(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2011 (09.09.2011)

PCT

(10) International Publication Number
WO 2011/106929 A1

(51) International Patent Classification:
C07D 307/82 (2006.01) *A61P 31/12* (2006.01)
A61K 31/343 (2006.01)

(21) International Application Number:
PCT/CN2010/070831

(22) International Filing Date:
2 March 2010 (02.03.2010)

(25) Filing Language: English

(26) Publication Language: English

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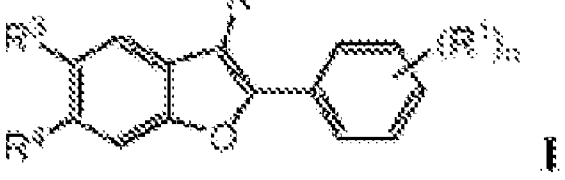
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: INHIBITORS OF HEPATITIS C VIRUS NS5B POLYMERASE



(57) Abstract: Compounds of formula I that are used 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 infection and for inhibiting HCV viral replication and /or viral production in a cell-based system.

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INHIBITORS OF HEPATITIS C VIRUS NS5B POLYMERASE

FIELD OF THE INVENTION

The present disclosure relates to antiviral 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).

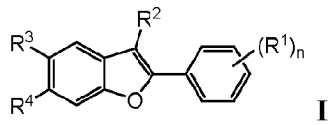
There is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection. Specifically, there is a need to develop compounds that selectively inhibit HCV viral replication and that would be useful for treating HCV-infected patients.

SUMMARY OF THE INVENTION

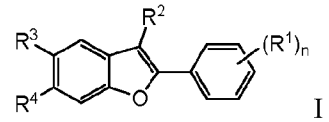
The present disclosure relates to novel compounds of formula **I** and/or pharmaceutically acceptable salts thereof. These compounds are useful, either as compounds or

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

More particularly, the present disclosure relates to a compound of formula **I**:



I



I

or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from the group consisting of halogens;

n is 0, 1, 2 or 3;

R^2 is $C(O)NR^AR^B$;

R^A and R^B are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and $O(C_1$-C_6 alkyl);

R^3 is ArA, wherein ArA is an aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings, and

ii) 8-, 9- or 10-membered bicyclic rings, and

wherein said ArA is substituted by 0, 1, 2 or 3 substitutents R^C;

each R^C is independently selected from the group consisting of:

a) halogen,

b) OH

c) C_1-C_6 alkyl,

d) $O(C_1$-C_6 alkyl),

e) CN,

f) $(CH_2)_{0-3}$-ArB, wherein each ArB is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

g) $(CH_2)_{0-3}NR^DC(O)R^E$,

h) $(CH_2)_{0-3}NR^DSO_2R^E$,

i) $(CH_2)_{0-3}C(O)NR^DR^E$, and

j) $(CH_2)_{0-3}SO_2R^E$,

wherein each R^C c) C_1-C_6 alkyl, d) $O(C_1$-C_6 alkyl), and f) $(CH_2)_{0-3}$-ArB is substituted by 0, 1, 2 or 3 substituents R^F;

each R^D is independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

each R^E is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, OC_{1-6}alkyl and 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, wherein each R^E C_{1-6}alkyl, OC_{1-6}alkyl and 5- or 6-membered monocyclic rings is substituted by 0, 1, 2, 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, $O(C_1$-C_6 alkyl), halogen and OH;

each R^F is independently selected from the group consisting of:

a) halogen,

b) C_1-C_6 alkyl,

c) $O(C_1$-C_6 alkyl),

d) CN,

e) NH_2,

f) $(CH_2)_{0-3}$-ArC, wherein each ArC is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein each R^F b) C_1-C_6 alkyl, c) $O(C_1$-C_6 alkyl), and f) $(CH_2)_{0-3}$-ArC is substituted by 0, 1, 2 or 3 substituents R^G;

each R^G is independently selected from the group consisting of halogen, CN, C_{1-6}alkyl, $O(C_1$-C_6 alkyl), CF_3 and C(O)OH;

R^4 is selected from the group consisting of NR^HR^I;

R^H is selected from the group consisting of:

a) hydrogen,

b) C_{1-6}alkyl,

c) $C(O)O(C_{1-6}$alkyl), and

d) SO_2R^J;

R^J is selected from the group consisting of C_{1-6}alkyl and NR^XR^Y, where R^X and R^Y are independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^I is selected from the group consisting of:

a) C_{1-6}alkyl,

b) C_{2-6}alkenyl,

c) C_{2-6}alkynyl,

d) $(CH_2)_{0-3}(C_{3-8}$cycloalkyl),

e) $(CH_2)_{0-3}(C_{3-8}$cycloalkenyl), and

f) $C(O)C_{1-6}$alkyl,

wherein R^I is substituted by 0, 1, 2, 3 or 4 R^K;

each R^K is independently selected from the group consisting of:

a) OR^L,

b) halogen,

c) CN,

d) NR^MR^N,

e) $OC(O)C_{1-6}$alkyl,

f) $C(O)OC_{1-6}$alkyl,

g) $(CH_2)_{0-3}$-ArD, wherein each ArD is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein each R^K e) $OC(O)C_{1-6}$alkyl, f) $C(O)OC_{1-6}$alkyl, and g) $(CH_2)_{0-3}$-ArD is substituted by 0, 1, 2 or 3 substituents R^O,

R^L is selected from the group consisting of hydrogen, C_{1-6}alkyl and phenyl;

R^M is selected from the group consisting of hydrogen, C_{1-6}alkyl and $(CH_2)_{0-3}$(phenyl);

R^N is selected from the group consisting of hydrogen, C_{1-6}alkyl, $SO_2(C_{1-6}$alkyl) and $C(O)(C_{1-6}$alkyl);

or R^M and R^N are taken together with the N to which they are attached to form a 5- to 7-membered ring substituted by 0, 1, 2 or 3 R^P;

each R^O is independently selected from the group consisting of halogen, C_{1-6}alkyl, OC_{1-6}alkyl and $C(O)O(C_{1-6}$alkyl);

each R^P is independently selected from the group consisting of halogen, C_{1-6}alkyl, OC_{1-6}alkyl, oxo and $C(O)O(C_{1-6}$alkyl);

or R^H and R^I are taken together with the N to which they are attached to form a 5- to 7-membered ring.

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.

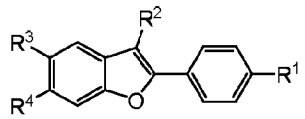
Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

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 a first embodiment of the invention, n is 1. In this embodiment, all other groups are as provided in the general formula above.

In a second embodiment of the invention, the compound is a compound of formula **Ia**:



Ia

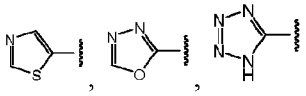
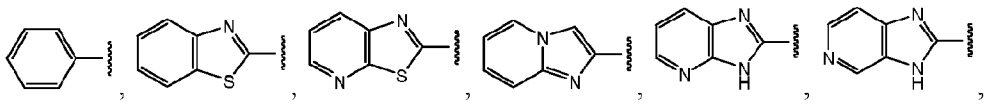
or a pharmaceutically acceptable salt thereof. In this embodiment, all other groups are as provided in the general formula above and/or in the first embodiment.

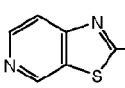
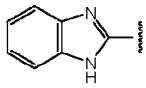
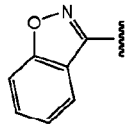
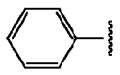
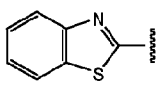
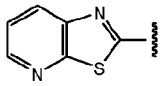
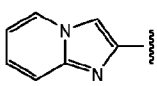
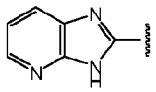
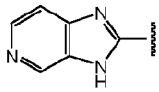
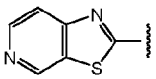
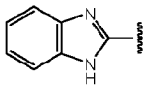
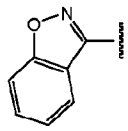
In a third embodiment of the invention, R^1 is selected from the group consisting of fluorine, bromine and chlorine. In a first aspect of this third embodiment, R^1 is fluorine. In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first or second embodiments.

In a fourth embodiment of the invention, R^A is hydrogen. In this embodiment, all other groups are as provided in the general formula above and/or in the first through third embodiments.

In a fifth embodiment of the invention, R^B is selected from the group consisting of $-CH_3$ and $-OCH_3$. In this embodiment, all other groups are as provided in the general formula above and/or in the first through fourth embodiments.

In a sixth embodiment of the invention, ArA is phenyl. In this embodiment, all other groups are as provided in the general formula above and/or in the first through fifth embodiments.

In a seventh embodiment of the invention, each R^C is independently selected from the group consisting of a) fluorine, b) OH, c) $C_{1\text{-}3}$alkyl, d) $OC_{1\text{-}3}$alkyl, e) CN, f) $(CH_2)_{0\text{-}1}$-ArB, wherein ArB is independently selected from the group consisting of  ,  .

  and  , g) $(CH_2)_{0-1}N(CH_3)SO_2CH_3$, h) $(CH_2)_{0-1}N(H)SO_2CH_3$, i) $(CH_2)_{0-1}N(CH_3)SO_2$phenyl, j) $C(O)NHCH_3$, k) $(CH_2)_{0-1}N(H)C(O)CH_3$, and l) $(CH_2)_{0-1}N(H)C(O)$phenyl. In a first aspect of this seventh embodiment each R^C is independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  . In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first through sixth embodiments.

In an eighth embodiment of the invention, R^H is selected from hydrogen, CH_3 and SO_2CH_3. In a first aspect of this eighth embodiment, R^H is SO_2CH_3. In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first through seventh embodiments.

In a ninth embodiment of the invention, R^I is selected from the group consisting of C_{1-6}alkyl and C_{2-6}alkenyl. In this embodiment, all other groups are as provided in the general formula above and/or in the first through eighth embodiments.

In a tenth embodiment of the invention, R^K is selected from the group consisting of a) OR^L, b) halogen, c) CN, d) NR^MR^N, e) $OC(O)C_{1-6}$alkyl, and f) $C(O)OC_{1-6}$alkyl. In this embodiment, all other groups are as provided in the general formula above and/or in the first through ninth embodiments.

In an eleventh embodiment of the invention, R^L is selected from the group consisting of C_{1-6}alkyl. In this embodiment, all other groups are as provided in the general formula above and/or in the first through tenth embodiments.

In a twelfth embodiment of the invention, R^M is selected from the group consisting of hydrogen and C_{1-6}alkyl. In this embodiment, all other groups are as provided in the general formula above and/or in the first through eleveth embodiments.

In a thirteenth embodiment of the invention, R^N is selected from the group consisting of C_{1-6}alkyl and $SO_2(C_{1-6}$alkyl). In this embodiment, all other groups are as provided in the general formula above and/or in the first through twelfth embodiments.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1 through 154 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.

As used herein, all ranges are inclusive, and all sub-ranges are included within such ranges, although not necessarily explicitly set forth. In addition, the term "or," as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term "or" includes each listed alternative separately as well as their combination.

As used herein, the term “alkyl” refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, “$C_{1\text{-}6}$ alkyl” (or “C_1-C_6 alkyl”) refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, “$C_{1\text{-}4}$ alkyl” refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. Alkyl groups may be substituted as indicated.

The term "halogenated" refers to a group or molecule in which a hydrogen atom has been replaced by a halogen. Similarly, the term “haloalkyl” refers to a halogenated alkyl group. 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 “alkoxy” refers to an “alkyl-O-” group. Alkoxy groups may be substituted as indicated.

The term "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, “$C_{3\text{-}8}$ cycloalkyl” (or “C_3-C_8 cycloalkyl”) refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl,

cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, and cyclooctenyl. The term "cycloalkoxy" refers to a "cycloalkyl-O-" group. Cycloalkyl groups may be substituted as indicated.

