634; Found: 635 $[M+H]^+$) and Example 24 (Enantiomer 2, peak 2 on SFC, HPLC_RT=9.32 min) as white solid 60 mg (93.8%) (LC-MS (ES, m/z) $C_{33}H_{32}F_2N_4O_5S$: 634; Found: 635 $[M+H]^+$).

Examples 25 and 26: 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)



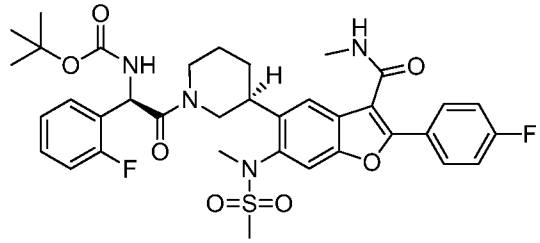


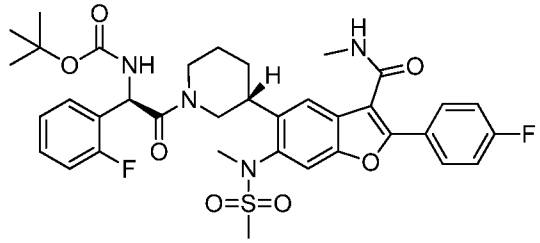
Synthesis of 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 1) and 5-(1-(4-fluoro-1-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.202 mmol), 4-fluoro-1-methyl-1H-indole-2-crboxylic acid (67.8 mg, 0.403 mmol), DMAP (1.232 mg, 10.08 μmol), N,N-diisopropylethylamine (130 mg, 1.008 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (62.6 mg, 0.403 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 3x25 cm, 40% MeOH(0.1%$NH_3.H_2O$)/CO_2 to afford Example 25 (Enantiomer 1, peak 1 on SFC, HPLC_RT=4.15

min) as white solid 41 mg (67.3%) (LC-MS (ES, m/z) $C_{32}H_{31}FN_4O_5S$: 602; Found: 603 $[M+H]^+$) and Example 26 (Enantiomer 2, peak 2 on SFC, HPLC_RT=5.49 min) as white solid 38 mg (62.4%) (LC-MS (ES, m/z) $C_{32}H_{31}FN_4O_5S$: 602; Found: 603 $[M+H]^+$).

Examples 27 and 28: tert-butyl ((1R)-1-(2-fluorophenyl)-2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (diastereomers 1 and 2)

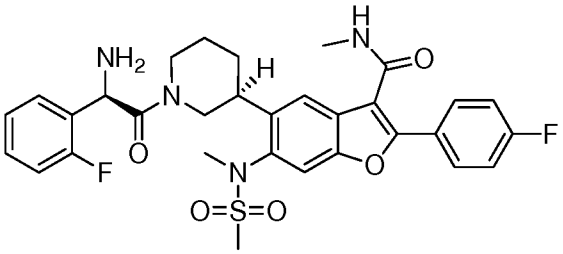


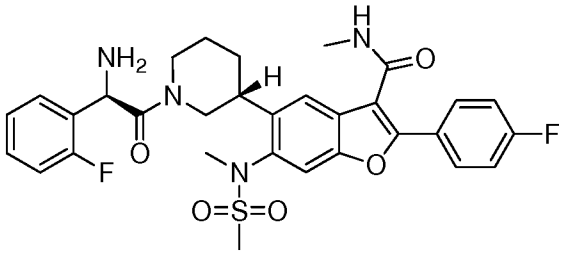


Synthesis of tert-butyl ((1R)-1-(2-fluorophenyl)-2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (diastereomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (110 mg, 0.222 mmol), (R)-2-((tert-butoxycarbonyl)amino)-2-(2-fluorophenyl)acetic acid (119 mg, 0.444 mmol), DMAP (1.355 mg, 0.011 mmol), N,N-diisopropylethylamine (143 mg, 1.109 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (68.9 mg, 0.444 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 3x25 cm, 25% EtOH(0.1%$NH_3.H_2O$)/CO_2 to afford Example 27 (Diasteromer 1, peak 1 on SFC, HPLC_RT=7.16 min) as white solid 31.5 mg (40%) (LC-MS (ES, m/z) $C_{36}H_{40}F_2N_4O_7S$: 710; Found: 711 $[M+H]^+$) and Example 28 (Diasteromer 2, peak 2 on SFC, HPLC_RT=7.84 min) as white solid 47.2 mg (60%) (LC-MS (ES, m/z) $C_{36}H_{40}F_2N_4O_7S$: 710; Found: 711 $[M+H]^+$)

Examples 29 and 30: 5-(1-((R)-2-amino-2-(2-fluorophenyl)acetyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (diastereomers 1 and 2)

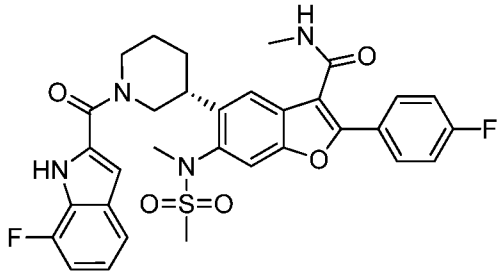




Synthesis of 5-(1-((R)-2-amino-2-(2-fluorophenyl)acetyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (diastereomers 1 and 2)

A mixture of tert-butyl ((1R)-1-(2-fluorophenyl)-2-(3-(2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-(N-methylmethylsulfonamido)benzofuran-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (130 mg, 0.183 mmol), and hydrochloric acid (0.457 ml, 1.829 mmol) in 1,4-Dioxane (0.5 ml) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak OD, 4.6x25 cm, 30% (3:1 MeOH/MeCN+0.2%DEA)/CO_2 to afford Example 29 (Diasteromer 1, peak 1 on SFC, HPLC_RT=3.99 min) as white solid 28 mg (56%) (LC-MS (ES, m/z) $C_{31}H_{32}F_2N_4O_5S$: 610; Found: 611 $[M+H]^+$) and Example 30 (Diasteromer 2, peak 2 on SFC, HPLC_RT=4.64 min) as white solid 28 mg (56%) (LC-MS (ES, m/z) $C_{31}H_{32}F_2N_4O_5S$: 610; Found: 611 $[M+H]^+$)

Example 31: (R)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

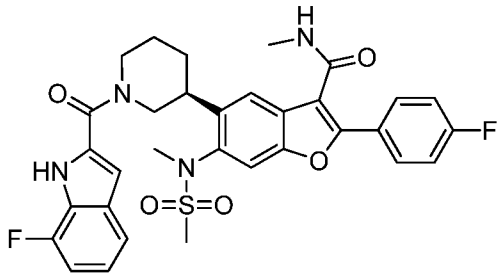


31

Synthesis of (R)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

To a solution of 7-fluoro-1H-indole-2-carboxylic acid (78 mg, 0.435 mmol), (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.218 mmol) in DCM (1 ml) was added N,N-diisopropylethylamine (169 mg, 1.306 mmol), and the reaction mixture stirred for 5 min at RT. Then 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (415 mg, 0.653 mmol) was added to the reaction mixture and stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-30% MeOH/EtOAc. This resulted in 68 mg (50.3%) of (R)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{32}H_{30}F_2N_4O_5S$: 620; Found: 621 $[M+H]^+$.

Example 32: (S)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



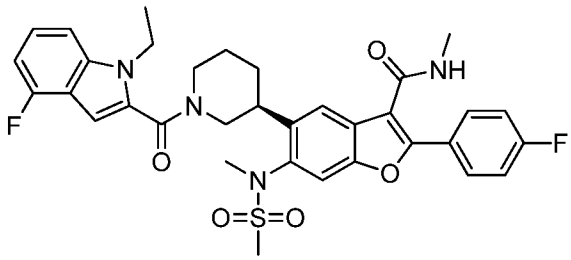
32

Synthesis of (S)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

To a solution of 7-fluoro-1H-indole-2-carboxylic acid (78 mg, 0.435 mmol), (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.218 mmol) in DCM (1 ml) was added N,N-diisopropylethylamine (169 mg, 1.306 mmol), and the reaction mixture stirred for 5 min at RT. Then 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (415 mg, 0.653 mmol) was added to the reaction mixture and stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-30% MeOH/EtOAc. This resulted in 78 mg (58%) of (S)-5-(1-(7-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-

(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{32}H_{30}F_2N_4O_5S$: 620; Found: 621 $[M+H]^+$.

Example 33: (S)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

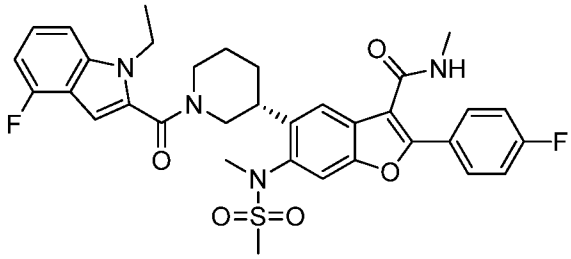


33

Synthesis of (S)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (60 mg, 0.131 mmol), 1-ethyl-4-fluoro-1H-indole-2-carboxylic acid (54.1 mg, 0.261 mmol), DMAP (0.798 mg, 6.53 μmol), N,N-diisopropylethylamine (84 mg, 0.653 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (40.5 mg, 0.261 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-10% MeOH/EtOAc. This resulted in 46 mg (54.3%) of (S)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{34}H_{34}F_2N_4O_5S$: 648; Found: 649 $[M+H]^+$.

Example 34: (R)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

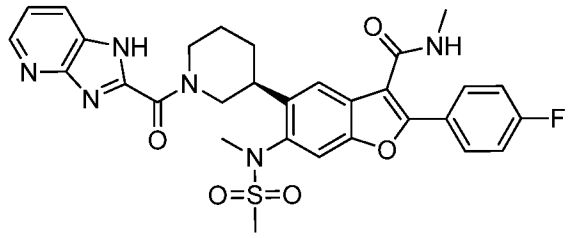


34

Synthesis of (R)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (60 mg, 0.131 mmol), 1-ethyl-4-fluoro-1H-indole-2-carboxylic acid (54.1 mg, 0.261 mmol), DMAP (0.798 mg, 6.53 μmol), N,N-diisopropylethylamine (84 mg, 0.653 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (40.5 mg, 0.261 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-10% MeOH/EtOAc. This resulted in 38 mg (44.9%) of (R)-5-(1-(1-ethyl-4-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{34}H_{34}F_2N_4O_5S$: 648; Found: 649 $[M+H]^+$.

Example 35: (S)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



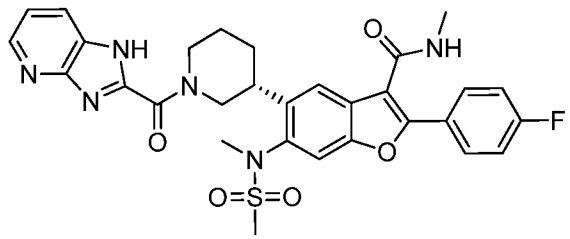
35

Synthesis of (S)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (70 mg, 0.152 mmol), 1H-imidazo[4,5-b]pyridine-2-

carboxylic acid (49.7 mg, 0.305 mmol), DMAP (0.93 mg, 7.62 μmol), N,N-diisopropylethylamine (98 mg, 0.762 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (47.3 mg, 0.305 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-10% MeOH/EtOAc. This resulted in 45 mg (48.9%) of (S)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{30}H_{29}FN_6O_5S$: 604; Found: 605 $[M+H]^+$.

Example 36: (R)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

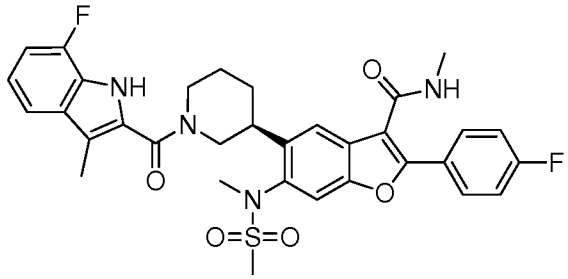


36

Synthesis of (R)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (70 mg, 0.152 mmol), 1H-imidazo[4,5-b]pyridine-2-carboxylic acid (49.7 mg, 0.305 mmol), DMAP (0.93 mg, 7.62 μmol), N,N-diisopropylethylamine (98 mg, 0.762 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (47.3 mg, 0.305 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-10% MeOH/EtOAc. This resulted in 58 mg (63%) of (R)-5-(1-(1H-imidazo[4,5-b]pyridine-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{30}H_{29}FN_6O_5S$: 604; Found: 605 $[M+H]^+$.

Example 37: Synthesis of (S)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

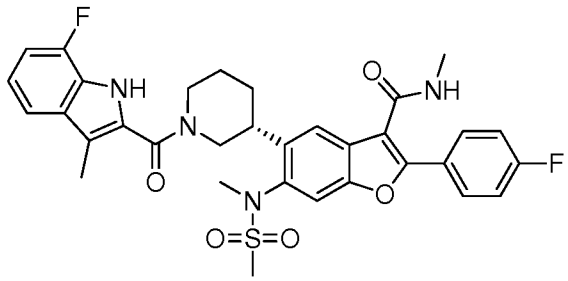


37

Synthesis of (S)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (75 mg, 0.163 mmol), 7-fluoro-3-methyl-1H-indole-2-carboxylic acid (63.1 mg, 0.326 mmol), DMAP (0.997 mg, 8.16 μmol), N,N-diisopropylethylamine (105 mg, 0.816 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (50.7 mg, 0.326 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-12% MeOH/EtOAc. This resulted in 58 mg (56%) of (S)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{33}H_{32}F_2N_4O_5S$: 634; Found: 635 $[M+H]^+$.

Example 38: (R)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

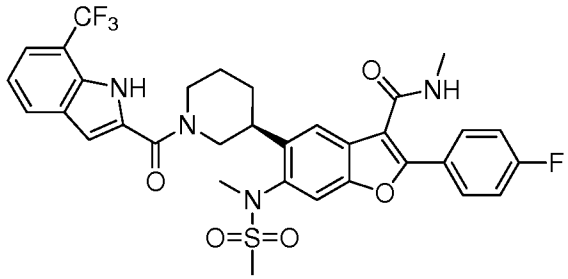


38

Synthesis of (R)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (75 mg, 0.163 mmol), 7-fluoro-3-methyl-1H-indole-2-carboxylic acid (63.1 mg, 0.326 mmol), DMAP (0.997 mg, 8.16 μmol), N,N-diisopropylethylamine (105 mg, 0.816 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (50.7 mg, 0.326 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-12% MeOH/EtOAc. This resulted in 58 mg (56%) of (R)-5-(1-(7-fluoro-3-methyl-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{33}H_{32}F_2N_4O_5S$: 634; Found: 635 $[M+H]^+$.

Example 39: (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide

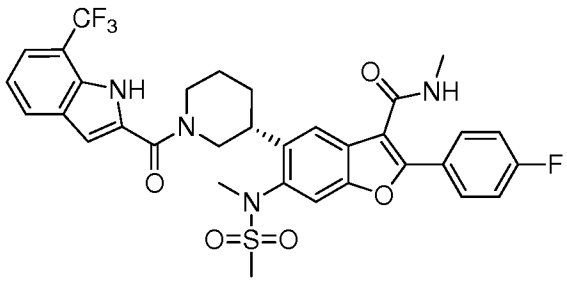


39

Synthesis of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide

A mixture of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (75 mg, 0.163 mmol), 7-(trifluoromethyl)-1H-indole-2-carboxylic acid (74.8 mg, 0.326 mmol), DMAP (0.997 mg, 8.16 μmol), N,N-diisopropylethylamine (105 mg, 0.816 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (50.7 mg, 0.326 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-100% EtOAc/Hexane. This resulted in 78 mg (71.3%) of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{33}H_{30}F_4N_4O_5S$: 670; Found: 671$[M+H]^+$.

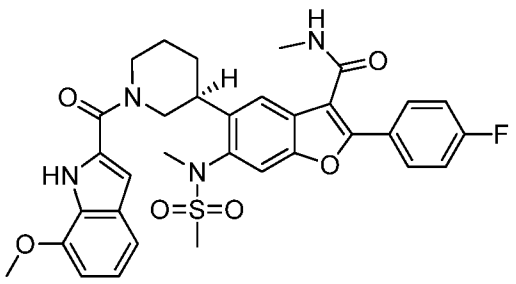
Example 40: (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide

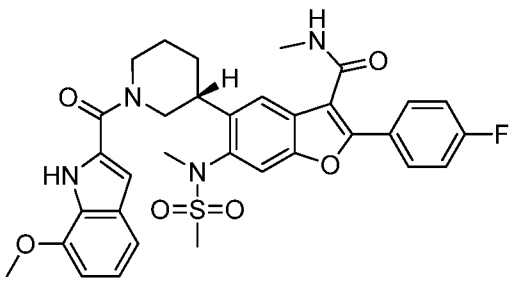


Synthesis of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide

A mixture of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3 yl)benzofuran-3-carboxamide (75 mg, 0.163 mmol), 7-(trifluoromethyl)-1H-indole-2-carboxylic acid (74.8 mg, 0.326 mmol), DMAP (0.997 mg, 8.16 μmol), N,N-diisopropylethylamine (105 mg, 0.816 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (50.7 mg, 0.326 mmol) in DCM (2 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated under vacuum, then applied onto a silica gel column and eluted with 0-100% EtOAc/Hexane. This resulted in 88 mg (80%) of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(7-(trifluoromethyl)-1H-indole-2-carbonyl)piperidin-3-yl)benzofuran-3-carboxamide as white solid. LC-MS (ES, m/z) $C_{33}H_{30}F_4N_4O_5S$: 670; Found: 671$[M+H]^+$.

Examples 41 and 42: 2-(4-fluorophenyl)-5-(1-(7-methoxy-1H-indole-2-carbonyl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

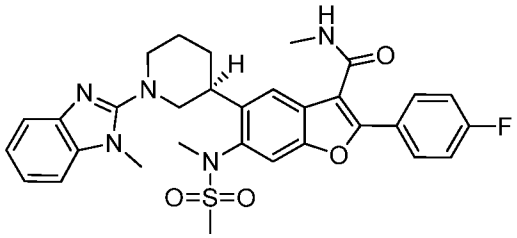


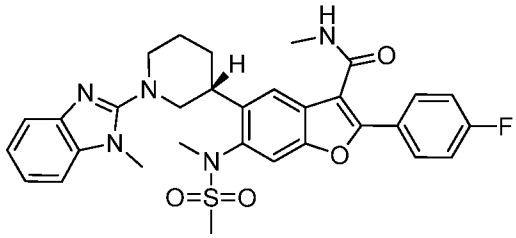


Synthesis of (R)-2-(4-fluorophenyl)-5-(1-(7-methoxy-1H-indole-2-carbonyl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide and (S)-2-(4-fluorophenyl)-5-(1-(7-methoxy-1H-indole-2-carbonyl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (100 mg, 0.218 mmol), 7-methoxy-1H-indole-2-carboxylic acid (83 mg, 0.435 mmol), DMAP (1.329 mg, 10.88 μmol), N,N-diisopropylethylamine (141 mg, 1.088 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (67.6 mg, 0.435 mmol) in DCM (5 mL) was stirred at RT overnight under N_2 protection. The reaction mixture was concentrated and separated by SFC on a ChiralPak AS-H, 3x25 cm, 40% MeOH (0.1%$NH_3.H_2O$) / CO_2 to afford Example 41 (Enantiomer 1, peak 1 on SFC, HPLC_RT=3.52 min) as white solid 24 mg (35%) (LC-MS (ES, m/z) $C_{33}H_{33}FN_4O_6S$: 632; Found: 633 $[M+H]^+$) and Example 42 (Enantiomer 2, peak 2 on SFC, HPLC_RT=6.21 min) as white solid 26 mg (37%) (LC-MS (ES, m/z) $C_{33}H_{33}FN_4O_6S$: 632; Found: 633 $[M+H]^+$).