The term "aryl" (or "aryl 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. Suitable aryl groups include phenyl, naphthyl, biphenylenyl, pyridinyl, pyrimidinyl and pyrrolyl, as well as those discussed below. Aryl groups may be substituted as indicated. 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 "carbocycle" (and variations thereof such as "carbocyclic") as used herein, unless otherwise indicated, refers to (i) a C_5 to C_7 monocyclic, saturated or unsaturated ring, or (ii) a C_8 to C_{10} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent of, or fused to, the other ring, and each ring is saturated or unsaturated. Carbocycle groups may be substituted as indicated. When the carbocycles contain one or more heteroatoms independently chosen from N, O and S, the carbocycles may also be referred to as "heterocycles," as defined below. The carbocycle may be attached to the rest of the molecule at any carbon or nitrogen atom that results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; *i.e.*, the term "fused bicyclic carbocycle" generally refers to a C_8 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which both rings are saturated is a saturated bicyclic ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, *e.g.*, cyclopropyl, cyclobutyl, *etc*. A fused bicyclic carbocycle in which one or both rings are unsaturated is an unsaturated bicyclic ring system. Carbocycle 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 ring systems can be attached to any ring atom, provided that such attachment results in formation of a stable ring system.

Unless indicated otherwise, the term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to (i) a stable 5- to 7-membered, saturated or

unsaturated monocyclic ring, or (ii) a stable 8- to 10-membered bicyclic ring system, wherein each ring in (ii) is independent of, or fused to, the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (*e.g.*, from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) independently selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the bicyclic ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Heterocycle groups may be substituted as indicated, and unless otherwise specified, the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl). Unless expressly stated to the contrary, the term "heteroaryl ring system" refers to aryl ring systems, as defined above, that include from 1 to 4 heteroatoms (non-carbon atoms) that are independently chosen from N, O and S. In the case of substituted heteraromatic rings containing at least one nitrogen atom (*e.g.*, pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl and benzo-1,3-dioxolyl.

Unless otherwise specifically noted as only "substituted", alkyl, cycloalkyl, and aryl groups are not substituted. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, $-CF_3$, $-NH_2$, $-N(C_1$-C_6 alkyl$)_2$, $-NO_2$, oxo, $-CN$, $-N_3$, $-OH$, $-O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$-, aryl-$S(O)_{0\text{-}2}$-, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, $-O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-,

(C_0-C_6 alkyl)C(O)$_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle and halo-heterocyclylalkyl.

As used herein, the term "compound" is intended to encompass chemical agents described by generic formula **I** in all forms, including hydrates and solvates of such chemical agents. In addition, the term "compound" is intended to encompass prodrugs of the chemical agents described by generic formula **I**.

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 "0 to 3 heteroatoms" means the ring can contain 0, 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.

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. 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).

As a result of the selection of substituents and substituent patterns, 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.

As would be recognized by one of ordinary skill in the art, 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.

The term "administration" and variants thereof (*e.g.*, "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of 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 "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the specified ingredients.

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 "subject" (alternatively referred to herein as "patient"), as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

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.

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 therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, R7025 (an enhanced interferon (Roche)), interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. The combination of pegylated-interferon and ribaviron represents the current Standard of Care for HCV treatment. The combination of one or more compounds of the present invention with the Standard of Care for HCV treatment, pegylated-interferon and ribaviron is specifically contemplated as being encompassed by the present invention. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as ROFERON interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (PEGASYS), interferon-α2b (such as INTRON-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PEGINTRON), a recombinant consensus interferon (such as interferon alphacon-1), albuferon (interferon-α bound to human serum albumin (Human Genome Sciences)), and a purified interferon-α product. Amgen's recombinant consensus interferon has the brand name INFERGEN. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in International Patent Application Publication WO 01/60379. In accordance with the method of the present invention,

the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the invention may also be administered in combination with the antiviral agent NS5B polymerase inhibitor R7128 (Roche). The compounds of the present invention also may be combined for the treatment of HCV infection with antiviral 2'-*C*-branched ribonucleosides disclosed in Rogers E. Harry-O'Kuru *et al.*, *A Short, Flexible Route toward 2'-C-Branched Ribonucleosides*, 62 J. ORG. CHEM. 1754-59 (1997); Michael S. Wolfe & Rogers E. Harry-O'Kuru, *A Concise Synthesis of 2'-C-Methylribonucleosides*, 36(42) TETRAHEDRON LETTERS 7611-14 (1995); U.S. Patent No. 3,480,613; and International Patent Application Publications WO 01/90121, WO 01/92282, WO 02/32920, WO 04/002999, WO 04/003000 and WO 04/002422; the entire contents of each of which are incorporated by reference. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Exemplary substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in International Patent Application Publications WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, WO 02/48116, WO 02/48172, WO 2008/057208 and WO 2008/057209, in British Patent No. GB 2 337 262, and in U.S. Patent Nos. 6,323,180 and 7,470,664.

The compounds of the present invention may also be combined for the treatment of HCV infection with nucleosides having anti-HCV properties, such as those disclosed in International Patent Application Publications WO 02/51425, WO 01/79246, WO 02/32920, WO 02/48165 and WO 2005/003147 (including R1656, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine, shown as compounds 3-6 on page 77); WO 01/68663; WO 99/43691; WO 02/18404 and WO 2006/021341, and U.S. Patent Application Publication US 2005/0038240, including 4'-azido nucleosides such as R1626, 4'-azidocytidine; U.S. Patent Application

Publications US 2002/0019363, US 2003/0236216, US 2004/0006007, US 2004/0063658 and US 2004/0110717; U.S. Patent Nos. 7,105,499, 7,125,855, 7,202,224; and International Patent Application Publications WO 02/100415, WO 03/026589, WO 03/026675, WO 03/093290, WO 04/011478, WO 04/013300 and WO 04/028481; the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in International Patent Application Publications WO 02/057287, WO 02/057425, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; U.S. Patent Nos. 6,777,392, 7,105,499, 7,125,855, 7,202,224 and U.S. Patent Application Publications US 2004/0067901 and US 2004/0110717; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (*see also* WO 2005/003147).

In one embodiment, additional nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS5B inhibitors are selected from the following compounds: 4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-

pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in U.S. Patent Applciation Publications US 2006/0100262 and US 2009/0048239; International Patent Application Publications WO 01/77091, WO 01/47883, WO 02/04425, WO 02/06246, WO 02/20497, WO 2005/016927 (in particular JTK003), WO 2004/041201, WO 2006/066079, WO 2006/066080, WO 2008/075103, WO 2009/010783 and WO 2009/010785; the content of each is incorporated herein by reference in its entirety.

In one embodiment, additional non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS5B inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*]

[2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine 11-carboxylic acid; *N*'-(11-carboxy-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocin-7-yl)-*N*,*N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

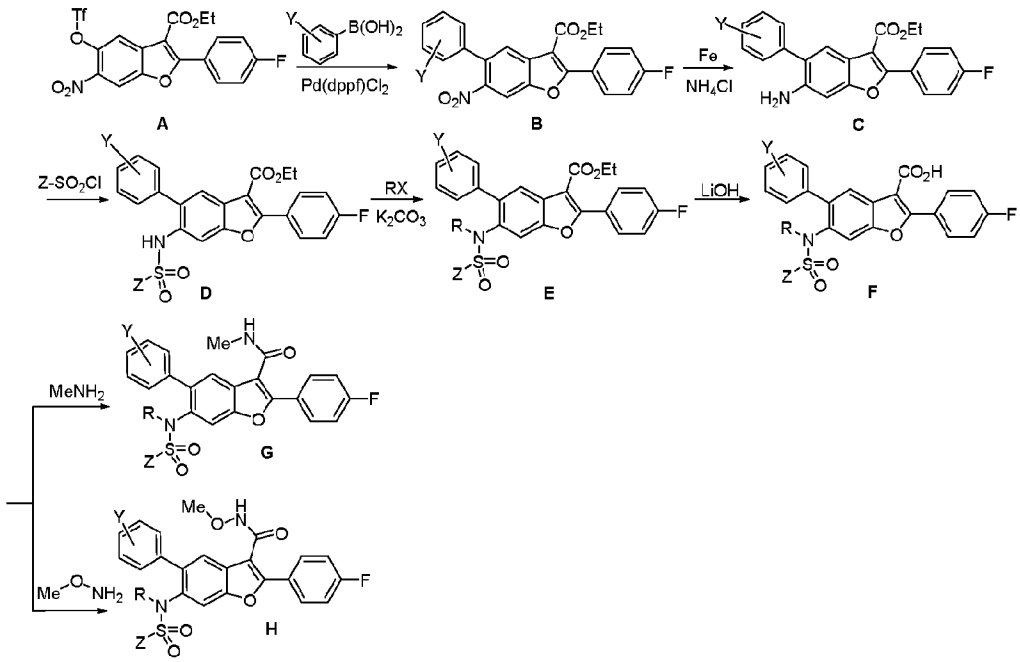
In another embodiment, the present HCV NS5B polymerase inhibitors are used in combination with non-nucleoside HCV NS5A inhibitors and pharmaceutically acceptable salts thereof.

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.

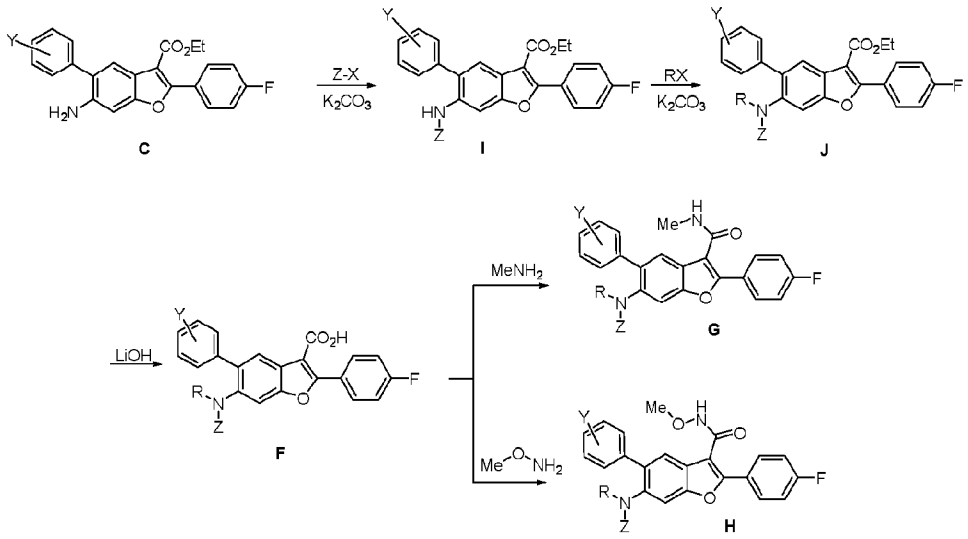
General Schemes

Scheme 1



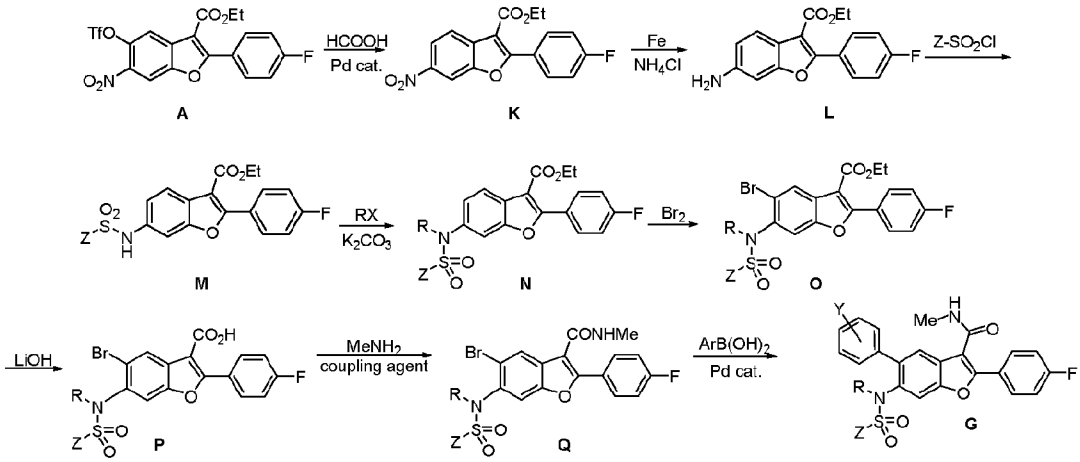
This scheme describes the preparation of compounds with the general structure of **G** and **H**. Starting from compound **A** (obtained according to procedure in WO 2004/041201 A2), coupling with a substituted or unsubstituted phenylboronic acid catalyzed by a transition metal, in this case $Pd(dppf)Cl_2$, furnishes compounds of the general structure **B**. This type of transition-metal-mediated cross-coupling is common and there are numerous conditions that one skilled in the art can use to execute such a transformation. Compounds of type **C** are next generated by reduction of the nitro group in compound **B**, which can be accomplished by exposure to common reducing conditions, in this case treatment by Fe in NH_4Cl solution under reflux. The amino group in compounds **C** is then sulfonylated with a sulphonyl chloride to give compounds of type **D**. The sulfonamide **D** can be coupled with an alkylating agent (an alkyl halide for example) in the presence of a suitable base, such as potassium carbonate, to provide compounds **E**. The ester functionality in compounds **E** is readily hydrolyzed by aqueous base to afford compounds **F**. The carboxylic acid of compound **F** was condensed with methanamine or *O*-methylhydroxylamine using common amide-forming reagents such as EDCI and HOBT to give compounds **G** or compounds **H**.