Examples 43 amd 44: 2-(4-fluorophenyl)-N-methyl-5-(1-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide



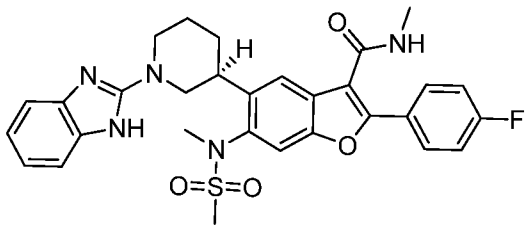


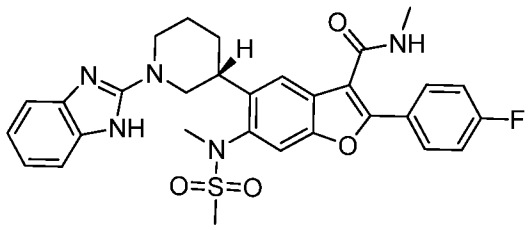
Synthesis of 2-(4-fluorophenyl)-N-methyl-5-(1-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.174 mmol), 2-chloro-1-methyl-1H-benzo[d]imidazole (58 mg, 0.348 mmol) and triethylamine (106 mg, 1.045 mmol) in DMF (1 ml) was heated to 170°C for 10 min. The reaction mixture was cooled to RT and partitioned between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-H, 4.6x25 cm, 5-40% EtOH(0.05%DEA)/CO_2

to afford Example 43 (Enantiomer 1, peak 1 on SFC, HPLC_RT=8.28 min) as white solid 12.3 mg (24%) (LC-MS (ES, m/z) $C_{31}H_{32}FN_5O_4S$: 589; Found: 590 $[M+H]^+$) and Example 44 (Enantiomer 2, peak 2 on SFC, HPLC_RT=9.13 min) as white solid 14.3 mg (27%) (LC-MS (ES, m/z) $C_{31}H_{32}FN_5O_4S$: 589; Found: 590 $[M+H]^+$).

Examples 45 and 46: 5-(1-(1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

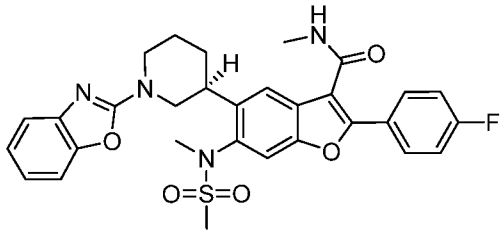


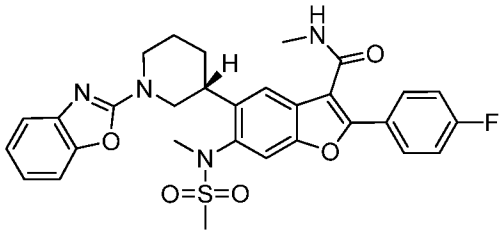


Synthesis of 5-(1-(1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.174 mmol), 2-chloro-1H-benzo[d]imidazole (34.5 mg, 0.226 mmol) and triethylamine (90 mg, 0.696 mmol) in DMF (1 ml) was heated to 170°C for 40 min. The reaction mixture was cooled to RT and partitioned between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-3, 4.6x15 cm, 40% EtOH(0.05%DEA)/CO_2 to afford Example 45 (Enantiomer 1, peak 1 on SFC, HPLC_RT=1.89 min) as white solid 30 mg (60%) (LC-MS (ES, m/z) $C_{30}H_{30}FN_5O_4S$: 575; Found: 576 $[M+H]^+$) and Example 46 (Enantiomer 2, peak 2 on SFC, HPLC_RT=2.68 min) as white solid 31 mg (62%) (LC-MS (ES, m/z) $C_{30}H_{30}FN_5O_4S$: 575; Found: 576 $[M+H]^+$).

Examples 47 and 48: 5-(1-(benzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

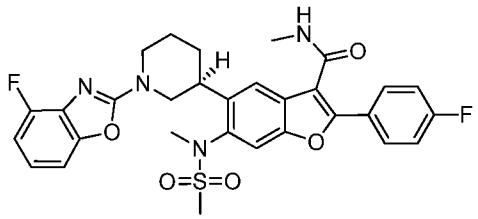


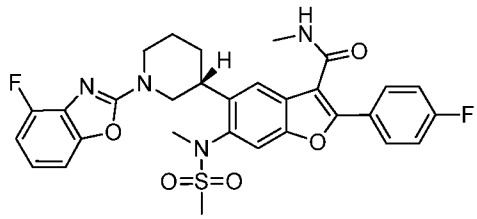


Synthesis of 5-(1-(benzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.174 mmol), 2-chlorobenzo[d]oxazole (34.8 mg, 0.226 mmol) and potassium carbonate (72.2 mg, 0.522 mmol) in DMF (1 ml) was heated to 60°C overnight under N_2 protection. The reaction mixture was cooled to RT and partitioned between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-H, 4.6x25 cm, 5-40% EtOH (0.05%DEA) / CO_2 to afford Example 47 (Enantiomer 1, peak 1 on SFC, HPLC_RT=8.68 min) as white solid 38 mg (76%) (LC-MS (ES, m/z) $C_{30}H_{29}FN_4O_5S$: 576; Found: 577 $[M+H]^+$) and Example 48 (Enantiomer 2, peak 2 on SFC, HPLC_RT=11.12 min) as white solid 30 mg (60%) (LC-MS (ES, m/z) $C_{30}H_{29}FN_4O_5S$: 576; Found: 577 $[M+H]^+$).

Examples 49 and 50



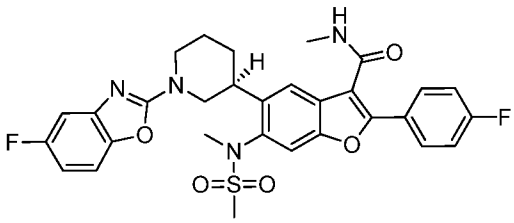


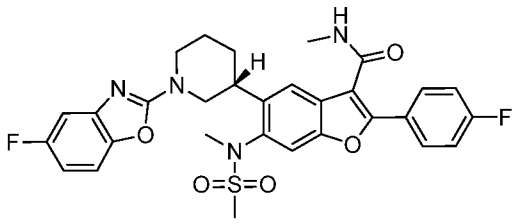
Synthesis of 5-(1-(4-fluorobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.174 mmol), 2-chloro-4-fluorobenzo[d]oxazole (38.8 mg, 0.226 mmol) and potassium carbonate (72.2 mg, 0.522 mmol) in DMF (1 ml) was heated to 60°C overnight under N_2 protection. The reaction mixture was cooled to RT and partitioned

between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-H, 4.6x25 cm, 35% EtOH (0.1%NH_3·H_2O) / CO_2 to afford Example 49 (Enantiomer 1, peak 1 on SFC, HPLC_RT=2.68 min) as white solid 42 mg (81%) (LC-MS (ES, m/z) $C_{30}H_{28}F_2N_4O_5S$: 594; Found: 595 $[M+H]^+$) and Example 50 (Enantiomer 2, peak 2 on SFC, HPLC_RT=3.37 min) as white solid 38 mg (73%) (LC-MS (ES, m/z) $C_{30}H_{28}F_2N_4O_5S$: 594; Found: 595 $[M+H]^+$).

Examples 51 and 52:

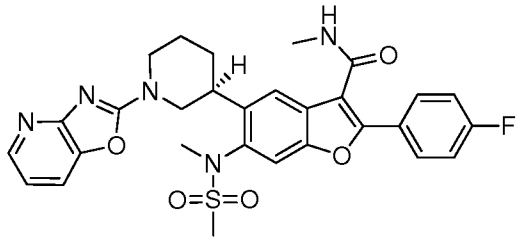


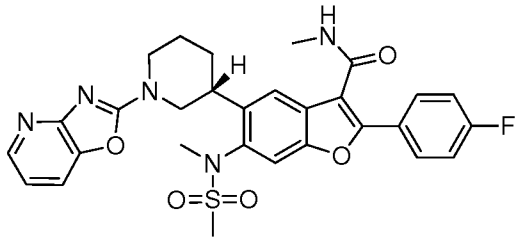


Synthesis of 5-(1-(5-fluorobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 1) and (S)-5-(1-(5-fluorobenzo[d]oxazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomer 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (120 mg, 0.261 mmol), 2-chloro-5-fluorobenzo[d]oxazole (58.2 mg, 0.339 mmol) and potassium carbonate (108 mg, 0.783 mmol) in DMF (1 ml) was heated to 60°C overnight under N_2 protection. The reaction mixture was cooled to RT and partitioned between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-H, 3x25 cm, 45% EtOH(0.1%NH_3.H_2O)/CO_2 to afford Example 51 (Enantiomer 1, peak 1 on SFC, HPLC_RT=2.54 min) as white solid 23 mg (29.6%) (LC-MS (ES, m/z) $C_{30}H_{28}F_2N_4O_5S$: 594; Found: 595 $[M+H]^+$) and Example 52 (Enantiomer 2, peak 2 on SFC, HPLC_RT=3.93 min) as white solid 31 mg (40%) (LC-MS (ES, m/z) $C_{30}H_{28}F_2N_4O_5S$: 594; Found: 595 $[M+H]^+$).

Examples 53 and 54: 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(oxazolo[4,5-b]pyridin-2-yl)piperidin-3-yl)benzofuran-3-carboxamide (enantiomers 1 and 2)

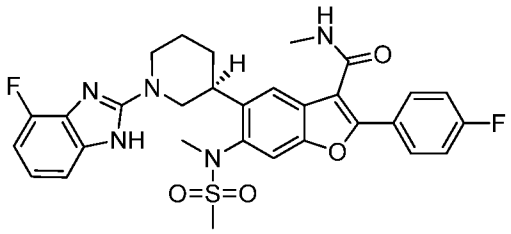


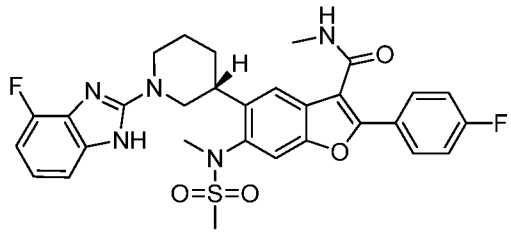


Synthesis of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(1-(oxazolo[4,5-b]pyridin-2-yl)piperidin-3-yl)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (120 mg, 0.261 mmol), 2-chlorooxazolo[4,5-b]pyridine (60.5 mg, 0.392 mmol) and potassium carbonate (108 mg, 0.783 mmol) in DMF (1 ml) was heated to 60°C overnight under N_2 protection. The reaction mixture was cooled to RT and partitioned between EtOAc and water, the organic layer dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralCel OJ-H, 3x25 cm, 40% Isopropanol (0.1%$NH_3.H_2O$)/CO_2 to afford Example 53 (Enantiomer 1, peak 1 on SFC, HPLC_RT=3.37 min) as white solid 22 mg (29.3%) (LC-MS (ES, m/z) $C_{29}H_{28}FN_5O_5S$: 577; Found: 578 $[M^+H]^+$) and Example 54 (Enantiomer 2, peak 2 on SFC, HPLC_RT=4.19 min) as white solid 20 mg (26.7%) (LC-MS (ES, m/z) $C_{29}H_{28}FN_5O_5S$: 577; Found: 578 $[M+H]^+$).

Examples 55 and 56: 5-(1-(4-fluoro-1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)



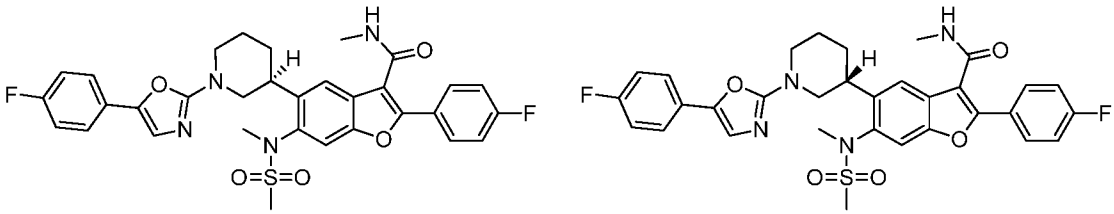


Synthesis of 5-(1-(4-fluoro-1H-benzo[d]imidazol-2-yl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (80 mg, 0.174 mmol), 2-chloro-4-fluoro-1H-benzo[d]imidazole (47.5 mg, 0.279 mmol) and triethylamine (90 mg, 0.696 mmol) in DMF (1 ml)

was heated to 170°C for 40 min. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a ChiralPark AD, 3x25 cm, 40% MeOH(0.1%$NH_3.H_2O$)/CO_2 to afford Example 55 (Enantiomer 1, peak 1 on SFC, HPLC_RT=3.91 min) as white solid 5 mg (10%) (LC-MS (ES, m/z) $C_{30}H_{29}F_2N_5O_4S$: 593; Found: 594 $[M+H]^+$) and Example 56 (Enantiomer 2, peak 2 on SFC, HPLC_RT=6.34 min) as white solid 5 mg (10%) (LC-MS (ES, m/z) $C_{30}H_{29}F_2N_5O_4S$: 593; Found: 594 $[M+H]^+$).

Examples 57 and 58: 2-(4-fluorophenyl)-5-(1-(5-(4-fluorophenyl)oxazol-2-yl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

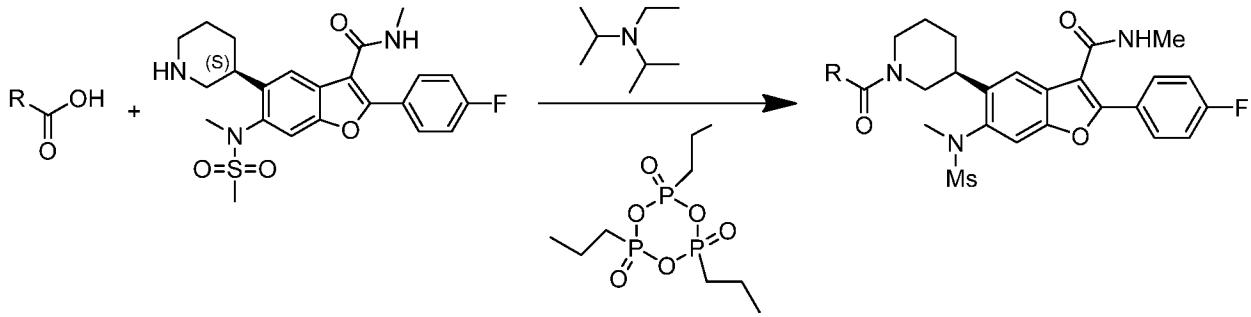


Synthesis of 2-(4-fluorophenyl)-5-(1-(5-(4-fluorophenyl)oxazol-2-yl)piperidin-3-yl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (enantiomers 1 and 2)

A mixture of 2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (120 mg, 0.261 mmol), 2-chloro-5-(4-fluorophenyl)oxazole (61.9 mg, 0.313 mmol) and DIEA (67.5 mg, 0.522 mmol) in DMF (1 ml) was heated to 160°C for 30 min. The reaction mixture was cooled to RT and partitioned between EtOAc and water The organic layer was dried in Na_2SO_4 and concentrated under vacuum. Then the reaction mixture separated by SFC on a WHELK-O1(S,S), 3x25 cm, 50% MeOH (0.1%$NH_3 H_2O$)/CO_2 to afford Example 57 (Enantiomer 1, peak 1 on SFC, HPLC_RT=9.19 min) as white solid 33 mg (40.7%) (LC-MS (ES, m/z) $C_{32}H_{30}F_2N_4O_5S$: 620; Found: 621 $[M+H]^+$) and Example 58 (Enantiomer 2, peak 2 on SFC, HPLC_RT=13.04 min) as white solid 30 mg (37%) (LC-MS (ES, m/z) $C_{32}H_{30}F_2N_4O_5S$: 620; Found: 621 $[M+H]^+$).

Examples 59-78

These examples were synthesized using library format. To individual acid (0.078 mmol) in DMF (1 ml) was added DIEA (0.027 ml) then 0.266 ml T3P solution (50% in EtOAc). The solution was then treated with a 0.025 ml solution of amine (24 mg, from a solution of 576 mg amine 4 in 0.6 ml DMF). The solution was stirred at room temp for 16 h.



The reaction was filtered into a 96 well plate and submitted to high throughput purification.

Purification method for amides:

Column: Waters Sunfire C18, 5u, 19x100 mm

50 ml/min

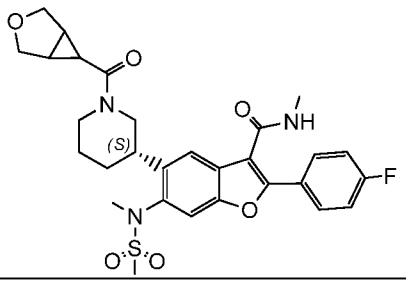
8 minute run time

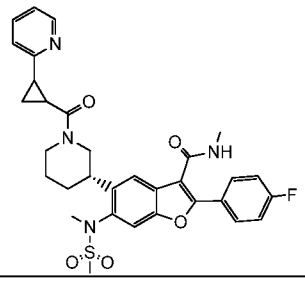
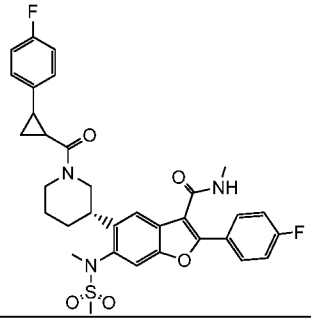
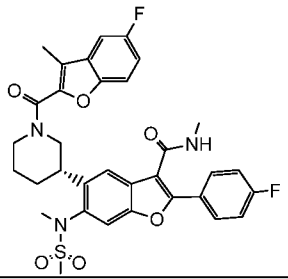
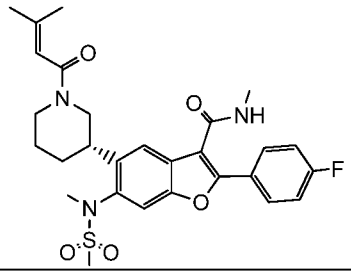
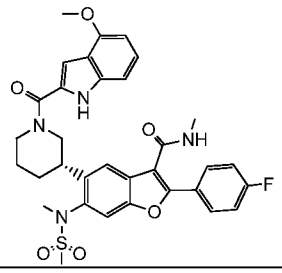
Mobile phase A = Water + .1% Formic Acid

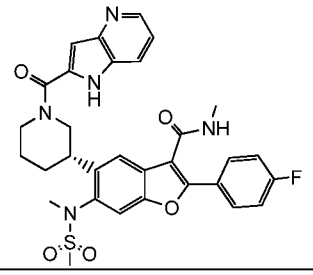
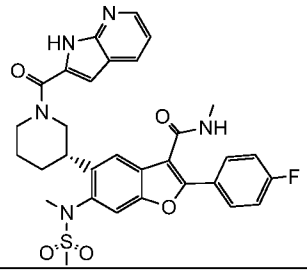
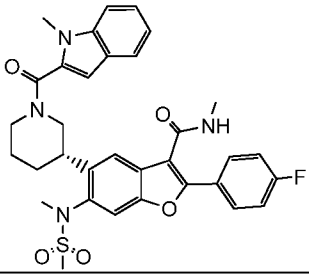
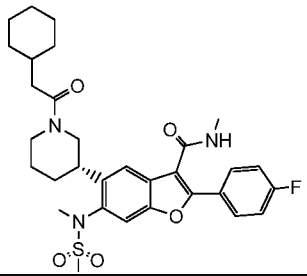
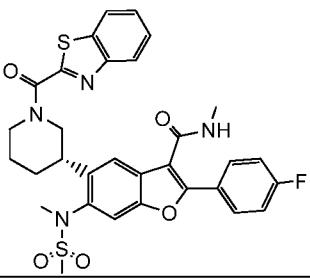
Mobile phase B = MeCN + .1% Formic Acid

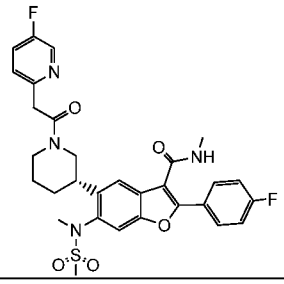
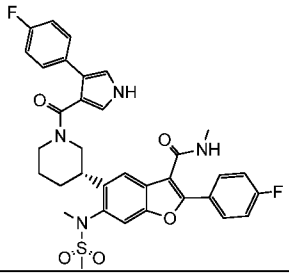
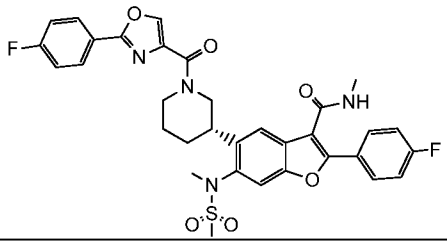
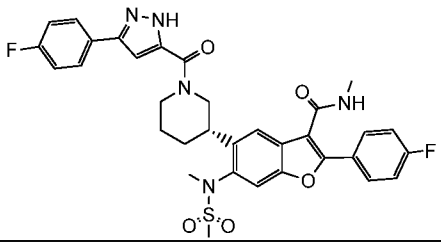
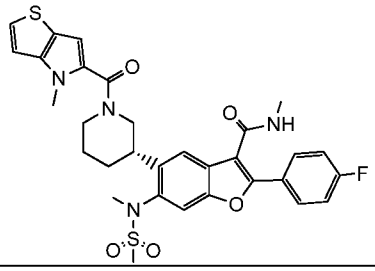
Gradient from 10 to 75% MeCN.

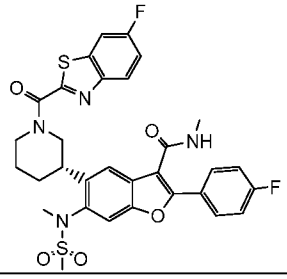
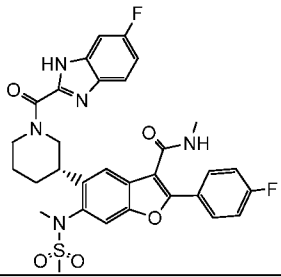
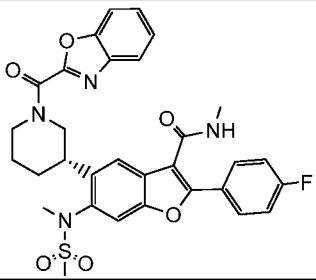
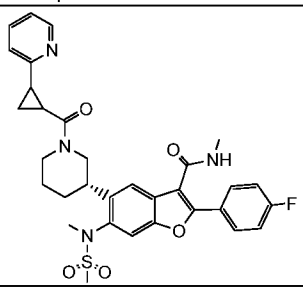
This work resulted in Examples 59 to 78.

Ex.	Product Structure	IUPAC Name	Exact Mass [M+H]+
59		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[1-(3-oxabicyclo[3.1.0]hex-6-ylcarbonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	570

60		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{1-[(2-pyridin-2-ylcyclopropyl)carbonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	605
61		2-(4-fluorophenyl)-5-(1-{[2-(4-fluorophenyl)cyclopropyl]carbonyl}piperidin-3-yl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	622
62		5-{1-[(5-fluoro-3-methyl-1-benzofuran-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	636
63		2-(4-fluorophenyl)-N-methyl-5-[1-(3-methylbut-2-enoyl)piperidin-3-yl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	542
64		2-(4-fluorophenyl)-5-{1-[(4-methoxy-1H-indol-2-yl)carbonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	633

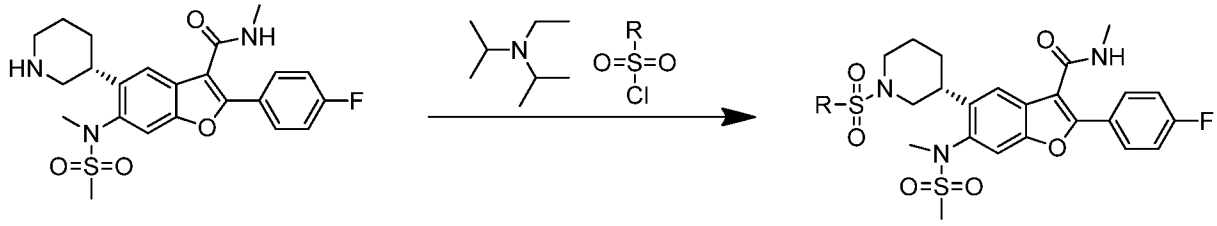
65		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[1-(1H-pyrrolo[3,2-b]pyridin-2-ylcarbonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	604
66		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[1-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	604
67		2-(4-fluorophenyl)-N-methyl-5-{1-[(1-methyl-1H-indol-2-yl)carbonyl]piperidin-3-yl}-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	617
68		5-[1-(cyclohexylacetyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	584
69		5-[1-(1,3-benzothiazol-2-ylcarbonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	621

70		2-(4-fluorophenyl)-5-{1-[(5-fluoropyridin-2-yl)acetyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	597
71		2-(4-fluorophenyl)-5-(1-{[4-(4-fluorophenyl)-1H-pyrrol-3-yl]carbonyl}piperidin-3-yl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	647
72		2-(4-fluorophenyl)-5-(1-{[2-(4-fluorophenyl)-1,3-oxazol-4-yl]carbonyl}piperidin-3-yl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	649
73		2-(4-fluorophenyl)-5-(1-{[3-(4-fluorophenyl)-1H-pyrazol-5-yl]carbonyl}piperidin-3-yl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	648
74		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{1-[(4-methyl-4H-thieno[3,2-b]pyrrol-5-yl)carbonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	623

75		5-{1-[(6-fluoro-1,3-benzothiazol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	639
76		5-{1-[(6-fluoro-1H-benzimidazol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	622
77		5-[1-(1,3-benzoxazol-2-ylcarbonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	605
78		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{1-[(2-pyridin-2-ylcyclopropyl)carbonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	605

Examples 79-84

These examples were synthesized using library format. To individual sulfonyl chlorides (0.109 mmol each) was added 1 ml MeCN solution of amine (25 mg) followed by DIEA (0.047 ml). The reactions were shaken for 16 h. Then the reactions were filtered using a filter plate to a 96 well plate, which was sealed and submitted to High Throughput Purification.



Purification method:

Waters Sunfire C18, 5u, 19x100 mm

25 ml/min

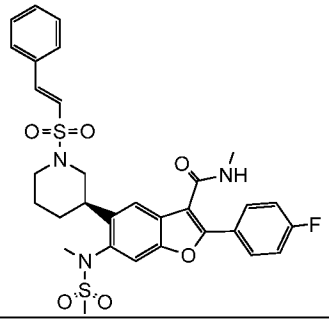
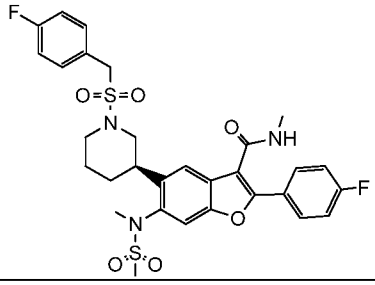
10-12 minute run time

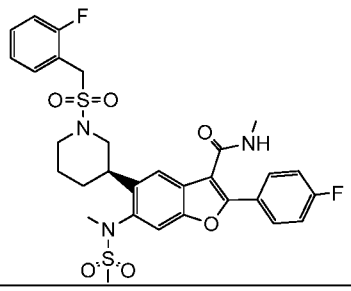
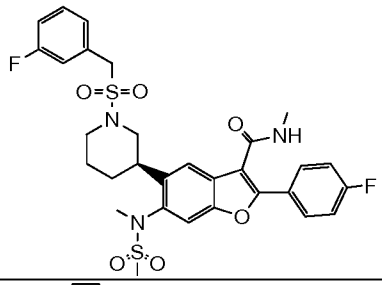
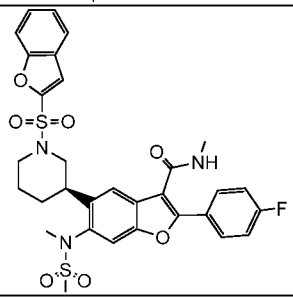
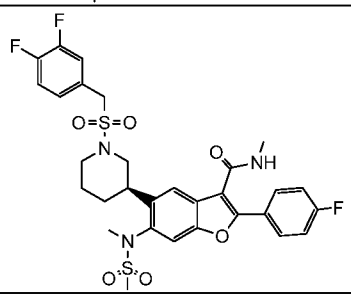
Mobile phase A = Water + .1% Formic Acid

Mobile phase B = MeCN + .1% Formic Acid

Gradient from 10 to 75% MeCN

This work resulted in Examples 79 to 84.

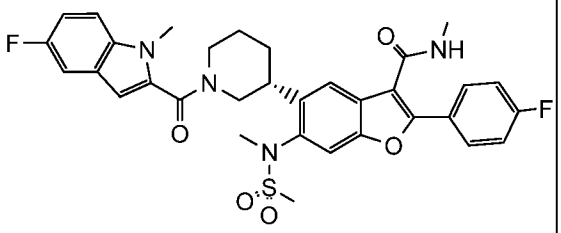
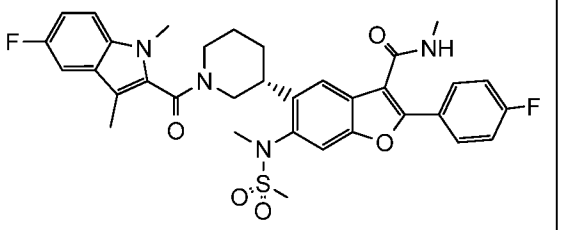
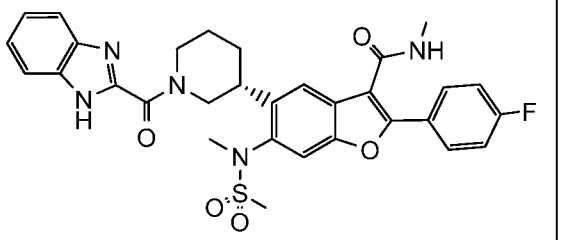
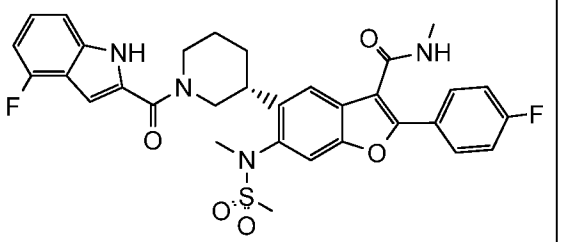
Example	Product Structure	IUPAC Name	Mass [M+H]+
79		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3R)-1-{[(E)-2-phenylethenyl]sulfonyl}piperidin-3-yl]-1-benzofuran-3-carboxamide	626
80		5-{(3R)-1-[(4-fluorobenzyl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	632

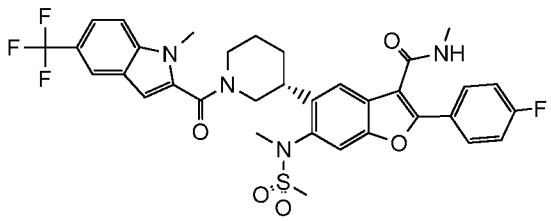
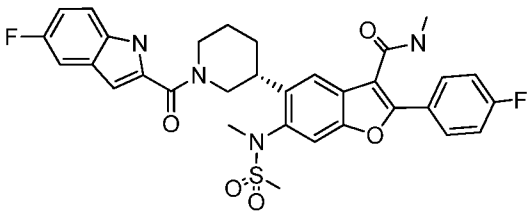
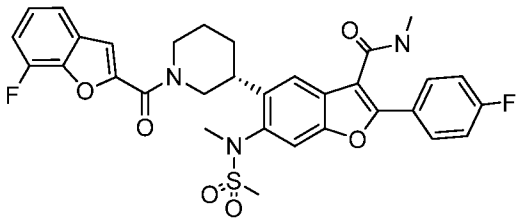
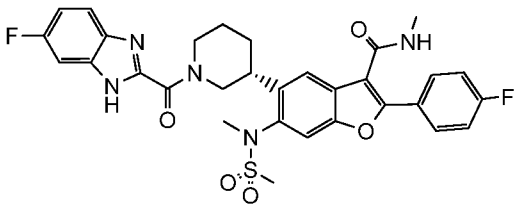
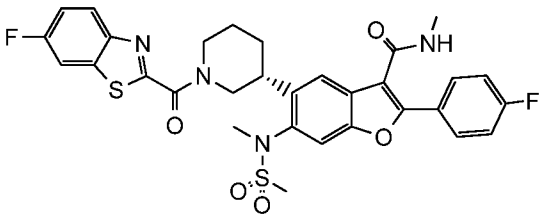
81		5-{(3R)-1-[(2-fluorobenzyl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	632
82		5-{(3R)-1-[(3-fluorobenzyl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	632
83		5-[(3R)-1-(1-benzofuran-2-ylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	640
84		5-{(3R)-1-[(3,4-difluorobenzyl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	650

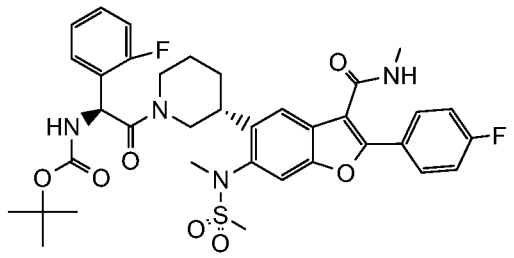
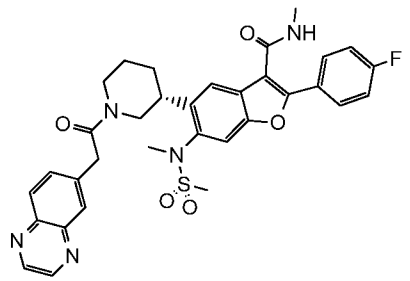
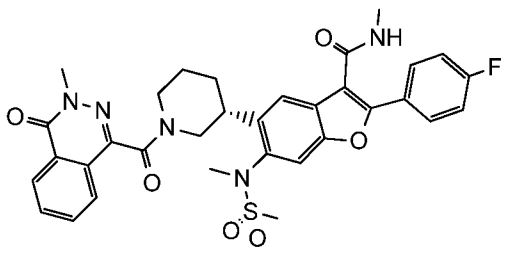
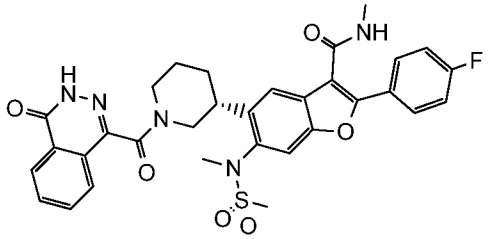
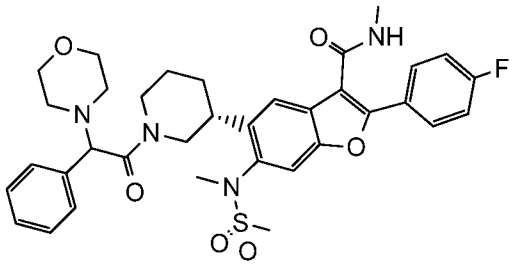
Examples 85-108

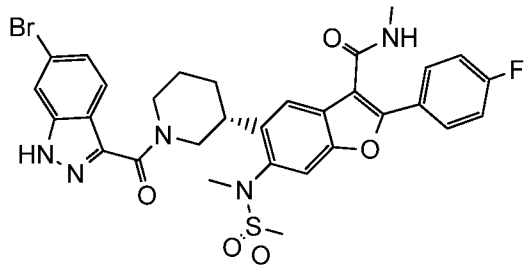
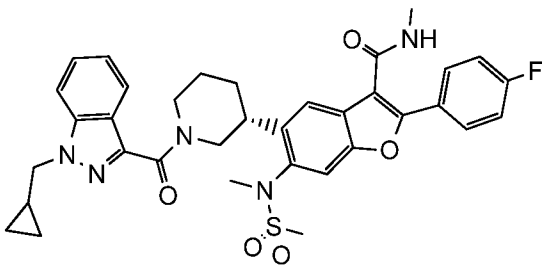
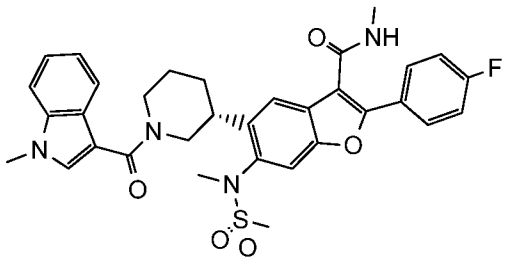
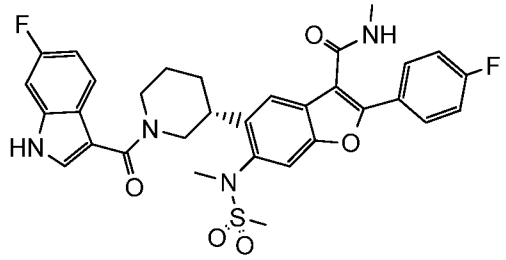
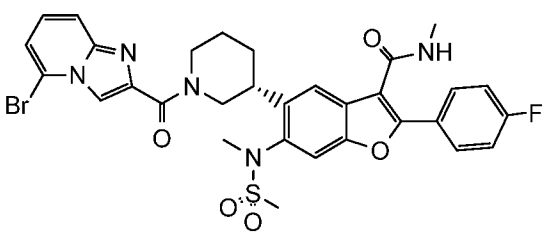
Examples 85 to 108 were prepared in library format. The procedure is exemplified by the synthesis of Example 85. To 5-fluoro-1-methyl-1*H*-indole-2-carboxylic acid (16 mg, was added a solution of (R)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperindin-3-yl)benzofuran-3-carboxamide (25mg, 0.054 mmol), O-(benzotriazol-1yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (34.9 mg, 0.109 mmol) and Hunig's base (14.1mg, 0.109 mmol) in 1 ml DMF. The mixture was stirred at room temperature for 18 h. The crude mixture was

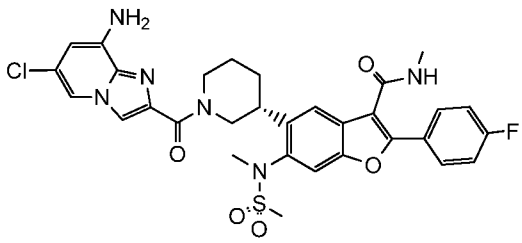
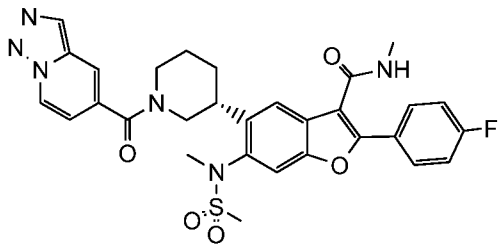
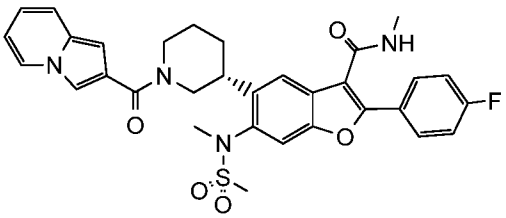
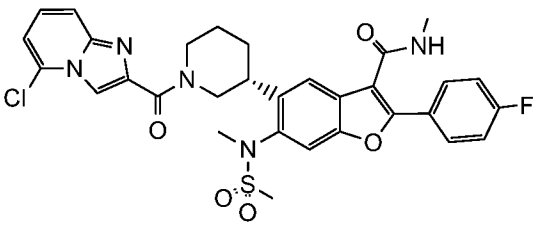
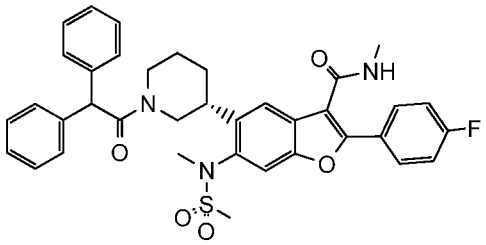
purified using mass directed reverse phase HPLC, Waters XBridge C18, 5u, 30 x 100 mm, 50 ml/min, 8 min run time, mobile phase A = water and ammonium, mobile phase B = acetonitrile and ammonium, gradient from 35% to 75% acetonitrile to give 5-{(3R)-1-[(5-fluoro-1-methyl-1H-indol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (25 mg, 71% yield). MS $(M+H)^+$: 635.