Scheme 2



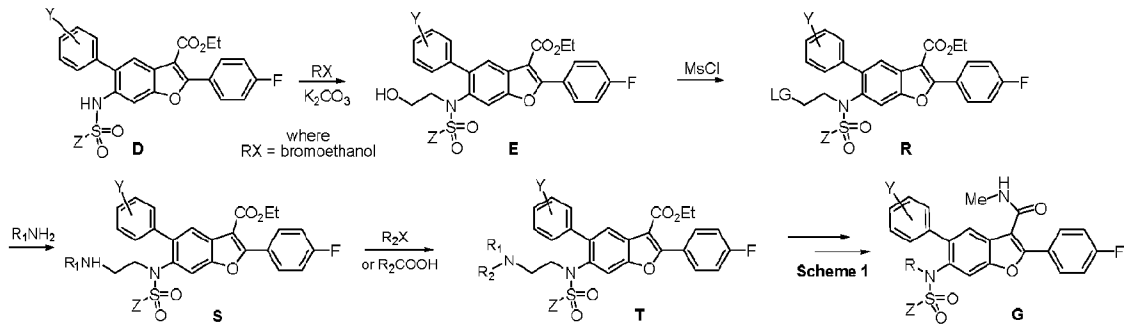
Compound **C** can be coupled with an alkylating agent (an alkyl halide for example) in the presence of a suitable base, such as potassium carbonate, to provide compounds **I** where Z represents an alkylated aniline. Alternatively **C** may be condensed with substituted carboxylic acid in the presence of coupling reagents, such as EDCI and HOBT, to afford compounds **I** where Z represents a substituted amide. Compounds **J** may be obtained from compounds **I** by further *N*-alkylation or *N*-acylation reaction. Compounds of general structure **I** or **J** are hydrolyzed by aqueous hydroxide to provide compounds **F**. The carboxylic acid of compound **F** may be condensed with an amine as shown in **Scheme 1** to provide target compounds of general structure **G** and **H**.

Scheme 3



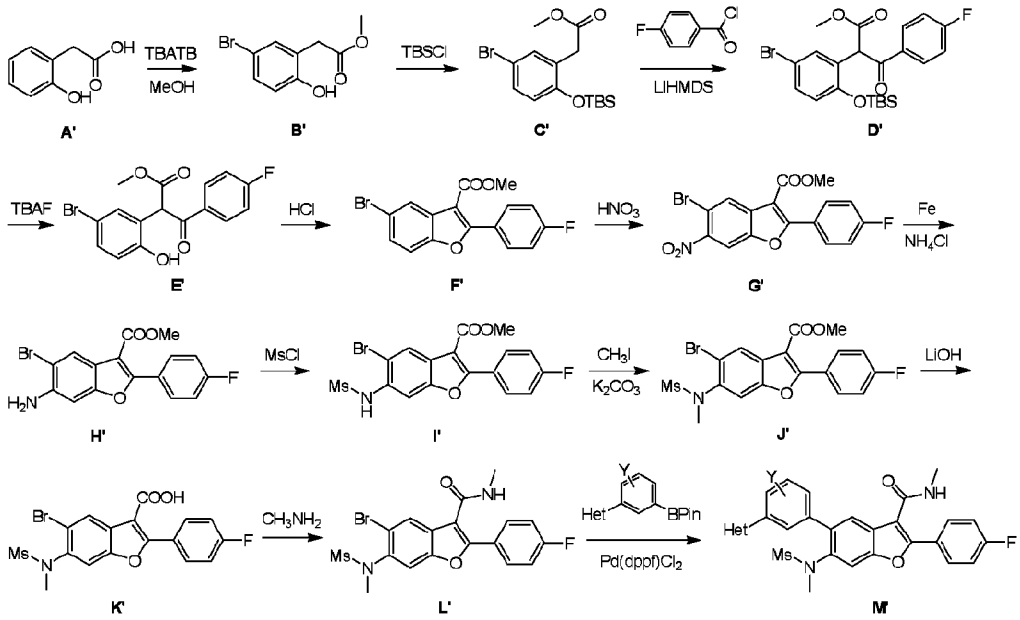
Compound **A** may be reduced by a catalyst in the presence of a hydrogen source (for example, Pd in the presence of formic acid) to afford compound **K**. Further reduction of **K** provides aniline **L**. The amino group of compound **L** is reacted with sulfonyl chloride to afford compound **M**, which can be further *N*-alkylated with a wide variety of alkylating agents in the presence of a suitable base, such as potassium carbonate, to provide compound **N**. Halogenation of compound **N**, in this case bromination with $FeCl_3$ and Br_2 in anhydrous CCl_4 gives compound **O**. Compounds of general structure **O** are hydrolyzed by aqueous hydroxide to provide compounds **P**. The carboxylic acid of compound **P** may be condensed with an amine as shown in **Scheme 1** to provide compounds of general structure **Q**. Transition metal mediated coupling of compounds **Q** with a boronic acid (alternatively alkyl tin, silicon, or other types of coupling partners may be used) provides the target compounds of general structure **G**.

Scheme 4



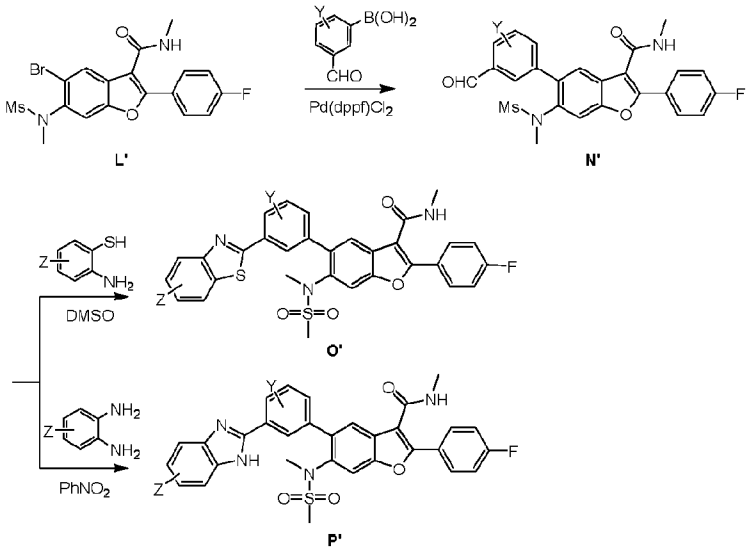
Compounds **E** that possess a hydroxyl group may be obtained from compounds **D** by reacting with 2-bromo ethanol. The hydroxyl group **E** can be converted to a leaving group (by reaction with MsCl for example) to afford compound **R**. Compound **R** may be treated with nucleophilic reagents such as an amine in the presence of a suitable base, such as triethylamine, to afford compound **S**. Compounds **T** can then be obtained from compound **S** by further *N*-alkylation or *N*-acylation. Compounds of structure **T** are readily converted to the target structures **G** following the general procedure described in **Scheme 1**.

Scheme 5



This scheme describes the preparation of compounds with the general structure of **M'**. Starting from compound **A'**, bromating and esterifying with TBATB in MeOH to afford compound **B'**. Protecting the phenol group of **B'** with TBSCl provides compound **C'**, which can be C-acylated with 4-fluorobenzoyl chloride to give compound **D'**. After de-protection with TBAF and cyclizing by concentrated HCl, compound **D'** affords compound **E'** and **F'** sequentially. Compound **F'** can be converted to compound **G'** by treated with fuming HNO_3. Compound **H'** is generated by reduction of the nitro group in compound **G'**, and the amino group in compound **H'** is then sulfonylated with MsCl to furnish compound **I'**. The sulfonamide **I'** can be coupled with MeI in the presence of potassium carbonate to provide compound **J'**. The ester functionality in compound **J'** is readily hydrolyzed by aqueous base to afford compound **K'**. The carboxylic acid of compound **K'** was condensed with methanamine using common amide forming reagents such as EDCI and HOBT to give compound **L'**. Transition metal mediated coupling of compound **L'** with a meta-heterocycle-substituted phenyl boronic ester (alternatively boronic acid, alkyl tin, silicon, or other types of coupling partners may be used) provides the target compounds of general structure **M'**.

Scheme 6



Coupling compound **L'** with a substituted or unsubstituted 3-formylphenylboronic acid catalyzed by a transition metal, in this case $Pd(dppf)Cl_2$, furnishes compounds of the general structure **N'**. Compounds of type **N'** were cyclized with ortho-amino anilines or ortho-amino thiophenols to provide the target compounds of general structure **O'** or **P'**.