Example	Structure	IUPAC Name	Mass [M+H]+
85		5-{(3R)-1-[(5-fluoro-1-methyl-1H-indol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	635
86		5-{(3R)-1-[(5-fluoro-1,3-dimethyl-1H-indol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	649
87		5-[(3R)-1-(1H-benzimidazol-2-ylcarbonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	604
88		5-{(3R)-1-[(4-fluoro-1H-indol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	621

89		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3R)-1-{[1-methyl-5-(trifluoromethyl)-1H-indol-2-yl]carbonyl}piperidin-3-yl]-1-benzofuran-3-carboxamide	685
90		(R)-5-(1-(5-fluoro-1H-indole-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide	621
91		(R)-5-(1-(7-fluorobenzofuran-2-carbonyl)piperidin-3-yl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide	622
92		5-{(3R)-1-[(6-fluoro-1H-benzimidazol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	622
93		5-{(3R)-1-[(6-fluoro-1,3-benzothiazol-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	639

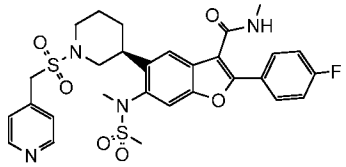
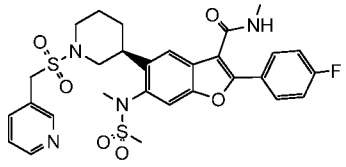
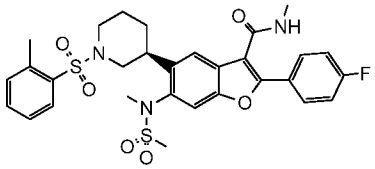
94		tert-butyl {(1S)-1-(2-fluorophenyl)-2-[(3R)-3-{2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-5-yl}piperidin-1-yl]-2-oxoethyl}carbamate	711
95		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3R)-1-(quinoxalin-6-ylacetyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	630
96		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)carbonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	646
97		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(4-oxo-3,4-dihydrophthalazin-1-yl)carbonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	632
98		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[morpholin-4-yl(phenyl)acetyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	663

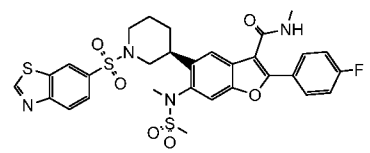
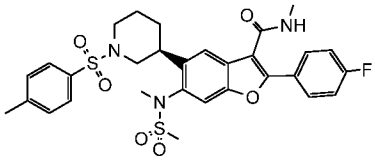
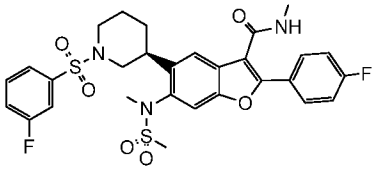
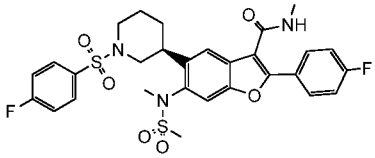
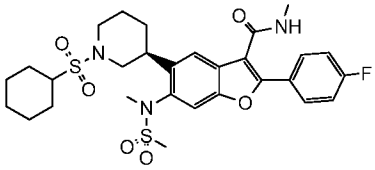
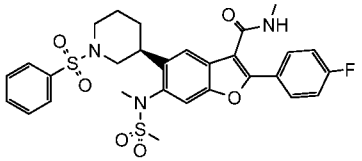
99		5-{(3R)-1-[(6-bromo-1H-indazol-3-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	682
100		5-[(3R)-1-{[1-(cyclopropylmethyl)-1H-indazol-3-yl]carbonyl}piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	658
101		2-(4-fluorophenyl)-N-methyl-5-{(3R)-1-[(1-methyl-1H-indol-3-yl)carbonyl]piperidin-3-yl}-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	617
102		5-{(3R)-1-[(6-fluoro-1H-indol-3-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	621
103		5-{(3R)-1-[(5-bromoimidazo[1,2-a]pyridin-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	682

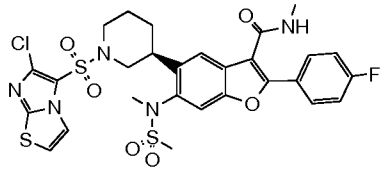
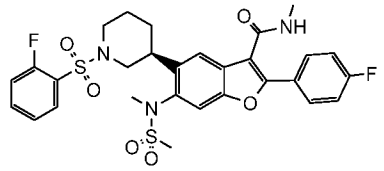
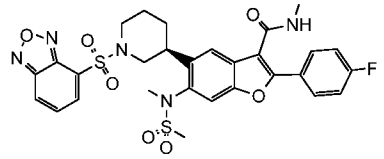
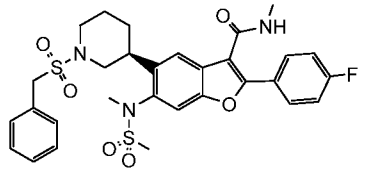
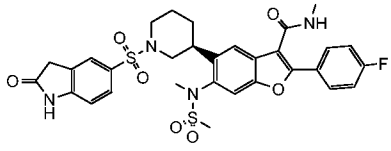
104		5-{(3R)-1-[(8-amino-6-chloroimidazo[1,2-a]pyridin-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	653
105		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3R)-1-([1,2,3]triazolo[1,5-a]pyridin-5-ylcarbonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	605
106		2-(4-fluorophenyl)-5-[(3R)-1-(indolizin-2-ylcarbonyl)piperidin-3-yl]-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	603
107		5-{(3R)-1-[(5-chloroimidazo[1,2-a]pyridin-2-yl)carbonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	638
108		5-[(3R)-1-(diphenylacetyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	654

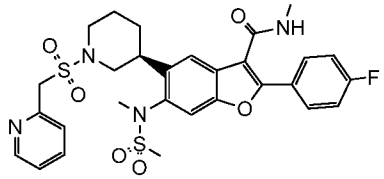
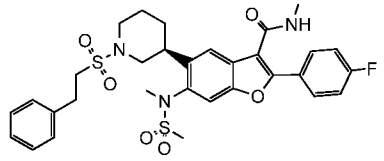
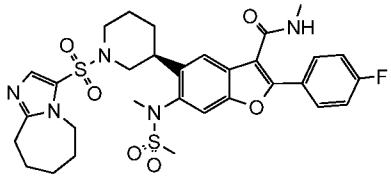
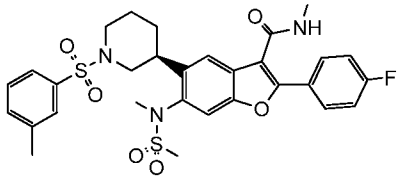
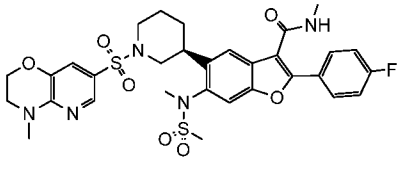
Examples 109 to 144

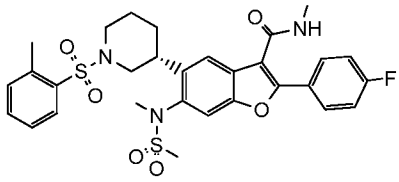
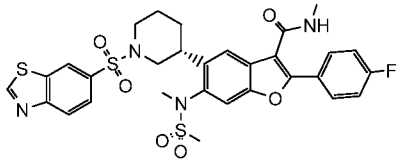
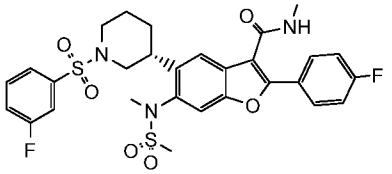
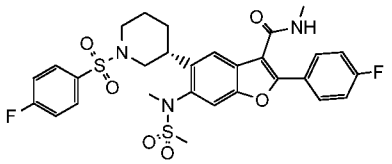
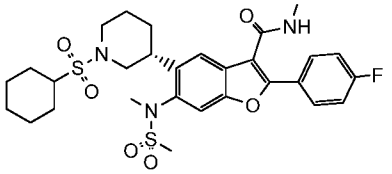
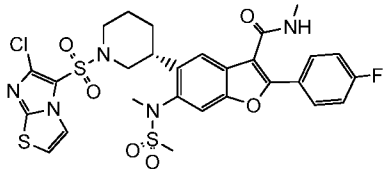
Examples 109 to 144 were prepared in library format. The procedure is exemplified by the synthesis of Example 111. To a solution of (S)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-5-(piperidin-3-yl)benzofuran-3-carboxamide (20 mg, 0.044 mmol) and Hunig's base (11.3 mg, 0.087 mmol) in DCM was added 2-methylbenzene-1-sufonyl chloride (17 mg, 0.089 mmol). The mixture was stirred uncapped for 18 hours. The crude mixture was purified using mass directed reverse phase HPLC, Waters Sunfire C18, 5u, 19 x 100 mm, 25 ml/min, 8 min run time, mobile phase A = water and 0.1% formic acid, mobile phase B = acetonitrile and 0.1% formic acid, gradient from 35% to 70% acetonitrile (14 mg, 51% yield) to afford 2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(2-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide. MS $(M+H)^+$: 614.

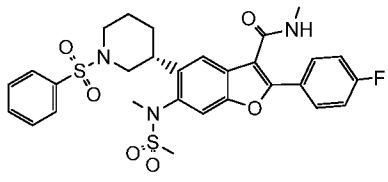
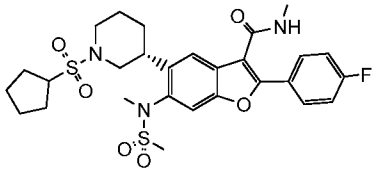
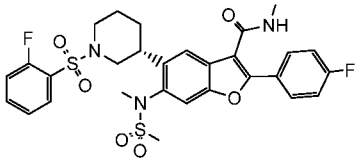
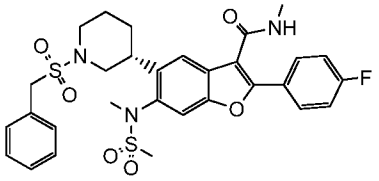
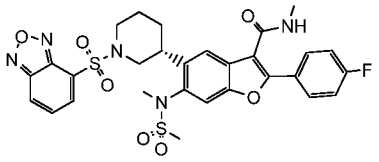
Example	Structure	IUPAC Name	Mass [M+H]+
109		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(pyridin-4-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615
110		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(pyridin-3-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615
111		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(2-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	614

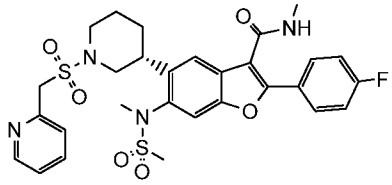
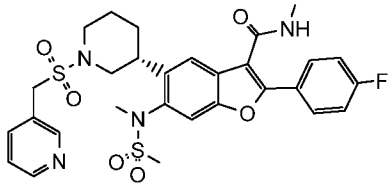
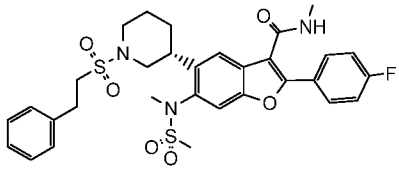
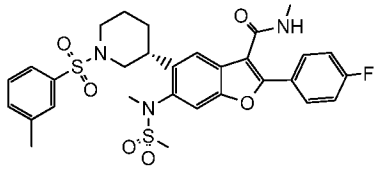
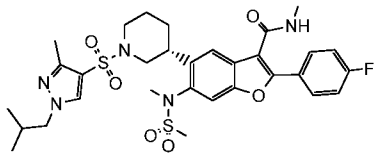
112		5-[(3S)-1-(1,3-benzothiazol-6-ylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	657
113		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(4-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	614
114		2-(4-fluorophenyl)-5-{(3S)-1-[(3-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
115		2-(4-fluorophenyl)-5-{(3S)-1-[(4-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
116		5-[(3S)-1-(cyclohexylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	606
117		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3S)-1-(phenylsulfonyl)piperidin-3-yl]-1-benzofuran-3-	600

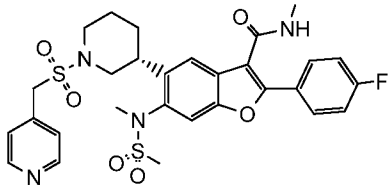
		carboxamide	
118		5-{(3S)-1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	680
119		2-(4-fluorophenyl)-5-{(3S)-1-[(2-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
120		5-[(3S)-1-(2,1,3-benzoxadiazol-4-ylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	642
121		5-[(3S)-1-(benzylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	614
122		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(2-oxo-2,3-dihydro-1H-indol-5-yl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	655

123		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(pyridin-2-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615
124		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(2-phenylethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	628
125		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3S)-1-(6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepin-3-ylsulfonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	658
126		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3S)-1-[(3-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	614
127		2-(4-fluorophenyl)-N-methyl-5-{(3S)-1-[(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)sulfonyl]piperidin-3-yl}-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	672

128		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(2-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	614
129		5-[(3R)-1-(1,3-benzothiazol-6-ylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	657
130		2-(4-fluorophenyl)-5-{(3R)-1-[(3-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
131		2-(4-fluorophenyl)-5-{(3R)-1-[(4-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
132		5-[(3R)-1-(cyclohexylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	606
133		5-{(3R)-1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)sulfonyl]piperidin-3-yl}-2-(4-fluorophenyl)-N-methyl-6-	680

		[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	
134		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[(3R)-1-(phenylsulfonyl)piperidin-3-yl]-1-benzofuran-3-carboxamide	600
135		5-[(3R)-1-(cyclopentylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	592
136		2-(4-fluorophenyl)-5-{(3R)-1-[(2-fluorophenyl)sulfonyl]piperidin-3-yl}-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	618
137		5-[(3R)-1-(benzylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	614
138		5-[(3R)-1-(2,1,3-benzoxadiazol-4-ylsulfonyl)piperidin-3-yl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	642

139		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(pyridin-2-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615
140		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(pyridin-3-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615
141		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(2-phenylethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	628
142		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(3-methylphenyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	614
143		2-(4-fluorophenyl)-N-methyl-5-[(3R)-1-{[3-methyl-1-(2-methylpropyl)-1H-pyrazol-4-yl]sulfonyl}piperidin-3-yl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	660

144		2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-{(3R)-1-[(pyridin-4-ylmethyl)sulfonyl]piperidin-3-yl}-1-benzofuran-3-carboxamide	615

Example 145: Measuring Compound Inhibitory Potency

Measurement of inhibition by compounds was performed using the HCV replicon system. Several different replicons encoding different HCV genotypes or mutations were used. In addition, potency measurements were made using different formats of the replicon assay, including different ways of measurements and different plating formats. *See* Jan M. Vrolijk *et al.*, *A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C*, 110 J. VIROLOGICAL METHODS 201 (2003); Steven S. Carroll *et al.*, *Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs*, 278(14) J. BIOLOGICAL CHEMISTRY 11979 (2003). However, the underlying principles are common to all of these determinations, and are outlined below.

Stable neomycin phosphotransferase encoding replicons-harboring cell lines were used, so all cell lines were maintained under G418 selection prior to the assay. Potency was deteremined using a cell ELISA assay with an antibody to the replicons encoded NS3/4a protease. *See* Caterina Trozzi *et al.*, *In Vitro Selection and Characterization of Hepatitis C Virus Serine Protease Variants Resistant to an Active-Site Peptide Inhibitor*, 77(6) J. Virol. 3669 (2003). To initiate an assay, replicon cells were plated in the presence of a dilution series of test compound in the absence of G418. Typically, the assays were performed in a 96-well plate formate for manual operation, or a 384-well plate format for automated assay. Replicon cells and compound were incubated for 96 hours. At the end of the assay, cells were washed free of media and compound, and the cells were then lysed. RNA was quantified indirectly through detection of replicon-encoded NS3/4A protein levels, through an ELISA-based assay with an antibody specific for NS3/4A. IC_{50}

determinations were calculated as a percentage of a DMSO control by fitting the data to a four-parameter fit function and the data obtained is provided in the table below.

Data for selected compounds of the present invention was obtained for genotypes 1a and 1b using this method and is provided in the table below:

5

Example#	1a IC_{50} (nM)	1b IC_{50} (nM)	Example #	1a IC_{50} (nM)	1b IC_{50} (nM)
1	56.91	34.3	73	50.5	23.36
2	84.07	41.04	74	54.75	43.37
3	148.2	109.4	75	72.29	12.02
4	7.026	6.525	76	49.36	9.961
5	53.68	19.34	77	64.3	19.24
6	11.12	17.37	78	248.2	81.15
7	5.79	11.59	79	64.78	33.12
8	28.22	36.89	80	3.165	4.5
9	53.98	67.85	81	14.13	11.63
10	16	26.58	82	2.203	3.262
11	21.36	17.23	83	38.22	22.45
12	92.81	37.76	84	2.774	3.035
13	140.5	165.2	85	25.99	12.49
14	25.87	2.768	86	233.7	115.2
15	125.4	11.25	87	267.1	111.6
16	332.6	106.4	88	70.72	38.69
17	137.7	58.2	89	84.36	45.18
18	187.8	72.25	90	41.59	20.72
19	43.76	50.83	91	180.1	62.56
20	48.04	46.9	92	274.2	96.96
21	16.22	9.96	93	180.7	102
22	40.84	18.77	94	299.9	167.6

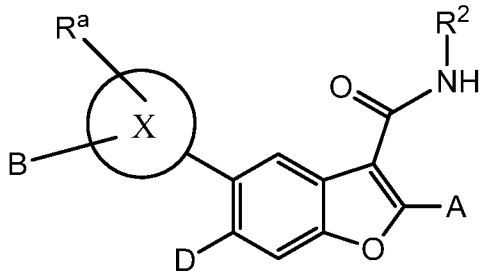
23	45.47	57.71	95	175.8	105.9
24	32.68	40.46	96	423.3	218.6
25	16.43	5.259	97	335.6	470.3
26	15.79	12.59	98	240.6	111.8
27	44.41	35.21	99	136.8	66.74
28	23.86	21.39	100	65.04	20.39
29	83.13	147.8	101	103.2	55.87
30	122.3	215.1	102	345.3	295.2
31	17.08	9.38	103	212.5	109.9
32	53.12	19.18	104	283.8	136.4
33	129.8	196.5	105	347	219.4
34	84.09	65.3	106	122.9	51.5
35	71.59	48.93	107	388.8	116.5
36	269.4	285.6	108	265.7	52.97
37	162.4	92.77	109	103.6	26.16
38	277.4	115.5	110	163.7	38.38
39	268.3	36.44	111	68.1	17.23
40	141.8	27.63	112	24.98	6.785
41	30.67	13.47	113	64.62	21.92
42	105.6	23.94	114	34.19	8.202
43	41.23	92.96	115	36.61	7.995
44	70.97	82.36	116	194.5	31.67
45	224.6	70.9	117	32.34	9.373
46	11.94	9.474	118	41.04	8.357
47	8.368	5.372	119	24.53	10.92
48	40.19	24.75	120	22.44	8.37
49	5.764	7.439	121	47.54	23.82
50	81.65	20.06	122	78.77	22.15
51	4.99	7.118	123	105.5	29.77

52	32.64	42.64	124	182	72.92
53	14.57	15.7	125	172.5	67.61
54	7.383	13.87	126	46.86	13.17
55	5.652	3.626	127	90.19	32.35
56	53.66	23.85	128	34.24	24.2
57	19.88	22.2	129	193.7	109.6
58	132.5	36.15	130	174.1	95.47
59	307.6	119.7	131	175.6	88.94
60	115.9	40.31	132	93.34	56.11
61	251.4	99.55	133	105.8	74.65
62	192.1	41.18	134	85.9	58.31
63	156	68.11	135	80.38	45.63
64	135.2	40.72	136	58.48	40.45
65	140.1	46.26	137	2.15	3.04
66	92.59	21.21	138	139.2	55.67
67	156.2	87.42	139	35.04	21.07
68	97.95	88.95	140	20.46	16.51
69	74.44	22.76	141	10.61	14.23
70	206.8	67.94	142	198.2	91.72
71	168.3	95.43	143	314.7	213.6
72	124.9	23.62	144	36.17	28.56

It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. Also that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

CLAIMS

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is a 5 or 6-membered saturated monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from N and O;

A is fluorophenyl;

B is a) hydrogen;

b) $-C(O)CH=C(CH_3)_2$;

c) Ar;

d) –C(O)-Ar;

e) $-C(O)CHR^y$-Ar;

f) $-C(O)CH(NHR^x)$-Ar;

g) $-SO_2(CH_2)_{0-2}$-Ar;

h) $-SO_2$-CH=CH-Ar;

i) –CO-Cyc;

j) $-COCH_2$-Cyc;

k) $-SO_2$-Cyc;

Ar is an aromatic ring system selected from:

(i) 5-6 membered monocyclic ring with 0, 1, or 2 heteroatom ring atoms independently selected from N or O, optionally substituted with 1 or 2 substituents independently selected from fluorophenyl, C_1-C_6 alkyl, and halo; and

(ii) 8-10 membered bicyclic rings with 1, 2 or 3 heteroatom ring atoms selected from N, O and S, optionally substituted with 1, 2 or 3 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CF_3, cyano, oxo, $-NH_2$, and cyclopropylmethyl;

Cyc is C_3-C_6 cycloalkyl optionally substituted with fluorophenyl or pyridine; or 3-oxabicyclo[3.1.0]hexane;

D is H or $NR^3SO_2R^4$;

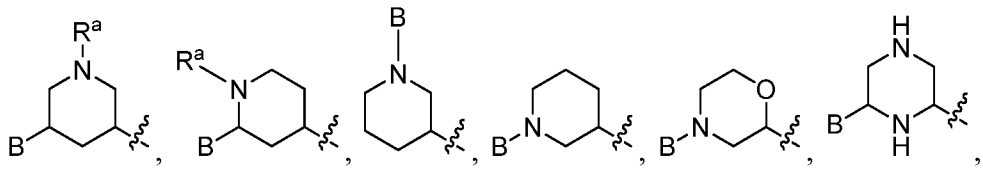
R^2, R^3, and R^4 are independently C_1-C_6 alkyl;

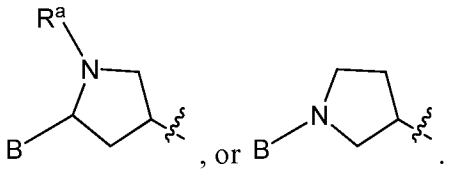
R^a is hydrogen or C_1-C_6 alkyl;

R^x is hydrogen or $C(O)OC(CH_3)_3$; and

R^y is hydrogen, morpholinyl or Ar.

2. The compound of claim 1, wherein X is



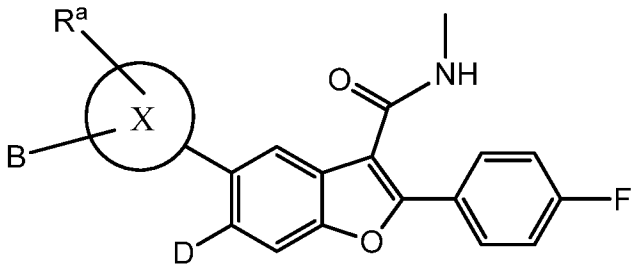


3. The compound of claim 1 or 2, wherein R^2, R^3 and R^4 are methyl.

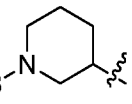
4. The compound of any one of claims 1 to 3, wherein D is $N(CH_3)SO_2CH_3$.

5. The compound of any one of claims 1 to 4, wherein each halo is F.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

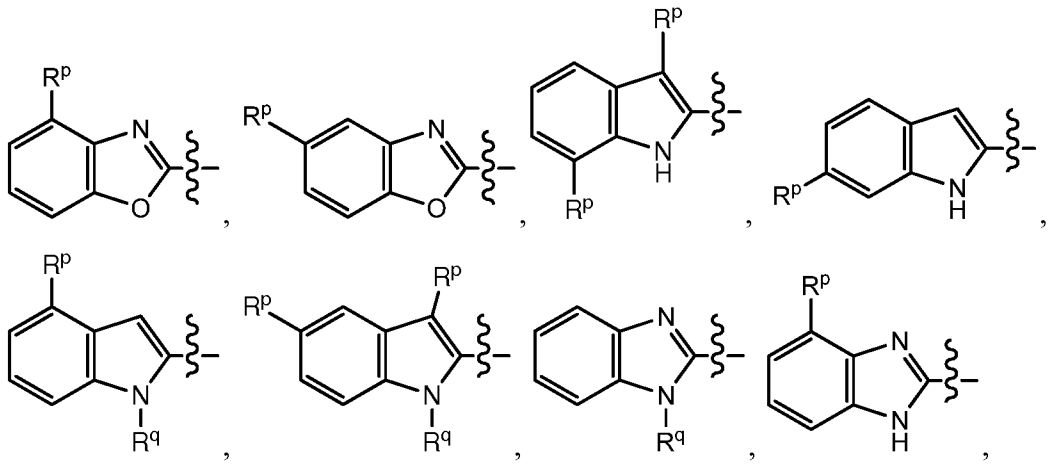


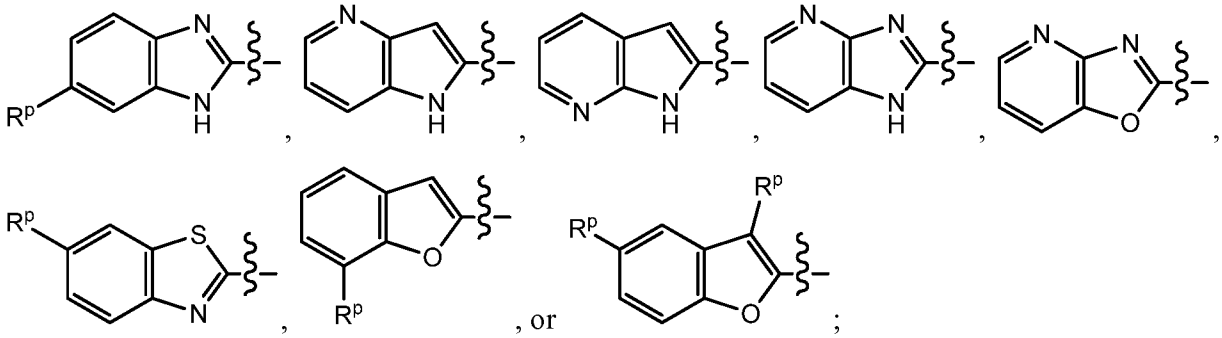
(Ia).

7. The compound of any one of claims 1 to 6, wherein X is  .

8. The compound of any one of claims 1 to 7, wherein B is Ar, –C(O)-Ar, or –SO_2-Ar; wherein Ar is a 9-membered bicyclic ring with 1, 2, or 3 heteroatom ring atoms selected from N, O and S, optionally substituted with 1, 2 or 3 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, F, CF_3, and cyano.

9. The compound of claim 8, wherein Ar is

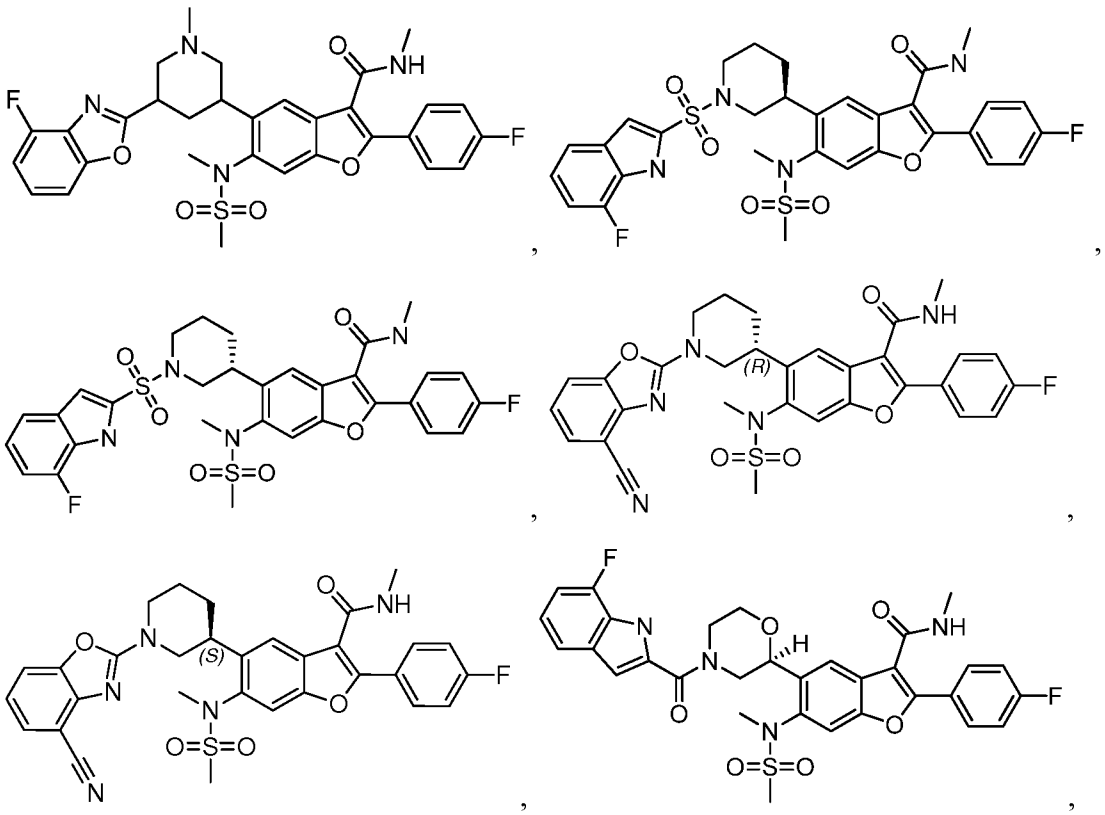


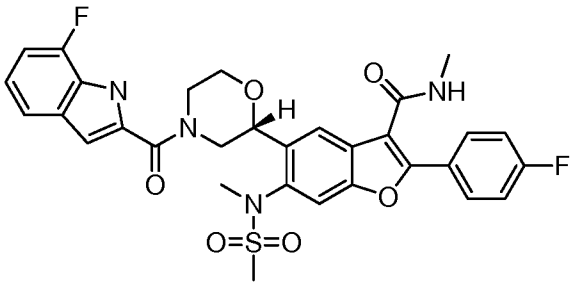
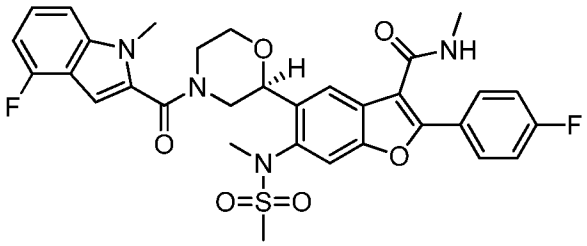
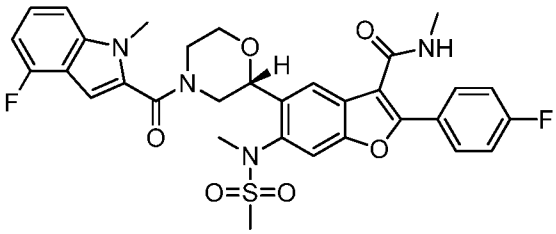
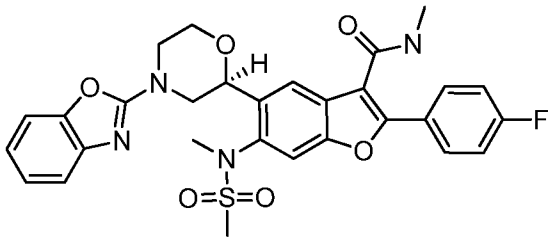
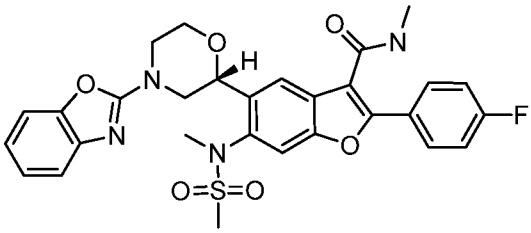
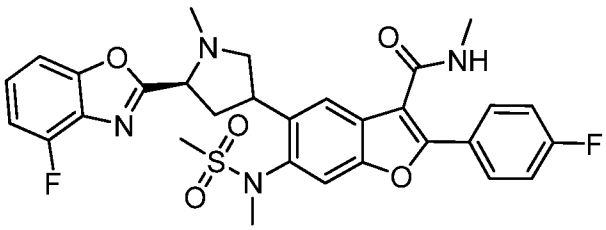
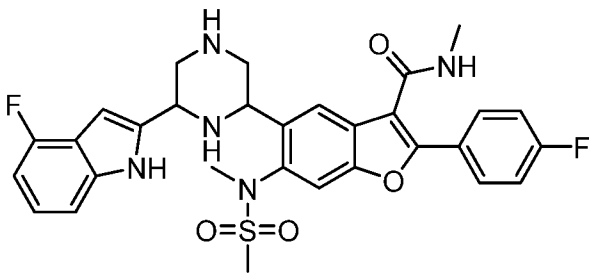
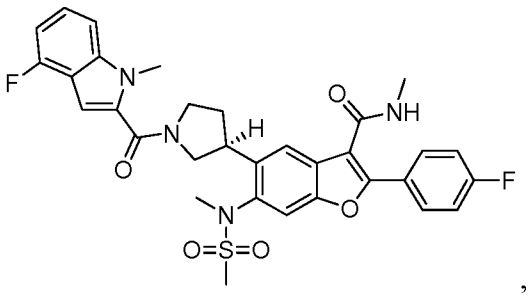
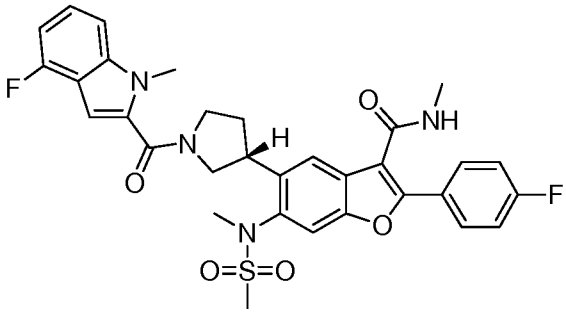
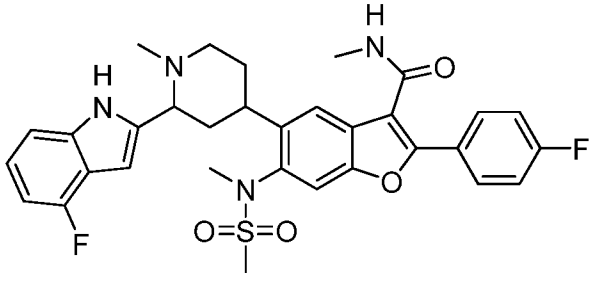


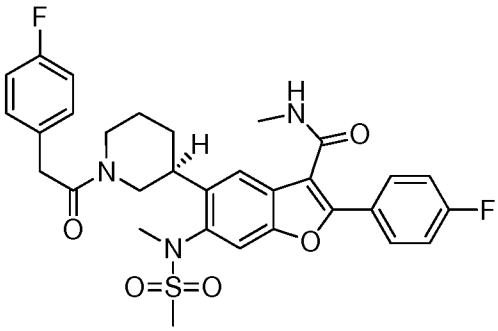
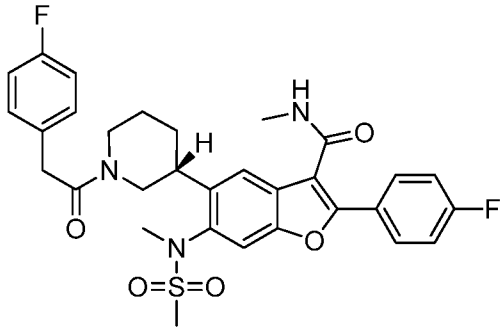
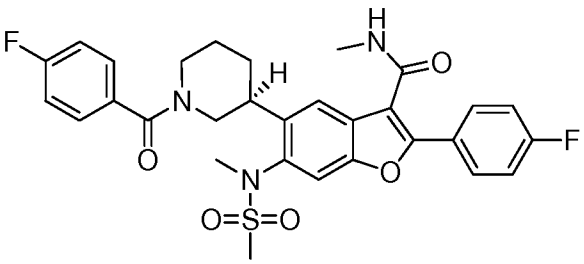
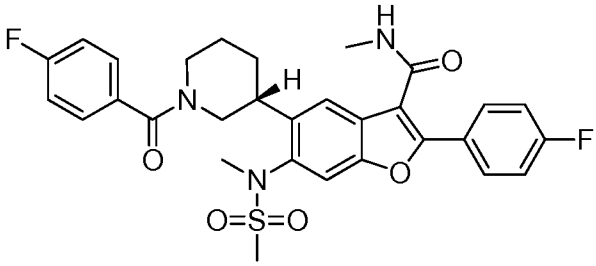
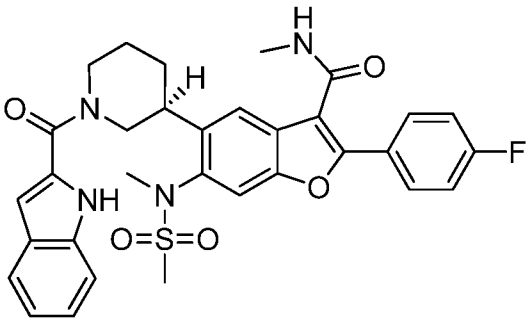
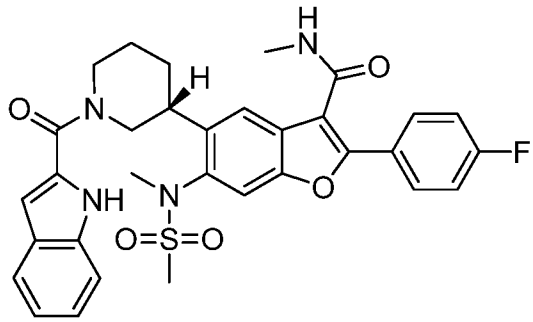
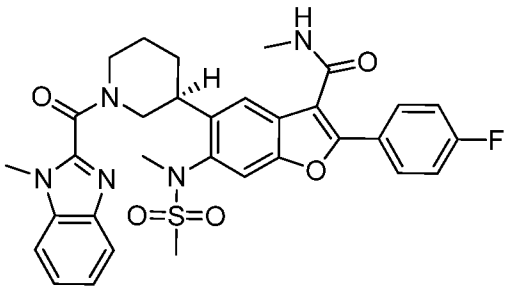
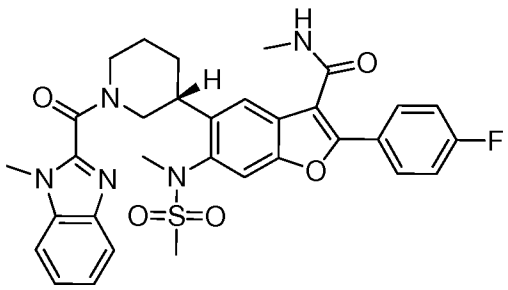
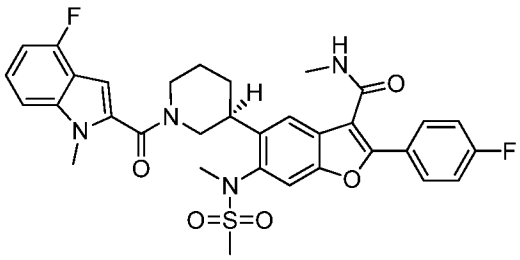
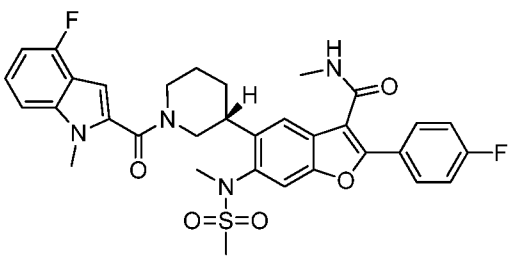
wherein each R^p is independently selected from hydrogen, methyl, methoxy, F, CF_3, or cyano, and R^q is hydrogen, methyl or ethyl.