List of Abbreviations

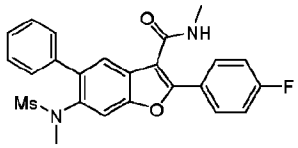
AcOH	Acetic acid
Br_2	Bromine
Bu_3N	*N*,*N*-dibutylbutan-1-amine
CCl_4	Carbon tetrachloride or tetrachloromethane
$CDCl_3$	Trichloro(^{2}H)methane or deuterio-trichloromethane
CH_3I	Methyl iodide
Cs_2CO_3	Cesium carbonate
CuI	Copper iodide
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDCI	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (also EDC)
Et_3N	Triethylamine

EtOAc	Ethyl acetate
EtOH	Ethanol
EtOOCCl, ClCOOEt	Ethyl chloroformate
Fe	Iron
$FeCl_3$	Ferric chloride or Iron(III) chloride
HCl	Hydrochloric acid
H_2	Hydrogen gas or atmosphere
H_2O	Water
HCOOH	Formic Acid
HOBT	1-Hydroxy benzotriazole
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
K_2CO_3	Potassium carbonate
KI	Potassium iodide
K_3PO_4	Potassium Phosphate
LiHMDS	Lithium bis(trimethylsilyl) amide
LiOH	Lithium hydroxide
$MeNH_2$, CH_3NH_2	Methanamine
MeCN, CH_3CN	Acetonitrile
MeOD	Methan(^{2}H)ol
MeOH	Methanol
$MeONH_2$, CH_3ONH_2	Methoxyamine
MS	Mass spectroscopy
Ms	Methanesulfonyl (or mesyl) group
MsCl	Methanesulfonyl chloride
N_2	Nitrogen gas or atmosphere
Ni	Nickel
Na_2SO_3	Sodium sulfite
Na_2SO_4	Sodium sulfate (anhydrous)
NaH	Sodium hydride
$NaNO_2$	Sodium nitrate
NH_4Cl	Ammonium chloride

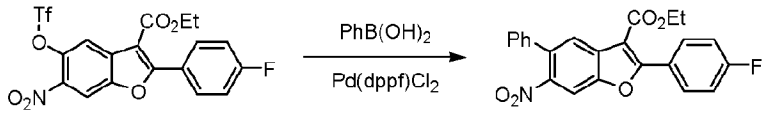
Pd	Palladium
$Pd(dppf)Cl_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride
$Pd(PPh_3)_2Cl_2$	1,1'-bis(tetrakis(triphenylphosphine))palladium(II)dichloride
Ph	Phenyl
$PhB(OH)_2$	Phenylboronic acid
$PhNO_2$	Nitrobenzene
Py	Pyridine
RT	Room temperature, approximately 25°C
$SOCl_2$	Thionyl chloride
TBAF	Tetrabutyl ammonium fluoride
TBATB	Tetrabutylammonium tribromide
TBS	Tert-butyldimethylsilyl
TBSCl	Tert-butyldimethylsilylchloride
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography

EXAMPLES

Example 1: 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Step 1: ethyl 2-(4-fluorophenyl)-6-nitro-5-phenyl-1-benzofuran-3-carboxylate

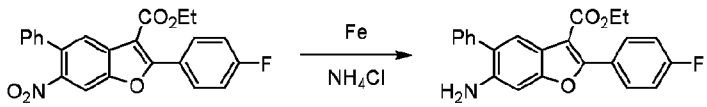


Phenylboronic acid (100 mg, 0.8 mmol) and $K_3PO_4 \cdot 3H_2O$ (119 mg, 0.8 mmol) were added to a suspension of ethyl 2-(4-fluorophenyl)-6-nitro-5-{[(trifluoromethyl)sulfonyl] oxy}-1-benzofuran-3-carboxylate (obtained according to procedure in WO 2004/041201 A2, 200 mg, 0.4 mmol) in dioxane (2 mL) and DMF (2 mL) under N_2 protection. Then, $Pd(dppf)Cl_2$ (5 mg, 0.08 mmol) was added to the mixture under N_2 protection. The reaction mixture was

heated to 90°C for 30 minutes. After cooling, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep-TLC to give pure ethyl 2-(4-fluorophenyl)-6-nitro-5-phenyl-1-benzofuran-3-carboxylate (35 mg, yield: 23%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88~7.98 (m, 2H), 7.62 (s, 1H), 7.44~7.48 (m, 4H), 7.32~7.38 (m, 1H), 7.06~7.12 (m, 2H), 6.78 (s, 1H), 4.29~4.35 (m, 2H), 1.27~1.30 (m, 3H)

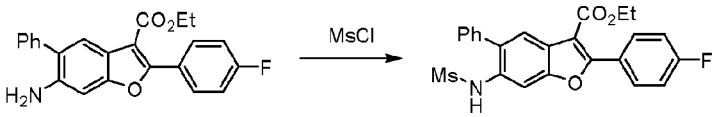
Step 2: ethyl 6-amino-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylate



A mixture of ethyl 2-(4-fluorophenyl)-6-nitro-5-phenyl-1-benzofuran-3-carboxylate (110 mg, 0.27 mmol), Fe (120 mg, 2.16 mmol) and NH_4Cl (217 mg, 4.05 mmol) in H_2O /MeOH /THF (1 mL /1 mL /1 mL) was refluxed for 4 hours. Then, H_2O was added to quench the reaction, and the mixture was extracted with EtOAc. After washing with brine and dried, the solvent was removed by distillation. The pure product of ethyl 6-amino-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylate was obtained (85 mg, yield: 85%) by prep-TLC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.03 (m, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.45~7.49 (m, 3H), 7.29~7.32 (m, 2H), 7.10~7.14 (m, 2H), 4.29~4.35 (m, 2H), 1.27~1.30 (m, 3H).

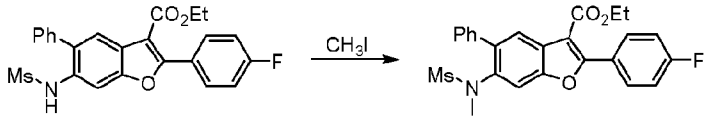
Step 3: ethyl 2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



MsCl (66 mg, 0.6 mmol) was added to a solution of the product of Step 2 (85 mg, 0.23 mmol) and pyridine (73 mg, 0.92 mmol) in dry DCM (2 mL). The reaction mixture was stirred overnight at RT. After dilution with H_2O and extraction with DCM, the organic layer was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by prep-TLC to give ethyl 2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate (90 mg, yield: 86%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.03 (m, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.45~7.49 (m, 3H), 7.29~7.32 (m, 2H), 7.10~7.14 (m, 2H), 6.50 (s, 1H), 4.29~4.35 (m, 2H), 2.80 (s, 3H), 1.27~1.30 (m, 3H).

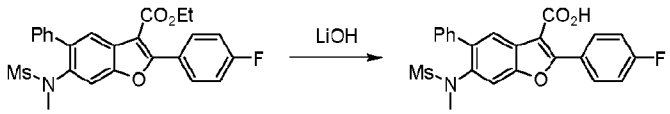
Step 4: ethyl 2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



NaH (60% in oil, 20 mg, 0.5 mmol) and CH_3I (85 mg, 0.6 mmol) were added to a solution of the product of Step 3 (90 mg, 0.2 mmol) in dry DMF under N_2 protection. The mixture was stirred overnight at RT, and then ice-cold diluted AcOH was added to the mixture. After extraction with EtOAc, the organic solvent was washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by prep-TLC to give ethyl 2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate (78 mg, yield: 84%).

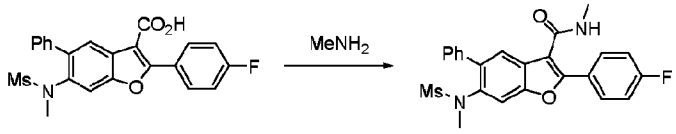
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.02 (m, 2H), 7.97~7.98 (m, 1H), 7.55~7.56 (m, 1H), 7.39~7.40 (m, 4H), 7.32~7.34 (m, 1H), 7.11~7.15 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.11 (s, 3H), 2.45 (s, 3H), 1.26~1.30 (t, J = 6.8 Hz, 3H).

Step 5: 2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



The product of Step 4 (78 mg, 0.17 mmol) was dissolved in THF (2 mL) and H_2O (2 mL). Then, LiOH (71 mg, 1.7 mmol) was added to the solution, and the mixture was stirred at RT overnight. After acidification with HCl (1 N) and extraction with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the product of 2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid (50 mg, yield: 67%). It was used for the next step without further purification.

Step 6: 2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide

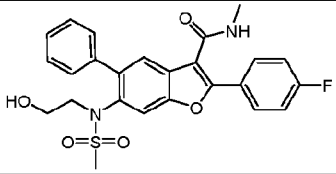
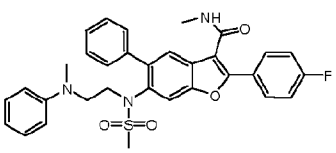
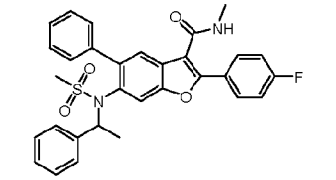


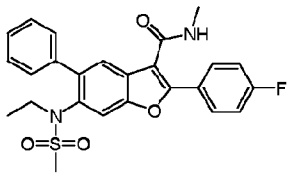
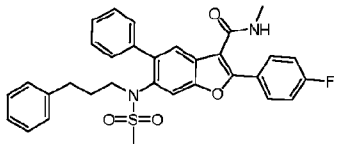
The product of Step 5 (50 mg, 0.11 mmol), HOBT (24.5 mg, 0.16 mmol) and EDCI (52 mg, 0.27 mmol) were dissolved in dry DMF (2 mL). The resulting solution was stirred for 30 minutes. Then, methanamine (HCl salt, 14 mg, 0.44 mmol) and Et_3N (50 mg, 0.47 mmol) were added to the mixture. After stirring overnight, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep-TLC to give pure 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide (20 mg, yield: 40%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92~7.96 (m, 2H), 7.59 (s, 1H), 7.52~7.54 (m, 1H), 7.29~7.47 (m, 5H), 7.11~7.18 (m, 2H), 5.84 (s, 1H), 3.25 (s, 3H), 2.98 (d, J = 7.2 Hz, 3H), 2.61 (s, 3H).

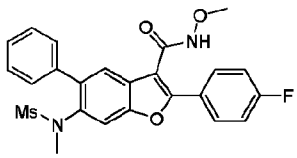
Examples 2-6

Examples 2 through 6 were prepared according to the general procedures of Example 1.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
2		2-(4-fluorophenyl)-6-[(2-hydroxyethyl) (methylsulfonyl) amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.86 ~7.90 (m, 2H), 7.72 (s, 1H), 7.59 (s, 1H), 7.47~7.50 (m, 2H), 7.32~7.40 (m, 3H), 7.10~7.16 (m, 2H), 5.80 (s, 1H), 3.28~3.47 (m, 4H), 2.90 (s, 6H).	483
3		2-(4-fluorophenyl)-*N*-methyl-6-[{2-[methyl(phenyl) amino]ethyl} (methylsulfonyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.90 ~7.91 (m, 2H), 7.74 (s, 1H), 7.51 (s, 1H), 7.31~7.43 (m, 5H), 7.08~7.18 (m, 4H), 6.60~6.63 (m, 1H), 6.48~6.50 (m, 2H), 5.78 (s, 1H), 3.24~3.41 (m, 4H), 2.92 (d, J = 4.8 Hz, 3H), 2.74 (s, 3H), 2.70 (s, 3H).	572
4		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl) (1-phenylethyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.86 ~7.93 (m, 2H), 7.65 (d, J = 2 Hz, 2H), 7.36~7.60 (m, 5H), 7.08~7.26 (m, 5H), 6.99~7.05 (m, 2H), 6.87 (s, 1H), 2.90 (t, J = 5.2 Hz, 3H), 2.87 (t, J = 6 Hz, 3H), 1.30 (t, J = 6.8 Hz, 3H).	543

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
5		6-[ethyl (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.88 ~7.92 (m, 2H), 7.77 (s, 1H), 7.5 (s, 1H), 7.32 ~7.42 (m, 5H), 7.14 (t, *J* = 8.8 Hz, 2H), 5.79 (s, 1H), 3.21~3.42 (m, 2H), 2.91 (d, *J* = 4.1 Hz, 3H), 2.67 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).	467
6		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl) (3-phenylpropyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.86 ~7.90 (m, 2H), 7.67 (s, 1H), 7.48 (s, 1H), 7.31~7.35 (m, 5H), 7.09~7.16 (m, 5H), 6.94 (d, *J* = 7.2 Hz, 2H), 5.10 (d, *J* = 4.4 Hz, 1H), 3.37 ~3.41 (m, 2H), 2.89 (d, *J* = 5.2 Hz, 3H), 2.69 (s, 3H), 2.36 (d, *J* = 5.6 Hz, 2H), 1.56 (d, *J* = 11.2 Hz, 2H).	557

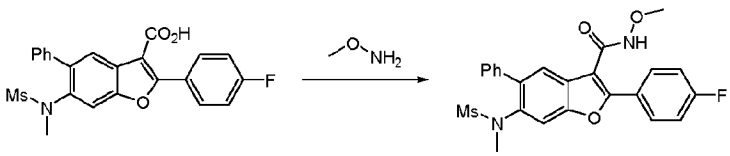
Example 7: 2-(4-fluorophenyl)-*N*-methoxy-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-5

Steps 1-5 were performed in accordance with Example 1, Steps 1-5.