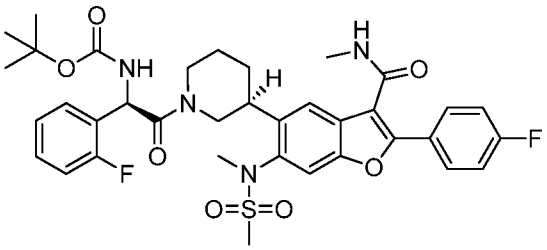
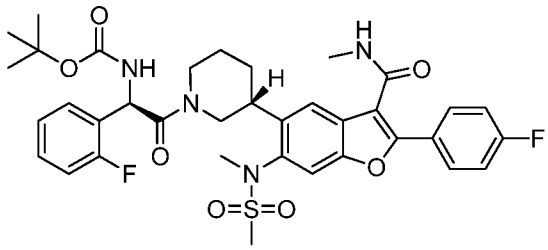
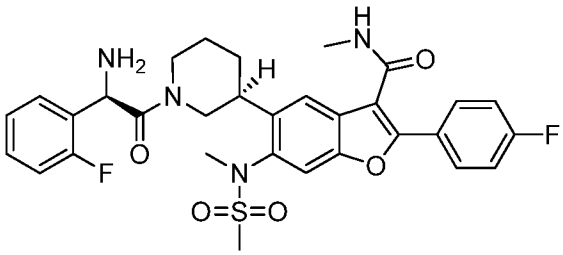
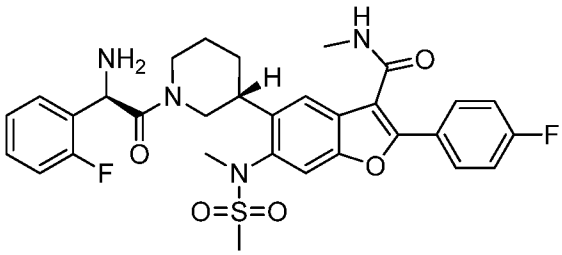
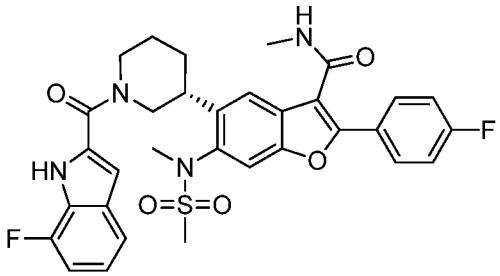
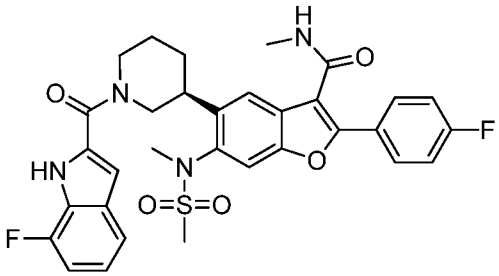
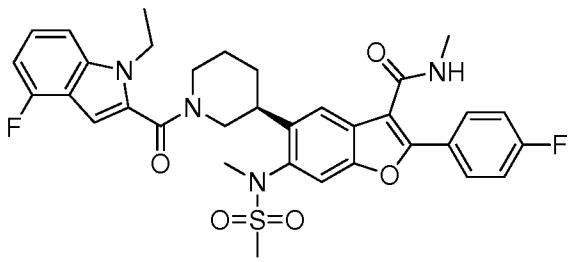
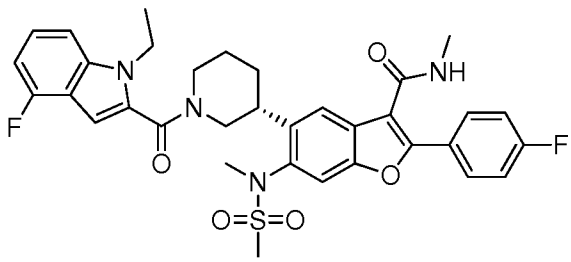
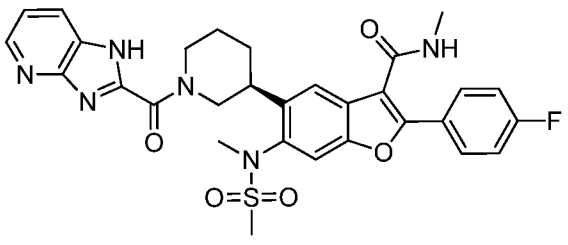
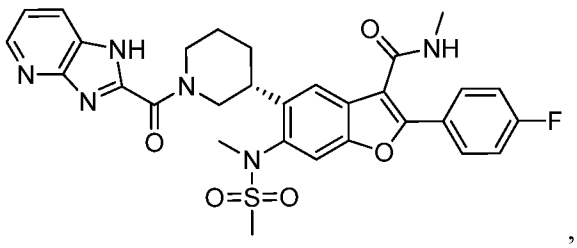
10. The compound of any one of claims 1 to 7, wherein B is $–SO_2$-Ar, $–SO_2CH_2$-Ar, $–SO_2CH_2CH_2$-Ar, –C(O)-Ar; or $–C(O)CH_2$-Ar; wherein Ar is phenyl, methylphenyl, fluorophenyl, difluorophenyl, pyridine, or fluoropyridine.

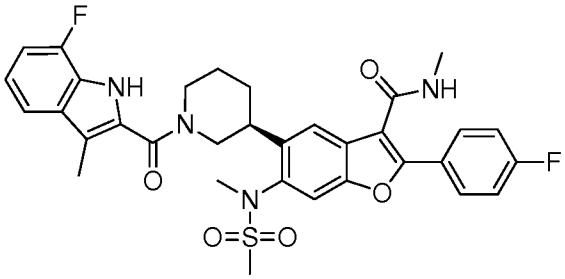
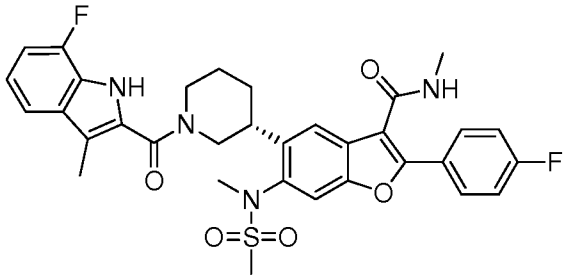
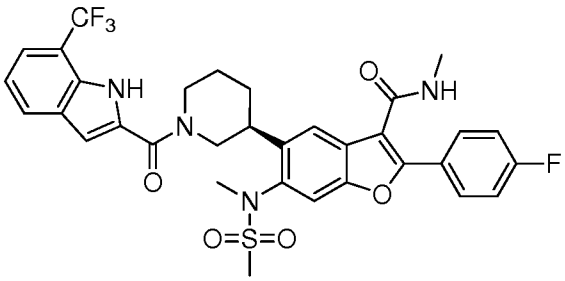
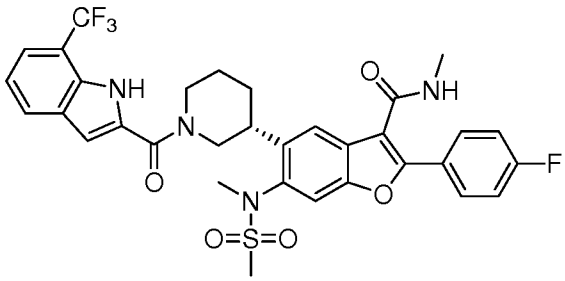
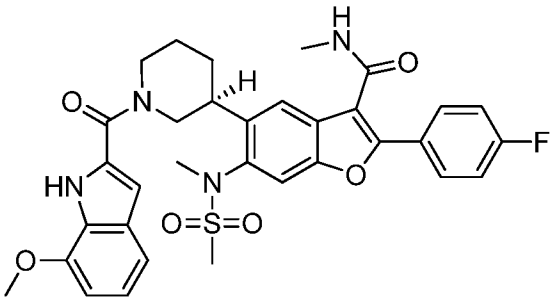
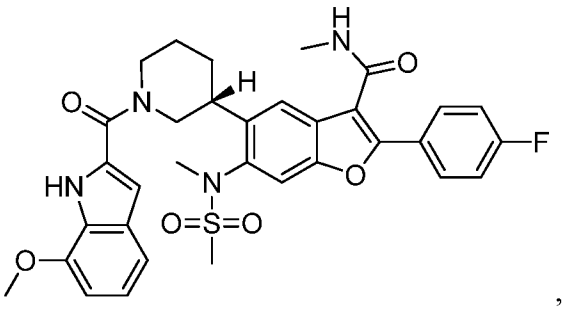
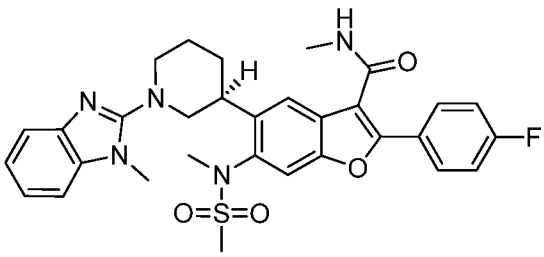
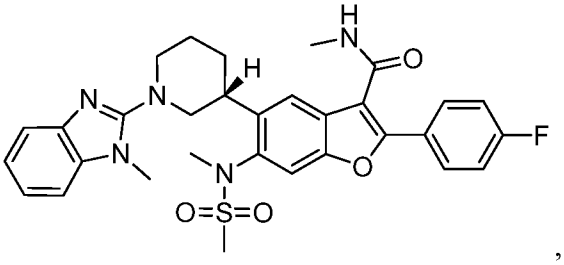
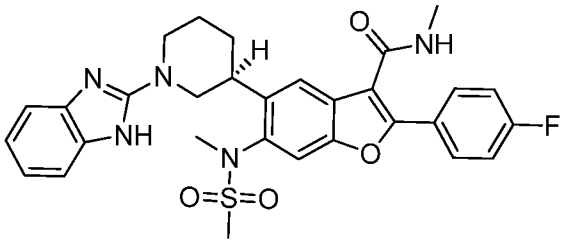
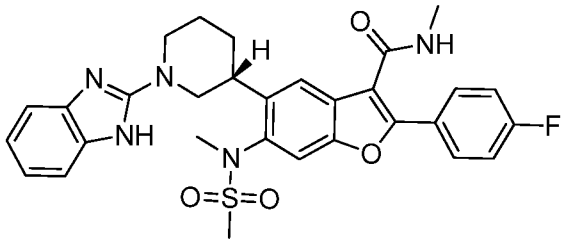
11. The compound of claim 1 which is any one of:

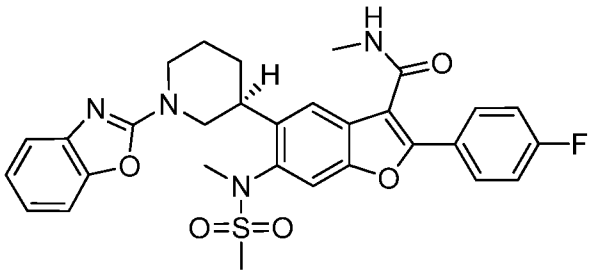
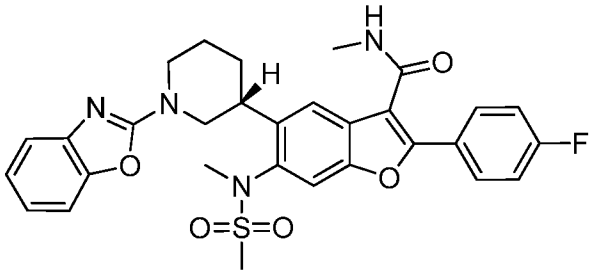
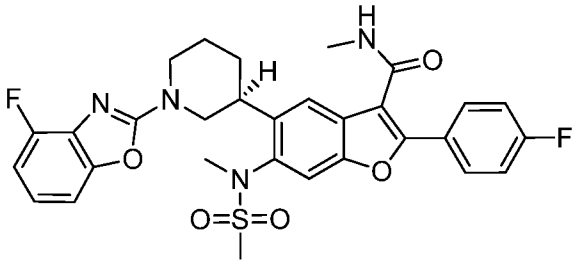
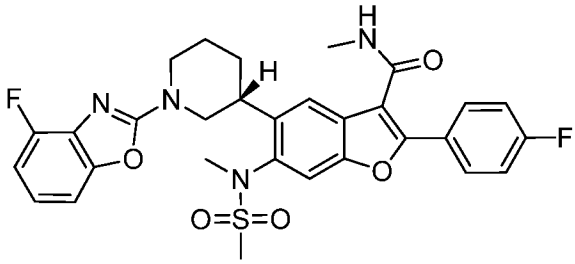
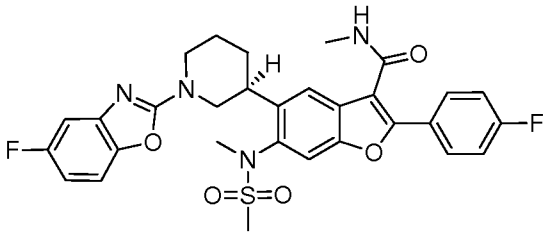
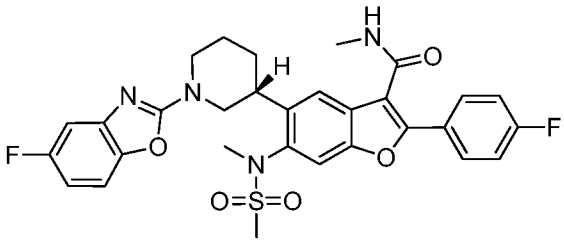
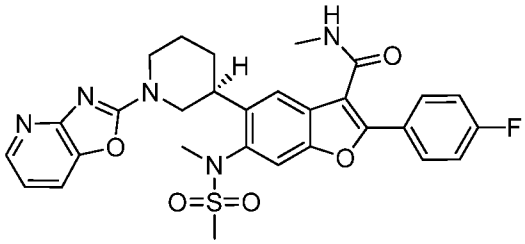
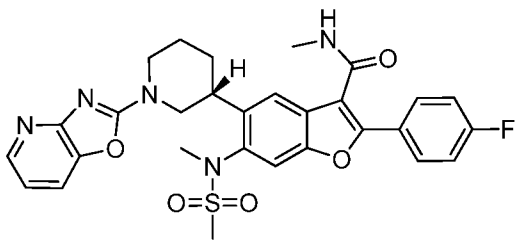
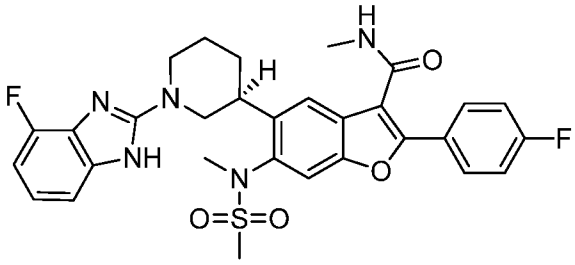
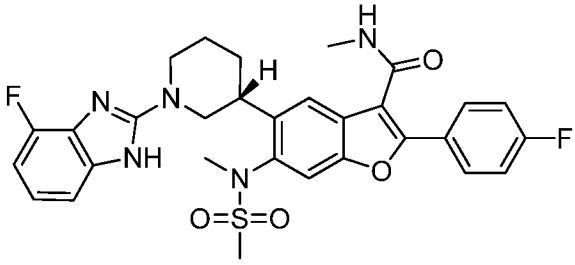


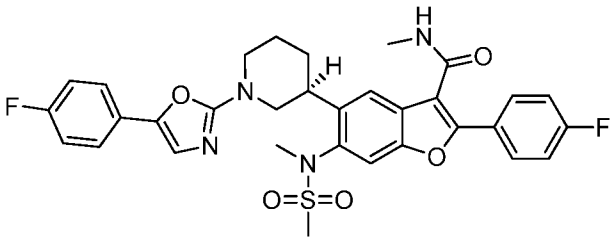
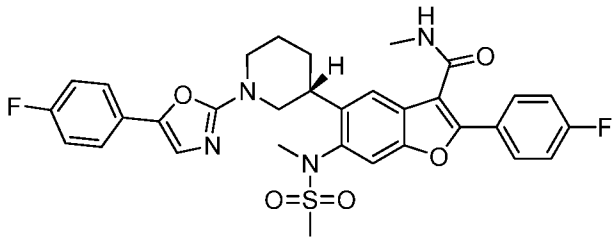
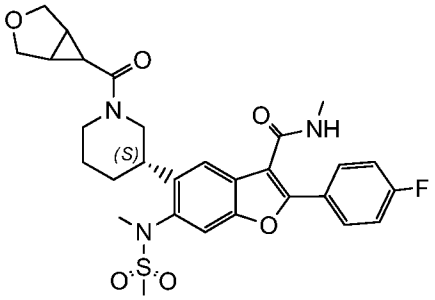
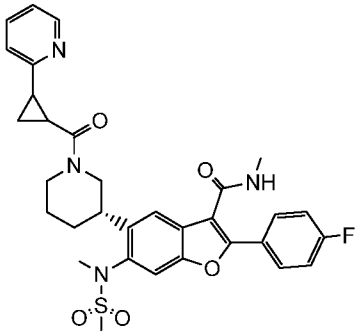
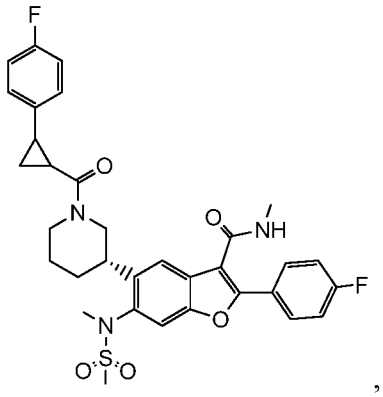
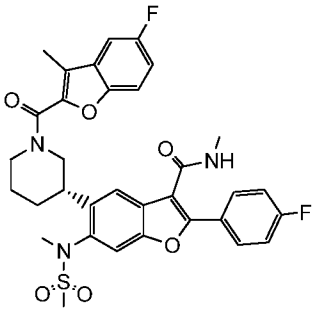
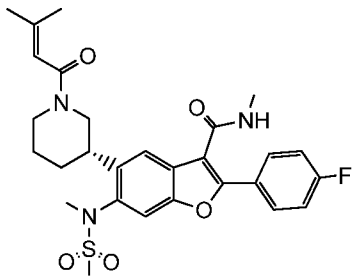
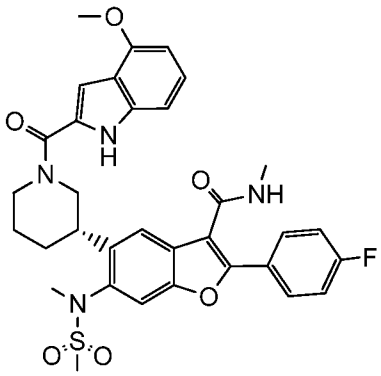
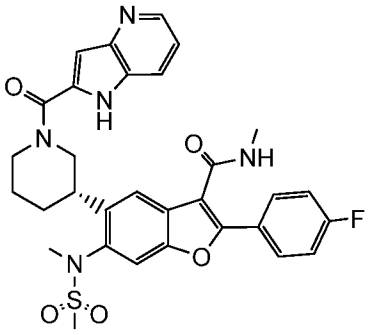
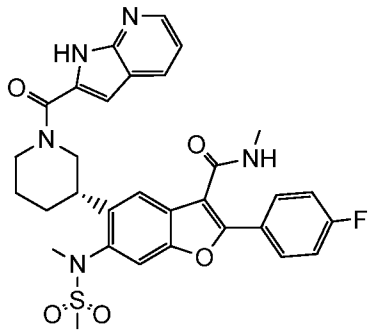
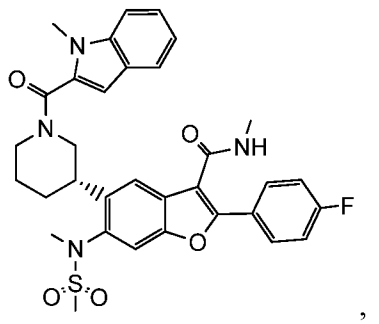

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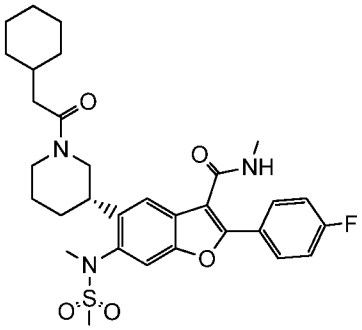
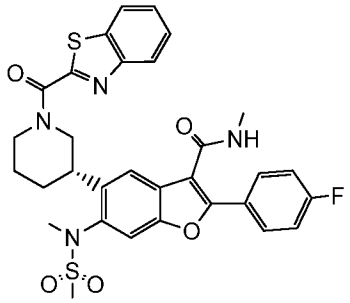
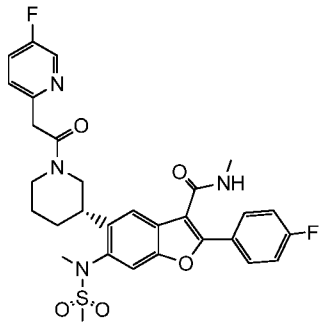
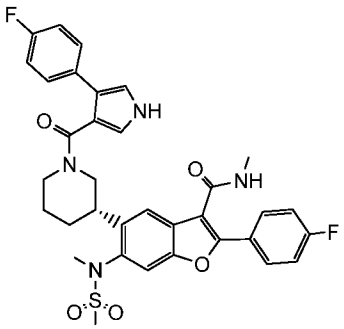
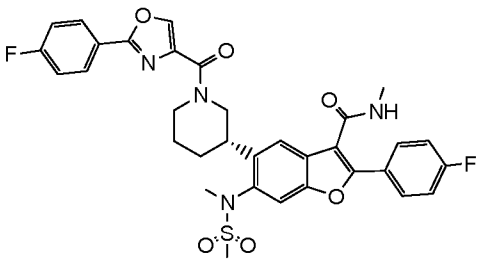
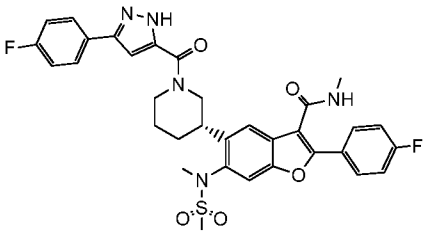
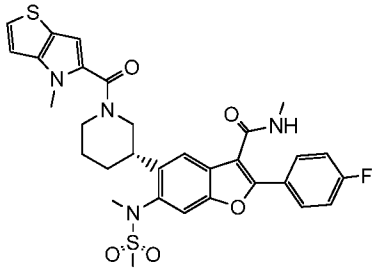
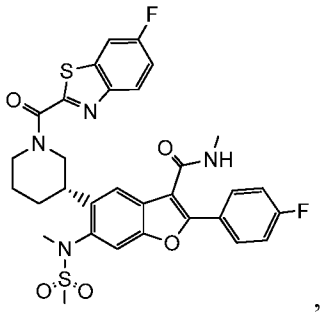
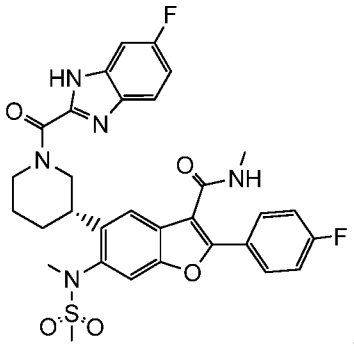
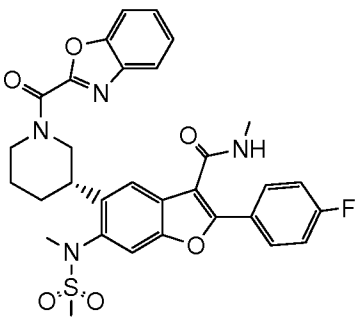
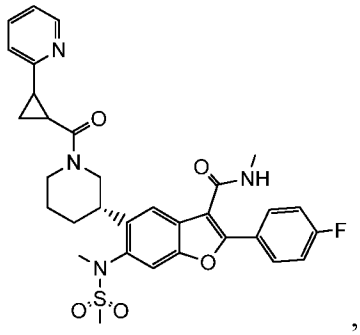