Step 6: 2-(4-fluorophenyl)-N-methoxy-6-[methyl(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide

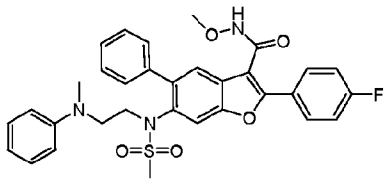
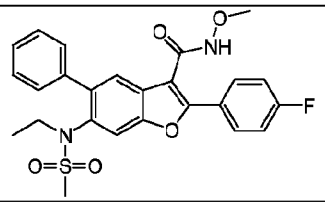
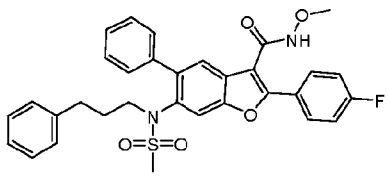
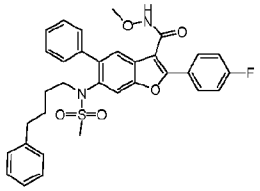
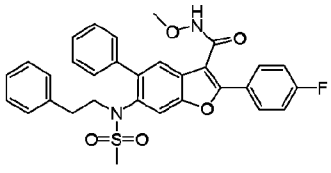


The product of Step 5 (50 mg, 0.11 mmol), HOBT (24.5 mg, 0.16 mmol) and EDCI (52 mg, 0.27 mmol) were dissolved in dry DMF (2 mL). The resulting solution was stirred for 30 minutes. Then, *O*-methylhydroxylamine (HCl salt, 36 mg, 0.44 mmol) and Et_3N (50 mg, 0.47 mmol) were added to the mixture. After stirred overnight, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep-TLC to give pure product (20 mg, yield: 40%).

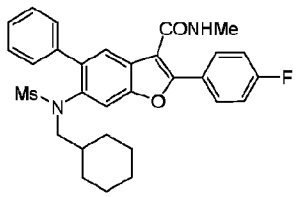
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26~8.27 (m, 1H), 7.70~7.87 (m, 2H), 7.56 (s, 1H), 7.41 (s, 1H), 7.34~7.39 (m, 5H), 7.12~7.16 (m, 2H), 3.78 (s, 3H), 3.10 (s, 3H), 2.45 (s, 3H). MS $(M+H)^+$: 469.

Examples 8-12

Examples 8-12 were prepared according to the general procedures of Example 7.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
8		2-(4-fluorophenyl)-*N*-methoxy-6-[{2-[methyl(phenyl) amino]ethyl} (methylsulfonyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	8.40 (s, 1H), 7.87~7.91 (m, 2H), 7.71 (s, 1H), 7.50 (s, 1H), 7.32~7.40 (m, 5H), 7.23~7.25 (m, 2H), 7.12~7.19 (m, 2H), 6.93~6.95 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.31~3.45 (m, 4H), 2.80 (d, *J* = 12.0 Hz, 3H), 2.74 (s, 3H).	588
9		6-[ethyl (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methoxy-5-phenyl-1-benzofuran-3-carboxamide	8.35 (s, 1H), 7.87 ~7.90 (m, 2H), 7.68 (s, 1H), 7.51 (s, 1H), 7.32 ~7.41 (m, 5H), 7.14 (t, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.23 ~3.50 (m, 2H), 2.65 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).	483
10		2-(4-fluorophenyl)-*N*-methoxy-6-[(methylsulfonyl) (3-phenylpropyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	8.35 (s, 1H), 7.86 ~7.89 (m, 2H), 7.64 (s, 1H), 7.48 (s, 1H), 7.31~7.35 (m, 5H), 7.09~7.19 (m, 5H), 6.94 (d, *J* = 7.2 Hz, 2H), 3.37 (s, 3H), 3.09~3.41 (m, 2H), 2.67 (s, 3H), 2.34 (d, *J* = 3.6 Hz, 2H), 1.68 (m, 2H).	573
11		2-(4-fluorophenyl)-*N*-methoxy-6-[(methylsulfonyl) (4-phenylbutyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.93 ~7.97 (s, 2H), 7.72 (s, 1H), 7.54 (s, 1H), 7.14~7.45 (m, 10H), 7.04 (d, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.12~3.40 (m, 2H), 2.73 (s, 3H), 2.47 (s, 2H), 1.36~1.45 (s, 4H).	587
12		2-(4-fluorophenyl)-*N*-methoxy-6-[(methylsulfonyl) (2-phenylethyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	8.28 (s, 1H), 7.93~7.91 (m, 2H), 7.73 (s, 1H), 7.48~7.43 (m, 2H), 7.40~7.33 (m, 3H), 7.121~7.11 (m, 4H), 7.00~6.98 (m, 2H) , 3.80 (s, 3H), 3.63~3.27 (m, 2H), 2.68~2.64 (m, 2H), 2.56 (s, 3H).	559

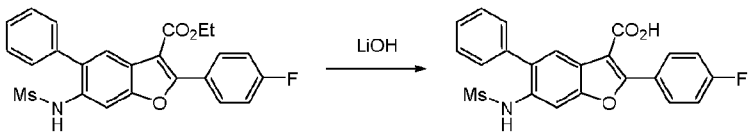
Example 13: 6-[(cyclohexylmethyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-3

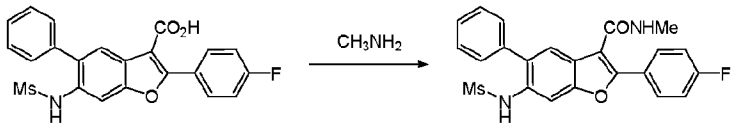
Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

Step 4: 2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



The compound prepared in Step 3 (1.3 g, 2.74 mmol) was dissolved in 1,4-dioxane (7 mL) and H_2O (7 mL). Then, LiOH (1.14, 27.4 mmol) was added to the solution, and the mixture was refluxed for 2 hours. After acidified with HCl (1 N) and extracted with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the carboxylic acid (990 mg, yield: 85%). It was used for the next step without further purification.

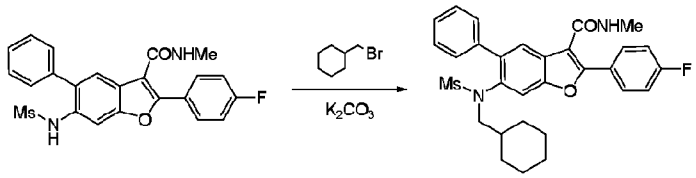
Step 5: 2-(4-fluorophenyl)-N-methyl-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



The carboxylic acid prepared in Step 4 (990 mg, 2.34 mmol), HOBT (631 mg, 4.7 mmol) and EDCI (900 mg, 4.7 mmol) were dissolved in dry DMF (10 mL). The resulting solution was stirred for 30 minutes. Then, methanamine (HCl salt, 640 mg, 9.4 mmol) and Et_3N (2 mL) were added to the mixture. After stirred overnight, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column to give pure 2-(4-fluorophenyl)-N-methyl-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide (900 mg, yield: 88%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82~7.86 (m, 2H), 7.79 (s, 1H), 7.63 (s, 1H), 7.41~7.46 (m, 3H), 7.27~7.33 (m, 2H), 7.10~7.44 (m, 2H), 6.51 (br, 1H), 5.84 (br, 1H), 2.91 (d, J = 4.8 Hz, 3H), 2.80 (s, 3H). MS $(M+H)^+$: 439.

Step 6: 6-[(cyclohexylmethyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-N-methyl-5-phenyl-1-benzofuran-3-carboxamide

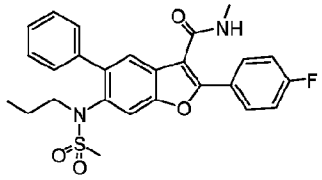


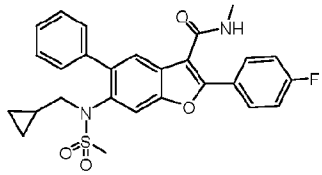
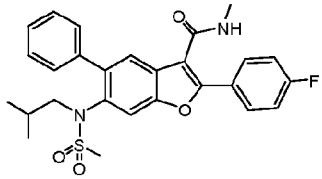
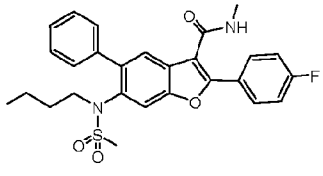
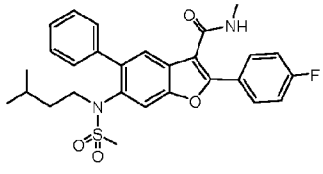
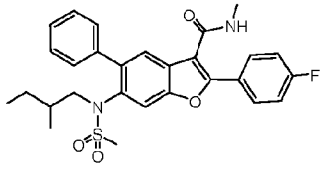
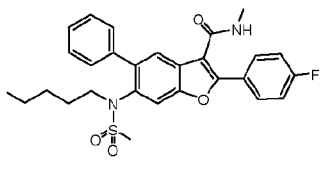
The compound prepared in Step 5 (35 mg, 0.08 mmol), (bromomethyl) cyclohexane (21 mg, 0.12 mmol), K_2CO_3 (22 mg, 0.16 mmol), KI (2 mg) in DMF (2 mL) was stirred at 90°C for 16 hours under N_2. The mixture was concentrated, diluted with DCM, washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by prep-HPLC to give pure product (15 mg, yield: 35%).

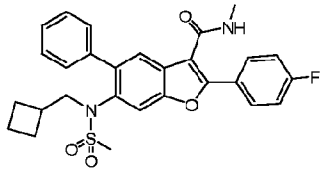
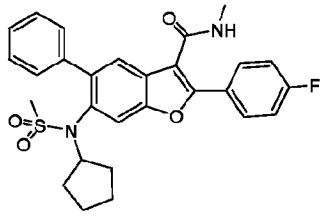
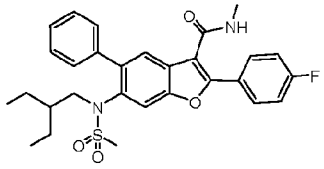
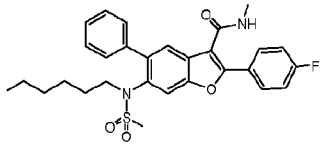
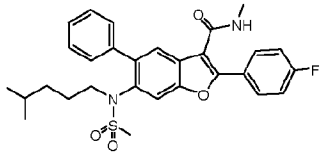
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97~7.93 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.84 (s, 1H), 3.18~3.13 (m, 1H), 2.99~2.97 (m, 4H), 2.95 (s, 3H), 1.74~1.58 (m, 1H),1.54~1.51 (m, 2H), 1.43~1.41 (m, 2H), 1.04~0.91 (m, 4H), 0.89~0.79 (m, 2H), 0.76~0.56 (m, 1H). MS $(M+H)^+$: 535.

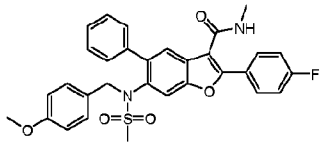
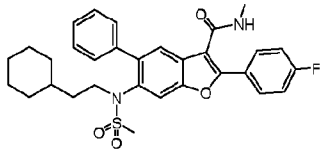
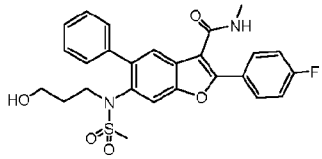
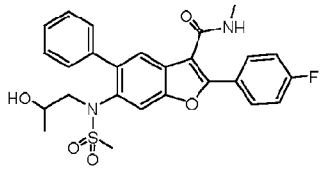
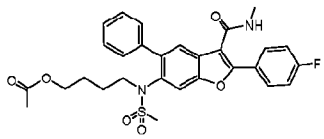
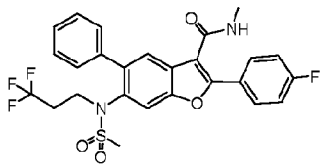
Examples 14-68

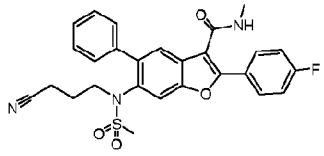
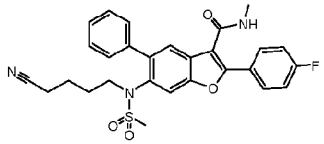
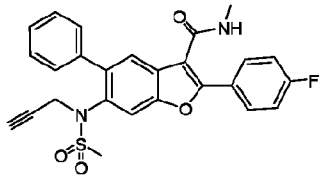
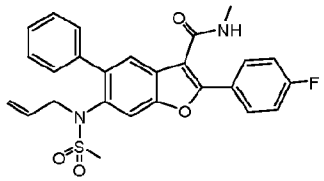
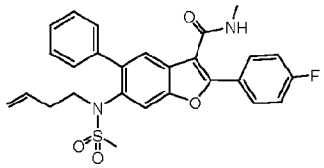
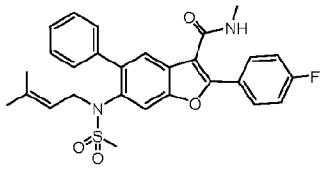
Examples 14-68 were prepared according to the general procedures of Example 13.

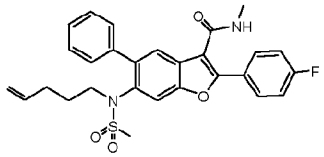
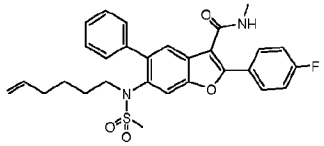
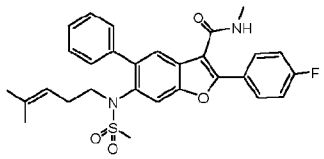
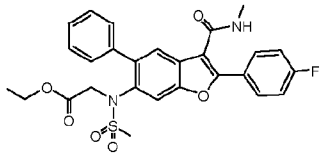
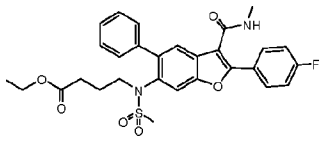
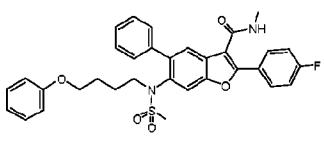
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
14		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(propyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.85 ~7.89 (m, 2H), 7.66 (s, 1H), 7.48 (s, 1H), 7.31~7.42 (m, 5H), 7.12 (t, J = 8.4 Hz, 2H), 5.89 (d, J = 3.6 Hz, 1H), 3.06~3.11 (m, 2H), 2.89 (d, J = 5.2 Hz, 3H), 2.70 (s, 3H), 1.36 (d, J = 4.4 Hz, 2H), 0.67 (t, J = 7.2 Hz, 3H).	481

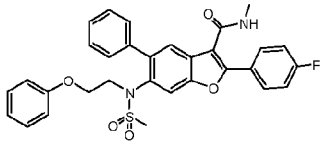
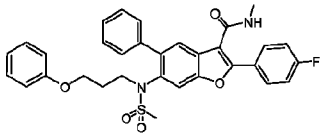
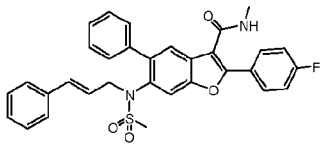
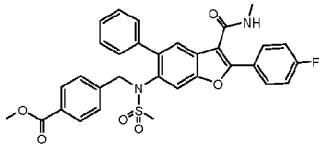
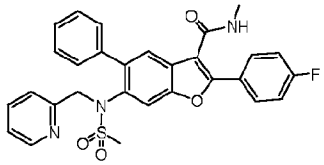
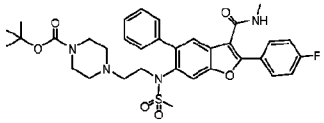
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
15		6-[(cyclopropylmethyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.95~7.99 (m, 2H), 7.76 (s, 1H), 7.65 (s, 1H), 7.50~7.52 (m, 2H), 7.40~7.43 (m, 3H), 7.18~7.26 (m, 2H), 5.88 (br s, 1H), 3.38~3.42 (m, 1H), 3.02~3.04 (m, 1H), 2.99 (d, *J* = 4.8 Hz, 3H), 0.88~0.92 (m, 1H), 0.44 (m, 2H), 0.11 (br s, 1H), 0.01 (br s, 1H), 0.65 (t, *J* = 7.2 Hz, 3H).	493
16		2-(4-fluorophenyl)-*N*-methyl-6-[(2-methylpropyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.89 (t, *J* = 4.8 Hz, 2H), 7.66 (s, 1H), 7.53 (s, 1H), 7.32~7.45 (m, 5H), 7.12 (t, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 3.06~3.11 (m, 1H), 2.80~2.91 (m, 7H), 1.33~1.40 (m, 1H), 0.73 (d, *J* = 6.4 Hz, 3H), 0.43 (d, *J* = 6.4 Hz, 3H).	495
17		6-[butyl(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.97~7.93 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.90 (s, 1H), 3.41~3.33 (m, 1H), 3.21~3.10 (m, 1H), 3.09 ~3.08 (d, *J* = 0.4 Hz, 3H), 2.84 (s, 3H), 1.38~1.37 (m, 2H), 1.24~1.12 (m, 2H), 0.80~0.76 (t, *J* = 1.6 Hz, 3H).	495
18		2-(4-fluorophenyl)-*N*-methyl-6-[(3-methylbutyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.90 ~7.94 (m, 2H), 7.72 (s, 1H), 7.53 (s, 1H), 7.37~7.47 (m, 5H), 7.17 (t, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 4.4 Hz, 1H), 3.13 ~3.69 (m, 4H), 2.96 (d, *J* = 4.8 Hz, 3H), 2.76 (s, 3H), 1.34 ~1.39 (m, 1H), 0.76 (d, *J* = 5.2 Hz, 6H).	509
19		2-(4-fluorophenyl)-*N*-methyl-6-[(2-methylbutyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.67~7.92 (m, 2H), 7.53 (s, 1H), 7.46 (s, 1H), 7.23~7.43 (m, 5H), 7.11~7.16 (m, 2H), 5.78 (br, 1H), 2.93~3.02 (m, 2H), 2.91 (s, 3H), 2.86 (d, *J* = 7.2 Hz, 3H), 1.11~1.251 (m, 2H), 0.94~0.97 (m, 1H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.59 (d, *J* = 7.2 Hz, 3H).	509
20		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(pentyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.89~7.92 (m, 2H), 7.70 (s, 1H), 7.51 (s, 1H), 7.34~7.43 (m, 5H), 7.11~7.16 (m, 2H), 5.78 (br, 1H), 3.03~3.43 (m, 2H), 2.92 (d, *J* = 5.2 Hz, 3H), 2.72 (s, 3H), 0.97~1.38 (m, 6H), 0.73~0.75 (d, *J* = 7.2 Hz, 3H).	509

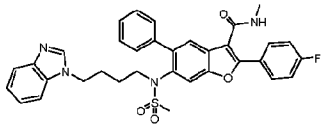
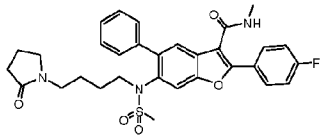
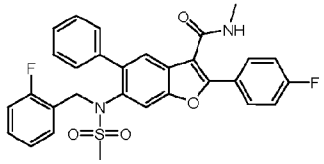
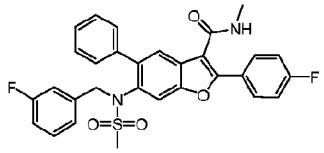
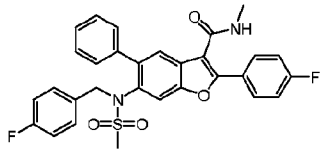
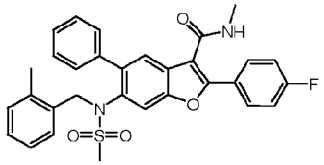
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
21		6-[(cyclobutylmethyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.88~7.92 (m, 2H), 7.68 (s, 1H), 7.47 (s, 1H), 7.34~7.45 (m, 5H), 7.11~7.16 (m, 2H), 5.78 (br, 1H), 3.07~3.43 (m, 2H), 2.92 (d, *J* = 5.2 Hz, 3H), 2.78 (m, 3H), 2.21~2.28 (m, 1H), 1.33~1.89 (m, 6H).	507
22		6-[cyclopentyl(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.92~7.95 (dd, *J* = 4.0 Hz, 2H), 7.75 (s, 1H), 7.41~7.44 (m, 3H), 7.37~7.39 (m, 2H), 7.22 (s, 1H), 7.17~7.20 (m, 2H), 5.95 (s, 1H), 3.96~4.02 (m, 1H), 2.98~3.00 (d, *J* = 8.0 Hz, 3H), 2.79 (s, 3H), 1.91~1.96 (m, 1H), 1.39~1.56 (m, 6H), 1.11~1.16 (m, 1H).	507
23		6-[(2-ethylbutyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.89~7.86 (m, 2H), 7.64 (s, 1H), 7.52 (s, 1H), 7.47~7.44 (m, 2H), 7.34~7.32 (m, 3H), 7.15~7.10 (m, 2H), 5.93 (s, 1H), 4.50~4.41 (m, 1H), 3.20~3.19 (m, 1H), 2.96 ~2.94 (d, *J* = 0.8 Hz, 3H), 2.88 (s, 3H), 1.21~1.16 (m, 2H), 1.13~1.04 (m, 1H), 1.00~0.92 (m, 2H), 0.67~0.64 (t, *J* = 1.2 Hz, 3H) , 0.53~0.50 (t, *J* = 1.2 Hz, 3H).	523
24		2-(4-fluorophenyl)-6-[hexyl(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 6.06 (s, 1H), 3.39~3.38 (m, 1H), 3.15~3.14 (m, 1H), 2.98 ~2.97 (d, *J* = 0.4 Hz, 3H), 2.76 (s, 3H), 1.38~1.35 (m, 2H), 1.18~1.12 (m, 6H), 0.82~0.78 (t, *J* = 1.6 Hz, 3H).	523
25		2-(4-fluorophenyl)-*N*-methyl-6-[(4-methylpentyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.85 (s, 1H), 3.39~3.38 (m, 1H), 3.17~3.14 (m, 1H), 2.98 ~2.97 (d, *J* = 0.4 Hz, 3H), 2.78 (s, 3H), 1.42~1.33 (m, 3H), 0.98~0.98 (m, 2H), 0.77~0.75 (t, *J* = 0.8Hz, 6H).	523