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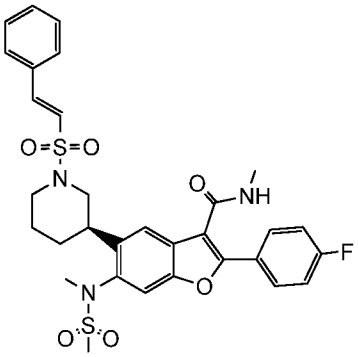
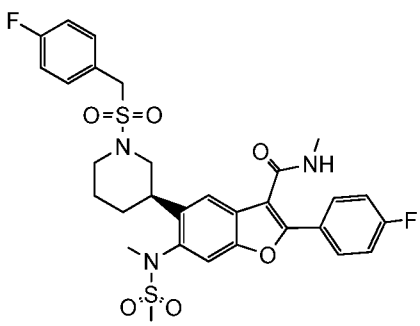
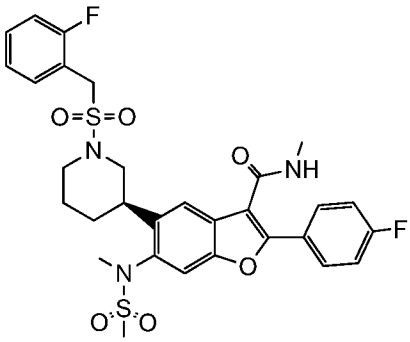
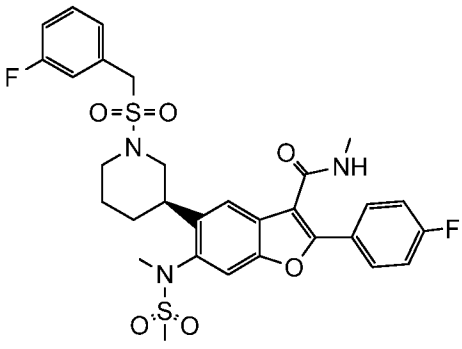
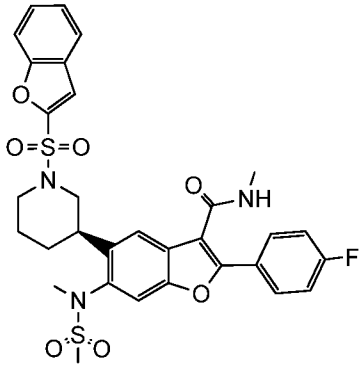
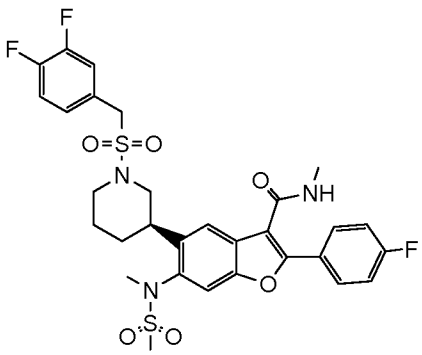
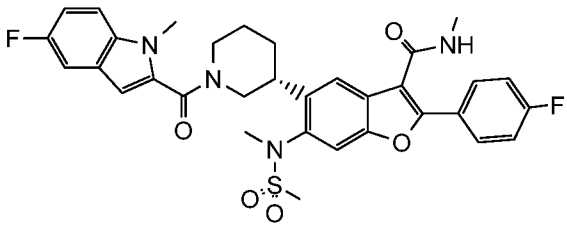
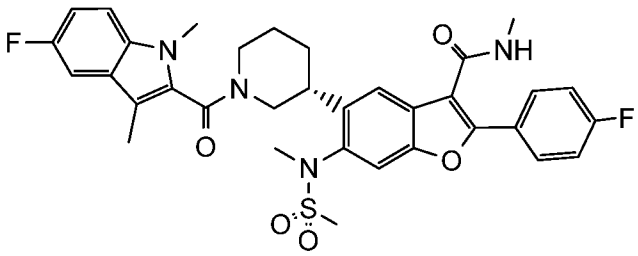
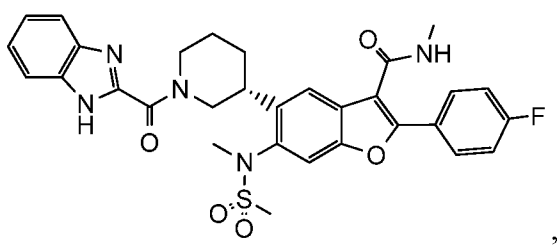

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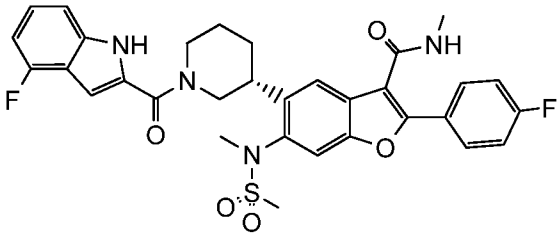
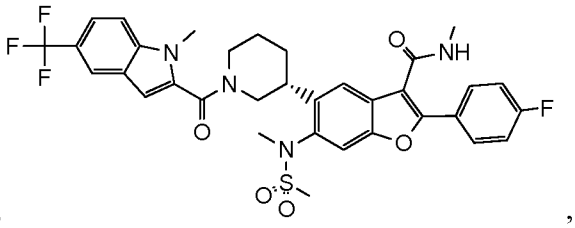
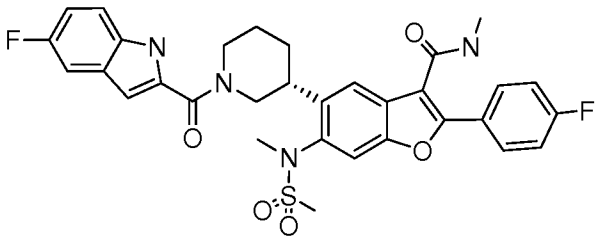
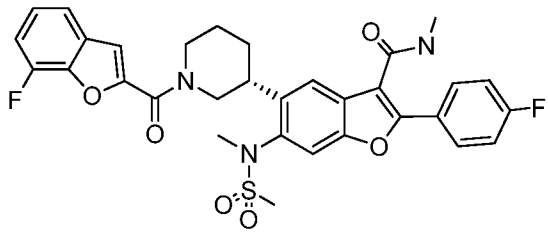
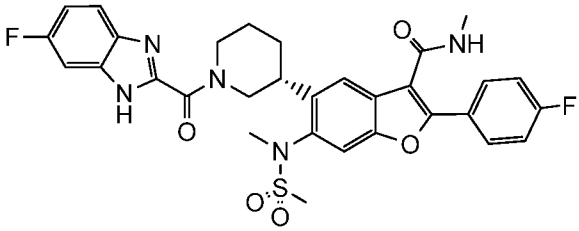
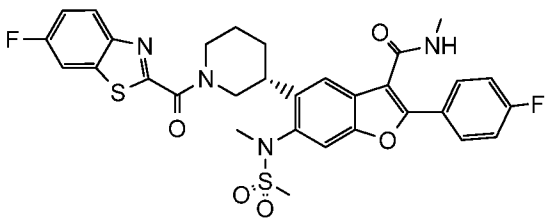
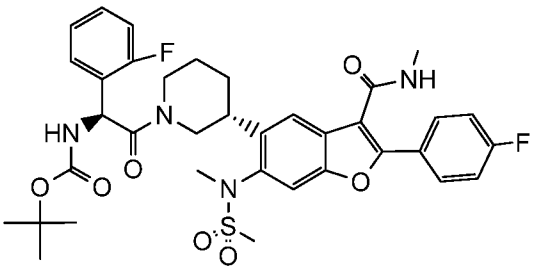
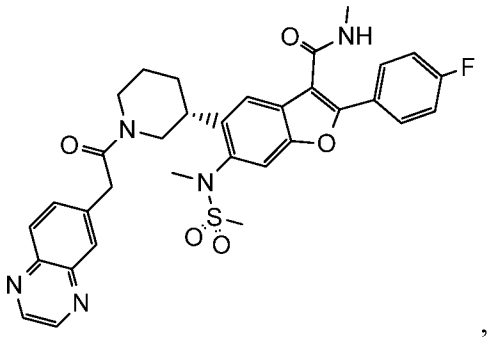
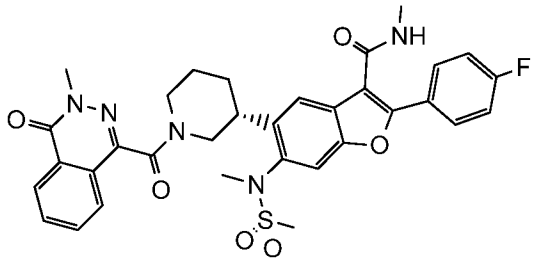
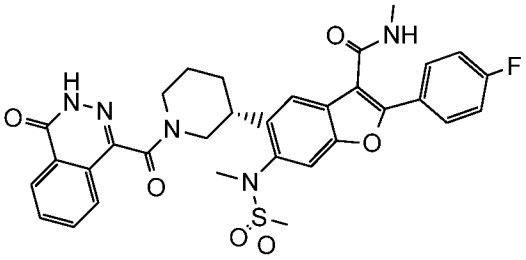

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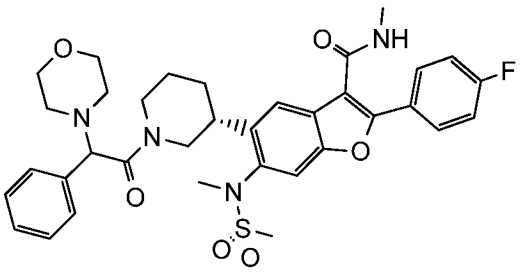
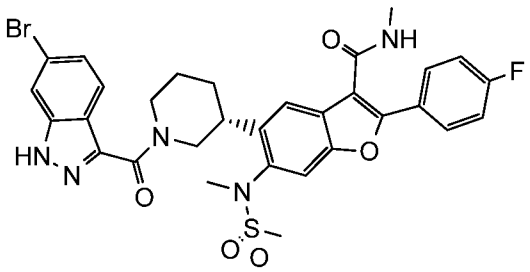
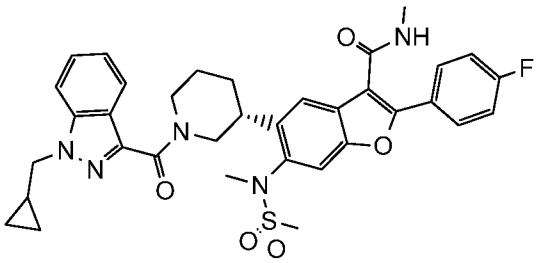
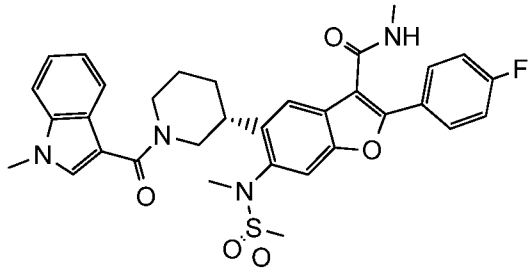
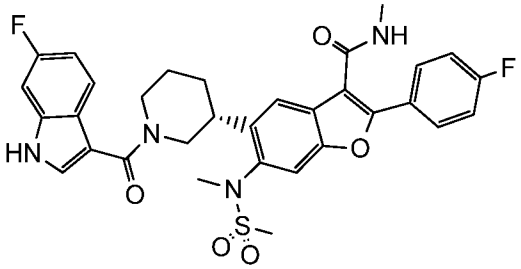
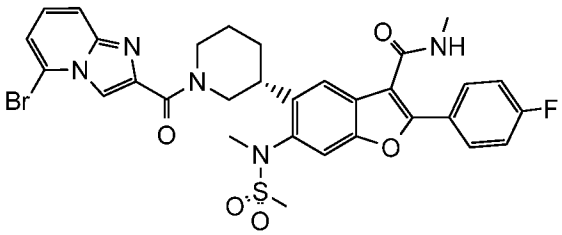
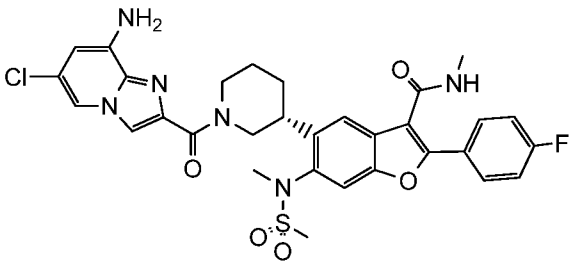
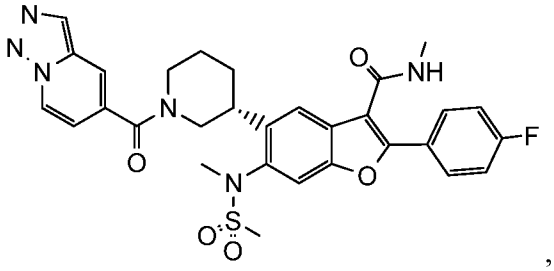
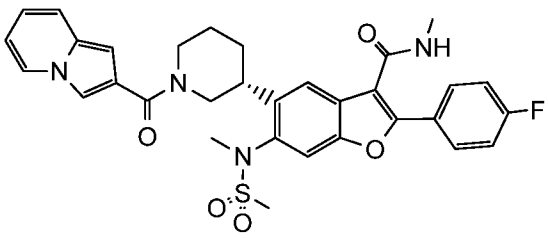
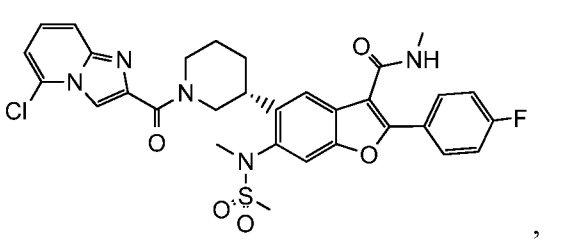

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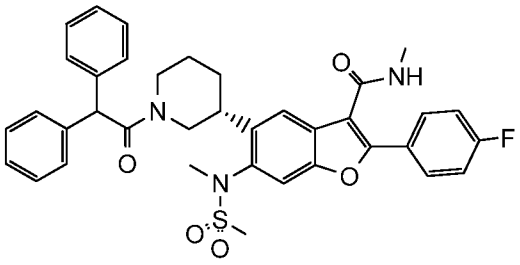
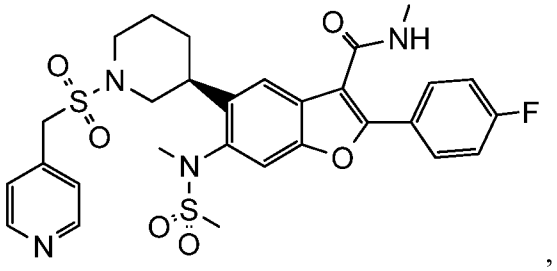
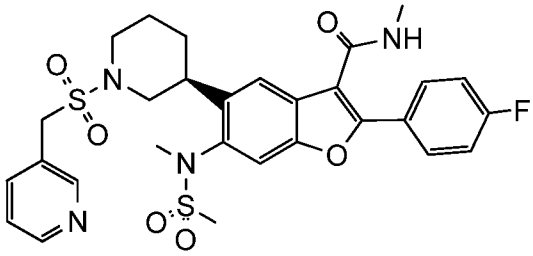
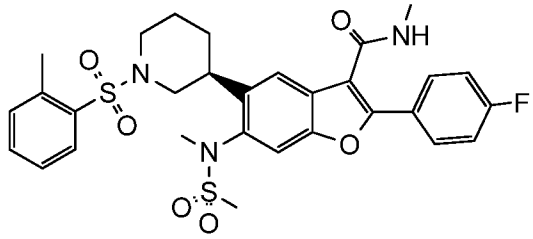
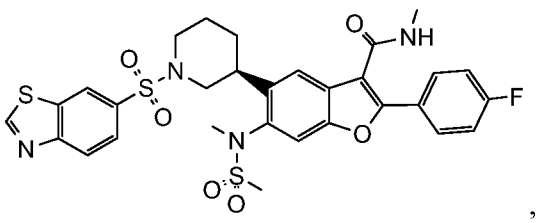
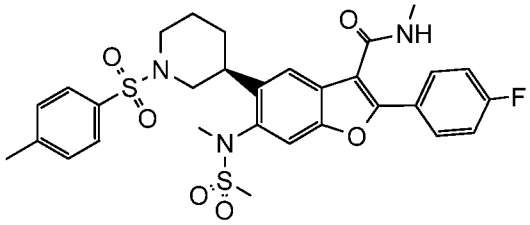
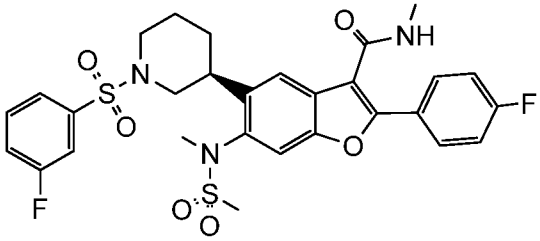
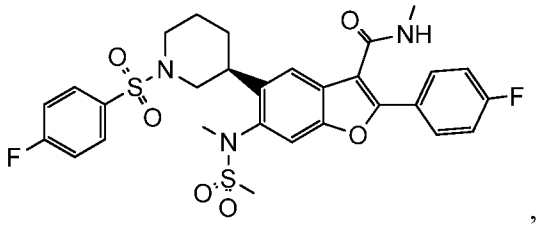
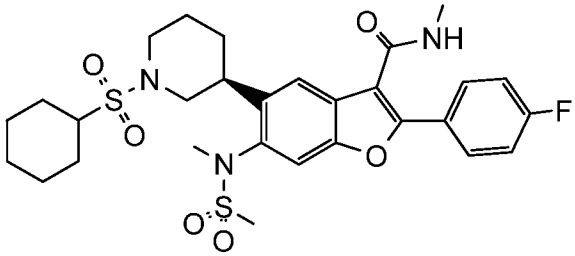
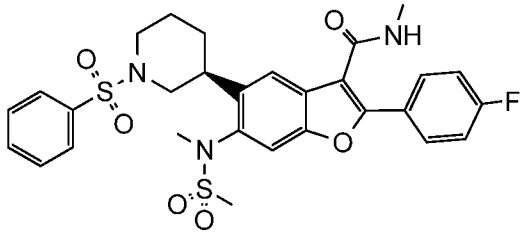
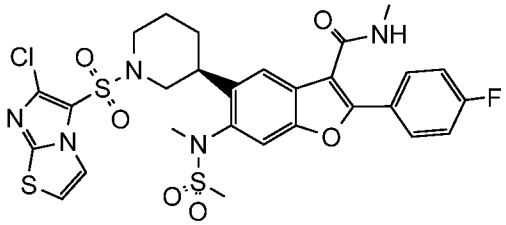
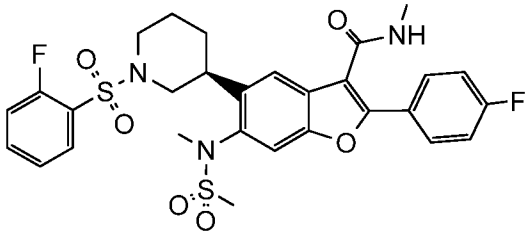