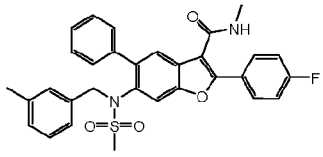
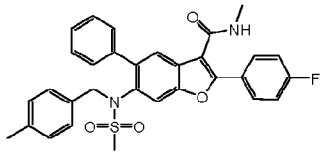
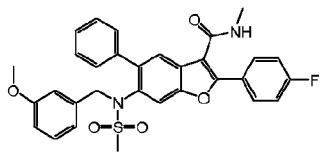
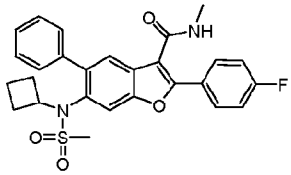
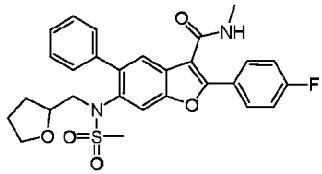
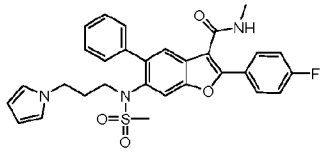
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
26		2-(4-fluorophenyl)-6-[(4-methoxybenzyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.85~7.89 (m, 2H), 7.64 (s, 1H), 7.30~7.35 (m, 5H), 7.26 (m, 1H), 7.09~7.14 (m, 2H), 6.88~6.90 (m, 2H), 6.66~6.68 (m, 2H), 5.87 (br s, 1H), 4.09~4.48 (br ABq, 2H), 3.70 (s, 3H), 2.89 (d, *J* = 4.8 Hz, 3H), 2.63 (s, 3H).	559
27		6-[(2-cyclohexylethyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.44~7.37 (m, 5H), 7.24~7.16 (m, 2H), 5.77 (s, 1H), 3.42~3.40 (m, 1H), 3.38~3.36 (m, 1H), 3.15 ~3.12 (d, *J* = 1.2 Hz, 3H), 2.71 (s, 3H), 1.56~1.50 (m, 5H), 1.24~1.23 (m, 2H), 1.11~1.01 (m, 4H), 0.95~0.72 (m, 2H).	549
28		2-(4-fluorophenyl)-6-[(3-hydroxypropyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.97~7.93 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.81 (s, 1H), 3.44~3.22 (m, 4H), 2.93~2.92 (d, *J* = 0.4 Hz, 3H), 2.79 (s, 3H), 1.19~1.17 (m, 2H).	497
29		2-(4-fluorophenyl)-6-[(2-hydroxypropyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.44~7.37 (m, 5H), 7.24~7.16 (m, 2H), 5.82 (s, 1H), 3.71~3.68 (m, 1H), 3.43~3.38 (m, 3H), 2.98 ~2.92 (m, 2H), 2.76 (s, 3H), 0.93 (m, 3H).	497
30		4-{[2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl](methylsulfonyl)amino}butyl acetate	7.88~7.92 (m, 2H), 7.71 (s, 1H), 7.52 (s, 1H), 7.33~7.44 (m, 5H), 7.12~7.16 (m, 2H), 5.78 (br, 1H), 3.82~3.85 (m, 2H), 3.07~3.50 (m, 2H), 2.92 (d, *J* = 4.8Hz, 3H), 2.76 (m, 3H), 1.95 (s, 3H), 1.28~1.57 (m, 4H).	553
31		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(3,3,3-trifluoropropyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.44~7.37 (m, 5H), 7.24~7.16 (m, 2H), 5.99 (s, 1H), 3.61~3.38 (m, 2H), 2.98 (s, 3H), 2.82 (s, 3H), 2.24~2.17 (m, 2H).	535

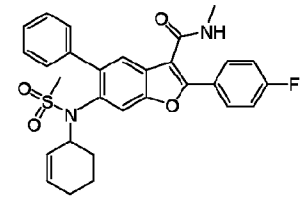
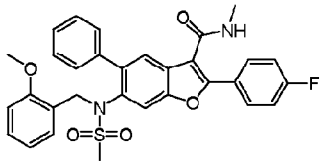
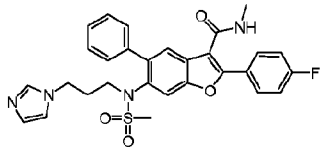
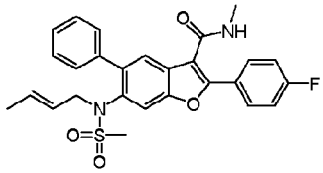
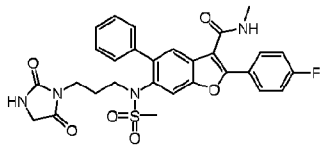
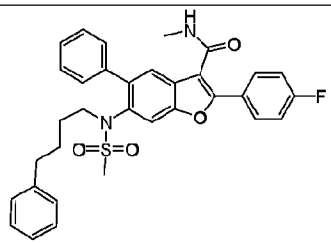
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
32		6-[(3-cyanopropyl) (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.87 ~7.90 (m, 2H), 7.74 (s, 1H), 7.52 (s, 1H), 7.35~7.47 (m, 5H), 7.15 (t, *J* = 8.4 Hz, 2H), 5.79 (d, *J* = 3.6 Hz, 1H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.91 (d, *J* = 5.2 Hz, 3H), 2.87 (s, 3H), 1.83 (d, *J* = 6.0 Hz, 2H), 1.59 (s, 2H).	506
33		6-[(4-cyanobutyl) (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91 ~7.95 (m, 2H), 7.77 (s, 1H), 7.56 (s, 1H), 7.39~7.50 (m, 5H), 7.20 (t, *J* = 8.4 Hz, 2H), 5.27 (d, *J* = 4.4 Hz, 1H), 3.29 ~3.38 (m, 2H), 2.96 (d, *J* = 4.8 Hz, 3H), 2.86 (s, 3H), 2.15 (d, *J* = 7.6 Hz, 2H), 1.48 (s, 2H), 1.36 (d, *J* = 4.8 Hz , 2H).	520
34		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl) (prop-2-yn-1-yl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.97~7.93 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.96 (s, 1H), 4.36~4.28 (m, 1H), 3.94~3.77 (m, 1H), 2.98~2.96 (m, 6H), 2.38 (s, 1H).	477
35		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl) (prop-2-en-1-yl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.85~7.89 (m, 2H), 7.68 (s, 1H), 7.36~7.46 (m, 6H), 7.11~7.19 (m, 2H), 5.86 (d, *J* = 4.0 Hz, 1H), 5.70~5.77 (m, 1H), 5.00~5.08 (m, 2H), 3.70~4.02 (m, 2H), 2.91 (d, *J* = 4.8 Hz, 3H), 2.67 (s, 3H).	479
36		6-[but-3-en-1-yl (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.92~7.96 (m, 2H), 7.75 (s, 1H), 7.55 (s, 1H), 7.44~7.50 (m, 2H), 7.39~7.42 (m, 3H), 7.16~7.21 (m, 2H), 5.97 (br s, 1H), 5.51~5.62 (m, 1H), 4.96~5.01 (m, 2H), 3.49 (br s, 1H), 3.17 (br s, 1H), 2.96 (d, *J* = 4.8 Hz, 3H), 2.81 (s, 3H), 2.15~2.17 (m, 2H).	493
37		2-(4-fluorophenyl)-*N*-methyl-6-[(3-methylbut-2-en-1-yl)(methylsulfonyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.91 ~7.95 (m, 2H), 7.77 (s, 1H), 7.56 (s, 1H), 7.39~7.50 (m, 5H), 7.17 (t, *J* = 8.4 Hz, 2H), 5.94 (s, 1H), 5.11 (t, *J* = 3.2 Hz, 1H), 3.76 ~4.02 (m, 2H), 2.95 (d, *J* = 4.8 Hz, 3H), 2.75 (s, 3H), 1.65 (s, 3H), 1.29 (s, 3H).	507

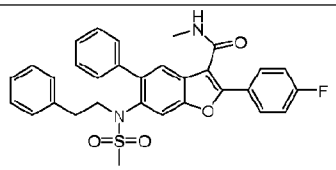
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
38		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(pent-4-en-1-yl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.93~7.96 (m, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.37~7.47 (m, 5H), 7.16~7.24 (m, 2H), 5.82 (s, 1H), 5.56~5.65 (m, 1H), 4.86~4.91 (m, 2H), 3.18~3.47 (m, 2H), 3.10 (d, *J* = 8.4 Hz, 3H), 2.77 (s, 3H), 1.82~1.85 (m, 2H), 1.50 (m, 2H).	507
39		2-(4-fluorophenyl)-6-[hex-5-en-1-yl(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.93~7.97 (m, 2H), 7.74 (s, 1H), 7.55 (s, 1H), 7.37~7.44 (m, 5H), 7.16~7.24 (m, 2H), 5.81 (s, 1H), 5.61~5.68 (m, 1H), 4.87~4.92 (m, 2H), 3.38~3.47 (m, 2H), 3.17 (d, *J* = 12 Hz, 3H), 2.77 (s, 3H), 1.88~1.92 (m, 2H), 1.39 (m, 2H), 1.18 (m, 2H).	521
40		2-(4-fluorophenyl)-*N*-methyl-6-[(4-methylpent-3-en-1-yl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.86~7.90 (m, 2H), 7.68 (s, 1H), 7.34~7.49 (m, 6H), 7.11~7.16 (m, 2H), 5.88 (s, 1H), 4.82 (s, 1H), 3.34~3.47 (m, 2H), 2.73~2.93 (m, 6H), 2.00~2.04 (m, 2H), 1.56 (s, 3H), 1.41 (s, 3H).	521
41		ethyl *N*-[2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl]-*N*-(methylsulfonyl)glycinate	7.86~7.90 (dd, *J* = 8.0 Hz, 2H), 7.82 (s, 1H), 7.69 (s, 1H), 7.48~7.50 (m, 2H), 7.34~7.38 (m, 3H), 7.11~7.15 (m, 2H), 5.86 (s, 1H), 4.90~4.24 (m, 2H), 4.03~4.08 (dd, *J* = 8.0 Hz, 2H), 3.18 (s, 3H), 2.91~2.93 (d, *J* = 8.0 Hz, 3H), 1.12~1.16 (m, 3H).	525
42		ethyl 4-{[2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl](methylsulfonyl)amino}butanoate	7.97~7.93 (m, 2H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52~7.50 (m, 2H), 7.44~7.37 (m, 3H), 7.24~7.16 (m, 2H), 5.76 (s, 1H), 4.02~3.99 (q, *J* = 1.2 Hz, 2H), 3.45~3.37 (m, 1H), 3.22~3.19 (m, 1H), 2.93~2.91 (d, *J* = 0.8 Hz, 3H), 2.77 (s, 3H), 2.00~1.95 (m, 2H), 1.69~1.63 (m, 2H), 1.16~1.13 (t, *J* = 1.2 Hz, 3H).	553
43		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(4-phenoxybutyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.93~7.97 (m, 2H), 7.74 (s, 1H), 7.57 (s, 1H), 7.46~7.48 (m, 2H), 7.36~7.42 (m, 3H), 7.16~7.23 (m, 4H), 6.88~6.92 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.81 (s, 1H), 3.79 (s, 2H), 3.47~3.54 (m, 1H), 3.22~3.30 (m, 1H), 2.97 (d, *J* = 4.0 Hz, 3H), 2.80 (s, 3H), 1.53 (m, 4H).	587

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
44		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(2-phenoxyethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.94 (m, 2H), 7.77 (s, 1H), 7.51~7.54 (m, 3H), 7.36~7.42 (m, 3H), 7.34 (s, 1H), 7.22 (s, 1H), 7.15~7.19 (m, 2H), 6.93~6.96 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 5.81 (s, 1H), 3.96 (s, 1H), 3.82 (s, 2H), 3.26 (s, 1H), 3.09 (s, 3H), 2.97 (d, *J* = 4.0 Hz, 3H).	559
45		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(3-phenoxypropyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.93~7.96 (m, 2H), 7.77 (s, 1H), 7.63 (s, 1H), 7.49~7.51 (m, 2H), 7.39~7.44 (m, 3H), 7.16~7.19 (m, 4H), 6.88~6.91 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.80 (s, 1H), 3.54~3.57 (m, 3H), 3.43 (s, 1H), 2.98 (d, *J* = 8.0 Hz, 3H), 2.79 (s, 3H), 1.84 (s, 1H), 1.81 (s, 3H).	573
46		2-(4-fluorophenyl)-*N*-methyl-6-{(methylsulfonyl)[(2*E*)-3-phenylprop-2-en-1-yl]amino}-5-phenyl-1-benzofuran-3-carboxamide	7.86~7.91 (m, 2H), 7.69 (s, 1H), 7.49 (s, 1H), 7.32~7.42 (m, 5H), 7.22~7.24 (m, 4H), 7.09~7.20 (m, 2H), 6.29 (d, *J* = 16 Hz, 1H), 5.96~6.04 (m, 1H), 5.73 (s, 1H), 4.13 (s, 1H), 4.15 (s, 1H), 2.91 (d, *J* = 4.0 Hz, 3H), 2.72 (s, 3H).	555
47		methyl 4-({[2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl](methylsulfonyl) amino}methyl) benzoate	7.85~7.89 (m, 2H), 7.78~7.82 (m, 2H), 7.66 (s, 1H), 7.72~7.35 (m, 6H), 7.10~7.14 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.74 (m, 1H), 4.55 (s, 1H), 4.23 (s, 1H), 3.83 (s, 3H), 2.91 (d, *J* = 4.0 Hz, 3H), 2.70 (s, 3H).	587
48		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl) (pyridin-2-ylmethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	8.49 (d, *J* = 4.0 Hz, 1H), 7.85~7.89 (m, 2H), 7.68~7.72 (m, 1H), 7.62 (m, 1H), 7.30~7.39 (m, 7H), 7.21 (s, 1H), 7.09~7.14 (m, 2H), 5.84 (m, 1H), 4.73 (s, 2H), 3.05 (s, 3H), 2.91 (d, *J* = 8.0 Hz, 3H).	530
49		*tert*-butyl 4-(2-{[2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl](methylsulfonyl) amino}ethyl) piperazine-1-carboxylate	7.93 (m, 2H), 7.73 (s, 1H), 7.51~7.54 (m, 3H), 7.36~7.41 (m, 3H), 7.14~7.18 (m, 2H) 6.08 (br s, 1H), 3.67 (br s, 1H), 3.36 (s, 4H), 3.04 (s, 4H), 2.93 (d, *J* = 4.8 Hz, 3H), 2.36 (br s, 3H), 2.22 (br s, 3H), 1.42 (s, 9H).	651