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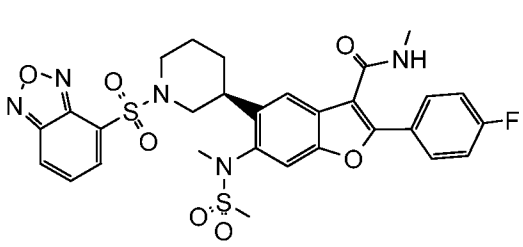
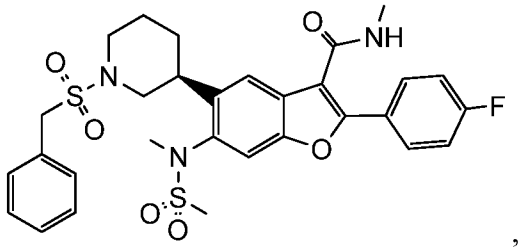
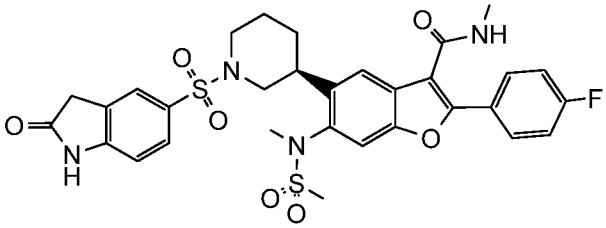
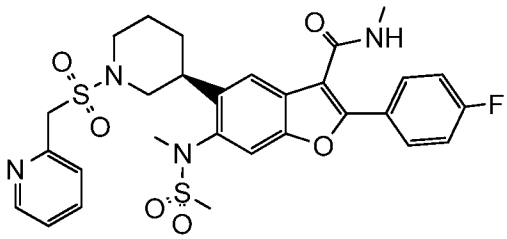
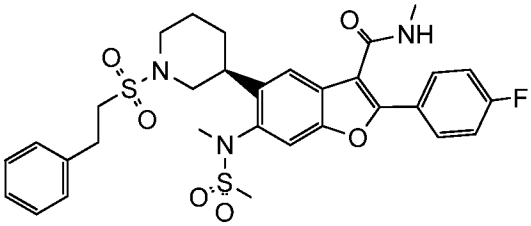
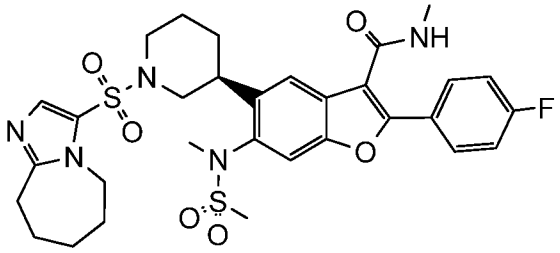
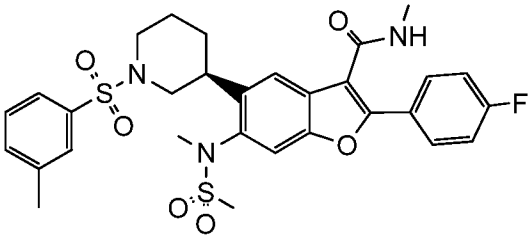
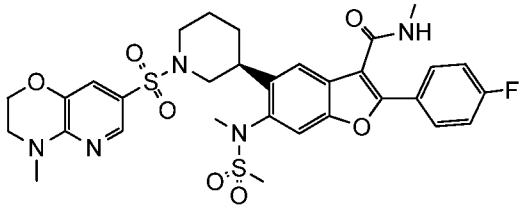
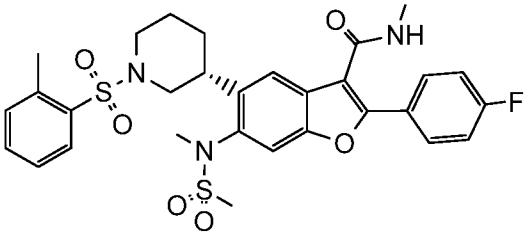
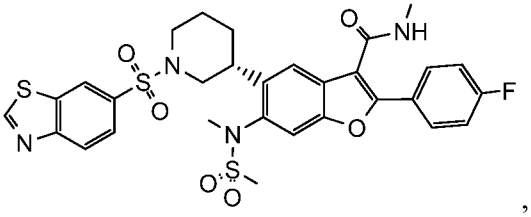

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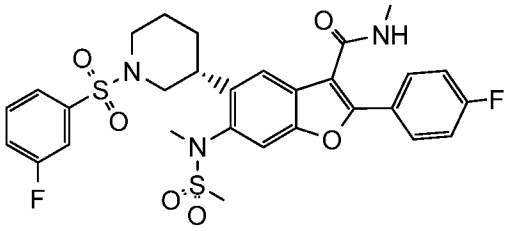
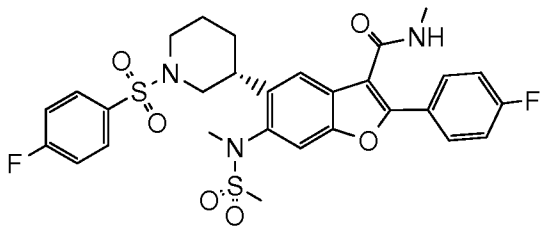
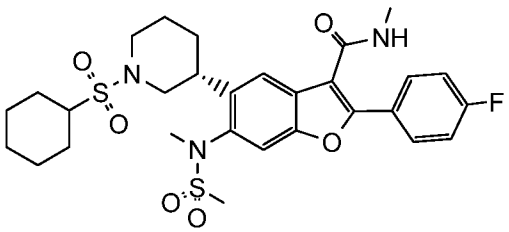
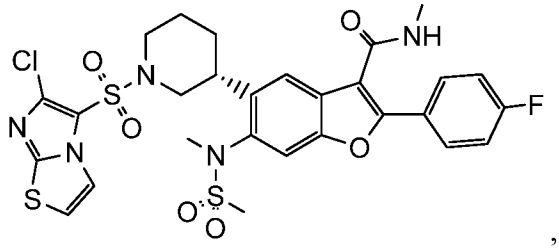
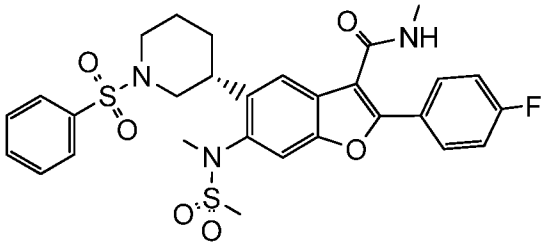
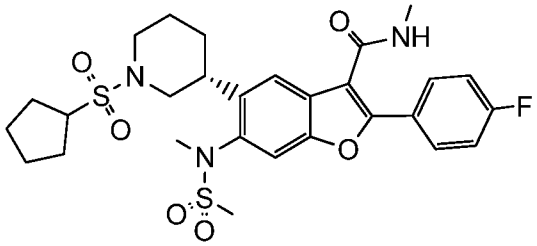
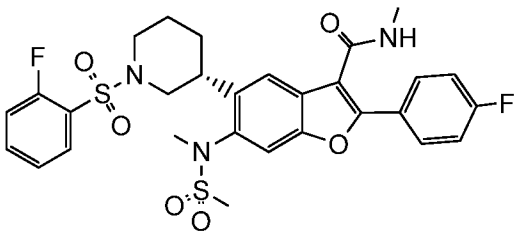
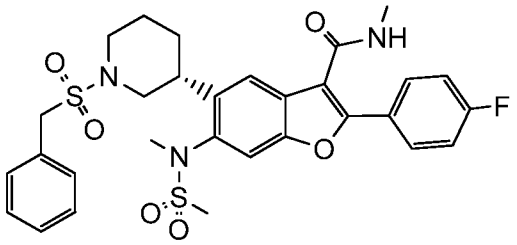
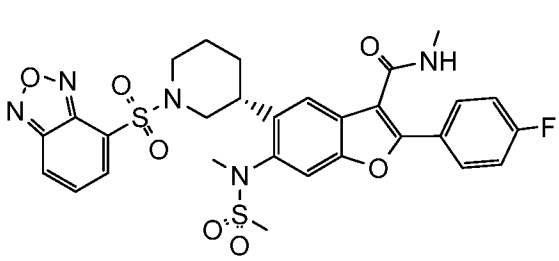
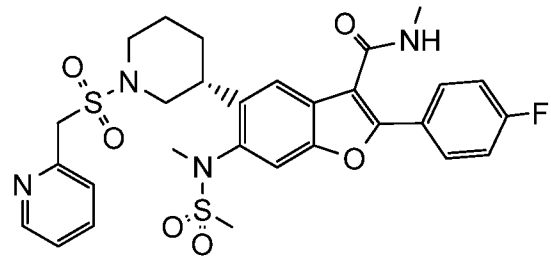
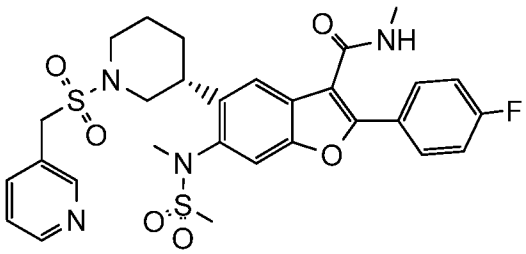
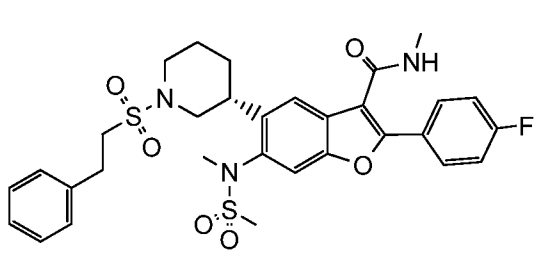

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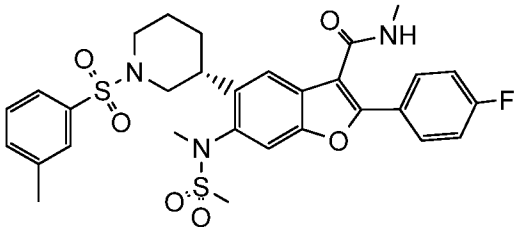
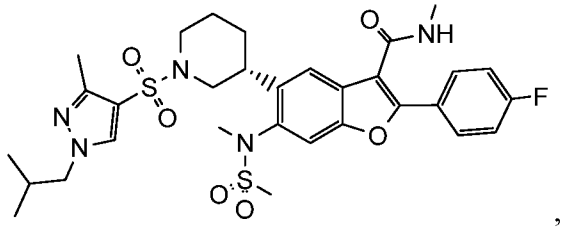
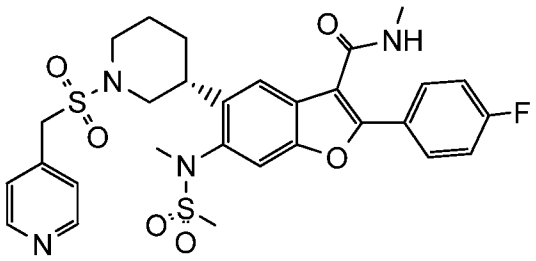

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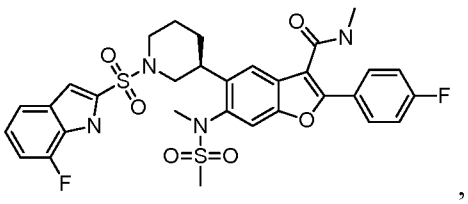
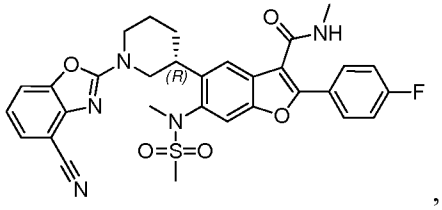
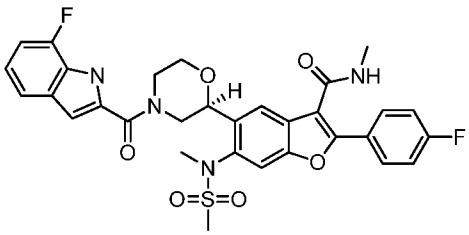
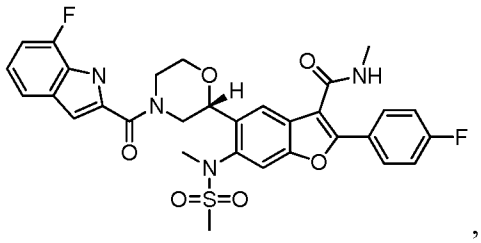
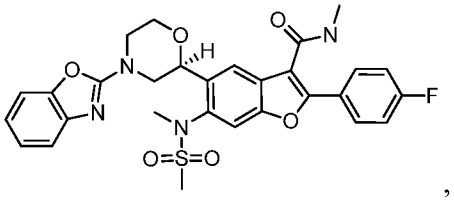
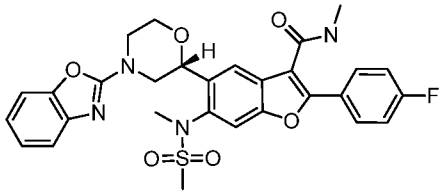

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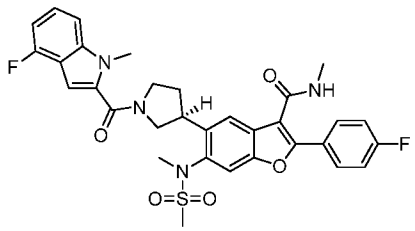
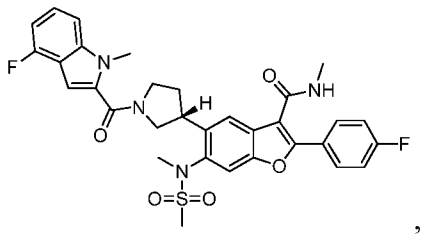
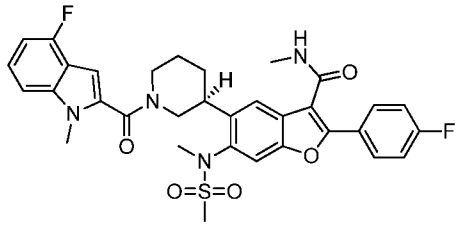
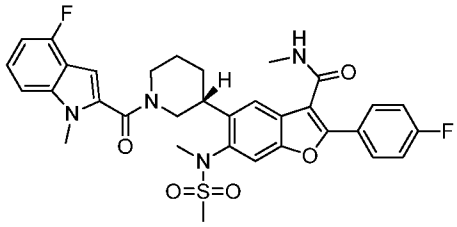
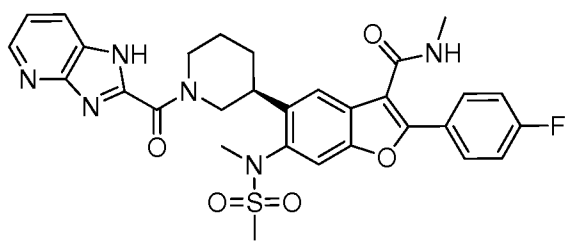
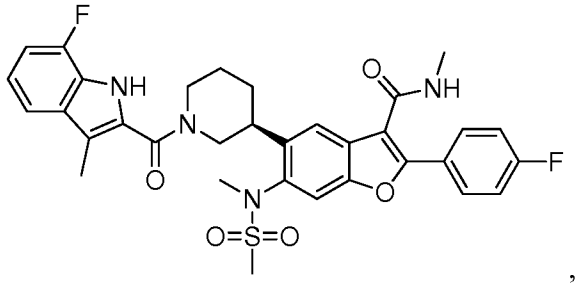
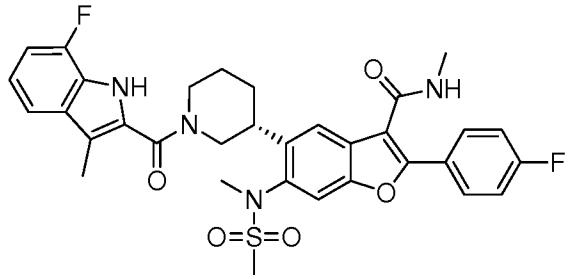
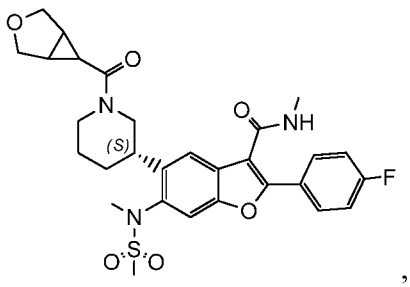

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or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is any one of


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or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) an effective amount of the compound of any one of claims 1-12 or a pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of claim 13, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

15. The pharmaceutical composition of claim 14, wherein the second therapeutic agent is selected from the group consisting of HCV NS3 and NS3/4A protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

16. A use of the compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting HCV NS5B activity or for preventing and/or treating infection by HCV in a patient in need thereof.

17. A compound according to any one of claims 1 to 12 for use in treating a patient infected with HCV.

18. A method of treating a patient infected with HCV, the method comprising administering to the patient the compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in an amount effective to prevent and/or treat infection by HCV in the patient.

19. The method of claim 18, further comprising administering to said patient an effective amount of at least one second therapeutic agent selected from the group consisting of HCV NS3 and NS3/4A protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000745

A. CLASSIFICATION OF SUBJECT MATTER

See the extra box

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)

IPC: C07D, A61K 31/-, A61P 31/14

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)

WPI; EPODOC; CNKI; CNPAT; REG; CAPLUS: benzofuran, hepatitis C virus, HCV, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 1731993 A (VIROPHARMA INCORPORATED et al.) 08 February 2006 (08.02.2006) See claims 1-25, description, page 17, lines 6-15, example 465 and Table 1	1-17
A	WO 2009137500 A1 (WYETH et al.) 12 November 2009 (12.11.2009) See the whole document, especially claims and examples	1-17
A	WO 2011112769 A1 (BRISTOL-MYERS SQUIBB CO et al.) 15 September 2011 (15.09.2011) See the whole document, especially claims and examples	1-17
A	WO 2011103063 A1 (GLAXO GROUP LIMITED et al.)25 August 2011 (25.08.2011) See the whole documents, especially claims and examples	1-17

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2014 (14.03.2014)	**27 Mar. 2014 (27.03.2014)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer SHA, Lei Telephone No. (86-10)62084375

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000745

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE Registry [Online]. COLUMBUS，OHIO，US：CHEMICAL ABSTRACTS SERVICE [retrieved on 09 June 2008]. Retrieved from STN International, Columbus, USA. RN 1026673-40-4	1, 3-6,

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000745

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 18-19 relates to a treatment method of human or animal body, and therefore, according to the criteria set out in Rule 39.1(iv), relates to subject matter for which an international search is not required.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000745

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 1731993 A	08.02.2006	TW 200418452 A	01.10.2004
		JP 2006510736 A	30.03.2006
		US 2007231318 A1	01.10.2007
		MX 265539 B	01.04.2009
		AU 2003290584 A1	07.06.2004
		MX 2005004608 A1	01.09.2005
		IN 200502291 P1	19.01.2007
		US 7265152 B2	04.09.2007
		IN 219490 B	27.06.2008
		IL 168282 A	18.11.2009
		WO 2004041201 A2	21.05.2004
		US 7666863 B2	23.02.2010
		KR 20050065661 A	29.06.2005
		SG 112386 B	31.10.2007
		US 2004162318 A1	19.08.2004
		ZA 200503501 A	25.10.2006
		US 2009281336 A1	12.11.2009
		JP 4537315 B2	01.09.2010
		NO 20052071 A	23.05.2005
		BR 0315937 A	13.09.2005
		EP 1581207 A2	05.10.2005
WO 2009137500 A1	12.11.2009	None	
WO 2011112769 A1	15.09.2011	US 8354410 B2	15.01.2013
		US 2012059019 A1	08.03.2012
		MX 2012010216 A	31.10.2012
		MX 313689 B	27.09.2013
		JP 2013522224 A	13.06.2013
		KR 20130016263 A	14.02.2013
		CN 102892767 A	23.01.2013
		IN 201207478 P4	27.12.2013

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000745

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		AU 2011224319 A1	01.11.2012
		EP 2545051 A1	16.01.2013
WO 2011103063 A1	25.08.2011	TW 201138786 A	16.11.2011

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/000745

A. CLASSIFICATION OF SUBJECT MATTER

C07D 307/84 (2006.01) i

C07D 405/14 (2006.01) i

C07D 413/14 (2006.01) i

C07D 405/10 (2006.01) i

C07D 411/14 (2006.01) i

A61K 31/453 (2006.01) i

A61P 31/14 (2006.01) i