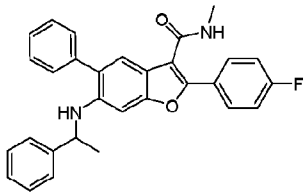
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
50		6-{[4-(1*H*-benzimidazol-1-yl)butyl](methylsulfonyl)amino}-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	9.12 (s,1H), 7.89~7.81 (m, 3H), 7.67 (s, 1H), 7.51~7.41 (m, 3H), 7.32~7.28 (m, 3H), 7.25~7.21 (m, 2H), 7.21 (s, 1H), 7.15~7.11 (m, 2H), 6.08 (s, 1H), 4.52~4.42 (m, 1H), 4.20~4.12 (m, 2H), 3.97~3.91 (m, 1H), 3.33~3.31 (m, 2H), 2.92 (s, 3H), 2.85 (s, 3H), 1.34~1.31 (m, 2H).	611
51		2-(4-fluorophenyl)-*N*-methyl-6-{(methylsulfonyl)[4-(2-oxopyrrolidin-1-yl)butyl]amino}-5-phenyl-1-benzofuran-3-carboxamide	7.88~7.92 (m, 2H), 7.69 (s, 1H), 7.50 (s, 1H), 7.41~7.43 (m, 2H), 7.31~7.38 (m, 3H), 7.11~7.15 (m, 2H), 5.84 (s, 1H), 3.08~3.36 (m, 6H), 2.92 (d, J = 8.0 Hz, 3H), 2.76 (s, 3H), 2.30 (t, J = 8.0 Hz, 2H), 1.18~1.19 (m, 2H), 1.27 (m, 4H).	578
52		6-[(2-fluorobenzyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.73 (s, 1H), 7.44~7.37 (m, 6H), 7.17~6.96 (m, 3H), 6.95~6.91 (m, 1H), 6.90~6.73 (m, 2H), 5.81 (s, 1H), 4.90~4.24 (m, 2H), 2.96 (s, 3H), 2.76 (s, 3H).	547
53		6-[(3-fluorobenzyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.86~7.88 (m, 2H), 7.59 (s, 1H), 7.36 (s, 1H), 7.29~7.31 (m, 3H), 7.11~7.16 (m, 5H), 6.80~6.96 (m, 3H), 5.87 (br, 1H), 4.28~4.60 (m, 2H), 2.92 (d, J = 5.2 Hz, 3H), 2.78 (m, 3H).	547
54		6-[(4-fluorobenzyl)(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.88~7.91 (m, 2H), 7.69 (s, 1H), 7.39~7.40 (m, 3H), 7.35~7.36 (m, 2H), 7.33~7.34 (m, 1H), 7.16~7.20 (m, 2H), 6.97~7.01 (m, 2H), 6.86~6.90 (m, 2H), 6.02 (br s, 1H), 4.20~4.60 (br ABq, 2H), 2.96 (d, J = 4.8 Hz, 3H), 2.74 (s, 3H).	547
55		2-(4-fluorophenyl)-*N*-methyl-6-[(2-methylbenzyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.90 (m, 2H), 7.52~7.23 (m, 2H), 7.21~7.18 (m, 3H), 7.14~7.03 (m, 5H), 6.93~6.91 (m, 2H), 6.88~6.75 (m, 1H), 5.85 (s, 1H), 4.43 (m, 2H), 2.89 (s, 3H), 2.81 (s, 3H), 1.81 (s, 3H).	543

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
56		2-(4-fluorophenyl)-*N*-methyl-6-[(3-methylbenzyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.89~ 7.85 (m, 2H), 7.63 (s, 1H), 7.34~ 7.27 (m, 6H), 7.14~7.10 (m, 2H), 7.05~ 7.00 (m, 2H), 6.98~6.74 (m, 2H), 5.82 (s, 1H), 4.43~ 4.18 (m, 2H), 2.91 (s, 3H), 2.63 (s, 3H), 2.18 (s, 3H).	543
57		2-(4-fluorophenyl)-*N*-methyl-6-[(4-methylbenzyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.89~ 7.85 (m, 2H), 7.63 (s, 1H), 7.34~7.27 (m, 6H), 7.14~7.10 (m, 2H), 7.05~7.00 (m, 2H), 6.98~6.74 (m, 2H), 5.79 (s, 1H), 4.46~ 4.13 (m, 2H), 2.91 (s, 3H), 2.63 (s, 3H), 2.23 (s, 3H).	543
58		2-(4-fluorophenyl)-6-[(3-methoxybenzyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~ 7.89 (m, 2H), 7.69 (s, 1H), 7.42~ 7.33 (m, 6H), 7.19~ 7.10 (m, 3H), 6.79~6.77 (m, 1H), 6.61~6.59 (m, 2H), 5.91 (s, 1H), 4.52~ 4.21 (m, 2H), 3.69 (s, 3H), 2.96 (s, 3H), 2.72 (s, 3H).	559
59		6-[cyclobutyl(methylsulfonyl)amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.92~7.96 (m, 2H), 7.75 (d, *J* = 10.8 Hz, 1H), 7.56 (d, *J* = 9.6 Hz, 1H), 7.37~7.49 (m, 5H), 7.19 (t, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 3.6 Hz, 1H), 3.37~3.49 (m, 2H), 2.98 (d, *J* = 4.8 Hz, 3H), 2.78 (d, *J* = 12.8 Hz, 3H), 1.53~2.11 (m, 1H), 0.86 ~0.92 (m, 1H), 0.43 (s, 2H), 0.08 (d, *J* = 9.6 Hz, 1H).	493
60		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(tetrahydrofuran-2-ylmethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.94~7.98 (m, 2H), 7.75 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.37~7.45 (m, 5H), 7.20 (t, *J* = 8.8 Hz, 2H), 5.84 (d, *J* = 2.8 Hz, 1H), 3.80~3.86 (m, 1H), 3.70 (d, *J* = 6.8 Hz, 2H), 3.47~3.54 (m, 1H), 3.27 (s, 3H), 2.96 (d, *J* = 5.2 Hz, 3H), 2.69~2.77 (m, 1H), 1.77 ~1.82 (m, 2H), 1.62~1.67 (m, 1H), 1.19~1.26 (m, 1H).	523
61		2-(4-fluorophenyl)-*N*-methyl-6-{(methylsulfonyl)[3-(1*H*-pyrrol-1-yl)propyl]amino}-5-phenyl-1-benzofuran-3-carboxamide	7.94~7.97 (m, 2H), 7.77 (s, 1H), 7.56 (s, 1H), 7.39~7.47 (m, 5H), 7.18~7.22 (m, 2H), 6.46 (s, 2H), 6.08 (s, 2H), 5.85 (s, 1H), 3.56 (m, 2H), 3.21~3.22 (m, 2H), 2.98~2.99 (d, *J* = 4.0 Hz, 3H), 2.80 (s, 3H), 1.84 (m, 2H).	546

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
62		6-[cyclohex-2-en-1-yl(methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.88~7.91 (m, 2H), 7.66 (s, 1H), 7.55 (s, 1H), 7.47~7.47 (m, 2H), 7.31~7.37 (m, 3H), 7.10~7.14 (m, 2H), 5.81~5.82 (m, 2H), 4.28 (s, 1H), 2.98 (s, 1H), 2.90 (d, *J* = 4.8 Hz, 3H), 2.67 (s, 3H), 1.60~1.90 (m, 2H), 1.18~1.49 (m, 4H).	519
63		2-(4-fluorophenyl)-6-[(2-methoxybenzyl) (methylsulfonyl) amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.91~7.89 (m, 2H), 7.52 (s, 1H), 7.43 (s, 1H), 7.25~7.24 (m, 3H), 7.16~7.12 (m, 3H), 7.10~7.04 (m, 2H), 6.68~6.60 (m, 3H), 5.75 (s, 1H), 4.45~4.41 (m, 2H), 3.52 (s, 3H), 2.90 (s, 3H), 2.77 (s, 3H).	559
64		2-(4-fluorophenyl)-6-{[3-(1*H*-imidazol-1-yl)propyl] (methylsulfonyl) amino}-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	8.62 (s, 1H), 7.96~7.94 (m, 2H), 7.85 (s, 1H), 7.65~7.60 (m, 3H), 7.43 (s, 1H),7.42~7.40 (m, 4H), 7.27~7.24 (m, 2H), 3.63~3.62 (m, 2H), 3.43~3.42 (m, 2H), 3.29~3.27 (m, 2H), 3.11 (s, 3H), 2.91 (s, 3H).	547
65		6-[(2*E*)-but-2-en-1-yl(methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	Not available	493
66		6-{[3-(2,5-dioxoimidazolidin-1-yl)propyl] (methylsulfonyl) amino}-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	Not available	579
67		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(4-phenylbutyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.89~7.92 (m, 2H), 7.68 (s, 1H), 7.48 (s, 1H), 7.31~7.40 (m, 5H), 7.06~7.16 (m, 5H), 6.99 (d, *J* = 6.4 Hz, 2H), 5.77 (s, 1H), 3.04~3.20 (m, 2H), 2.92 (d, *J* = 4.8 Hz, 3H), 2.70 (s, 3H), 2.36~2.45 (m, 2H), 1.33~1.42 (m, 4H).	571

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
68		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl)(2-phenylethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide	7.90~7.86 (m, 2H), 7.70 (s, 1H), 7.44~7.43 (m, 3H), 7.37~7.30 (m, 3H), 7.18~7.09 (m, 5H), 6.98~6.96 (m, 2H) , 5.99 (s, 1H), 3.60~3.18 (m, 2H), 2.77 (s, 3H), 2.64~2.60 (m, 2H), 2.52 (s, 3H).	543

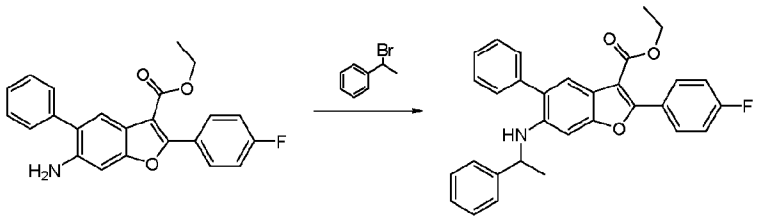
Example 69: 2-(4-fluorophenyl)-*N*-methyl-5-phenyl-6-[(1-phenylethyl)amino]-1-benzofuran-3-carboxamide



Steps 1-3

Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

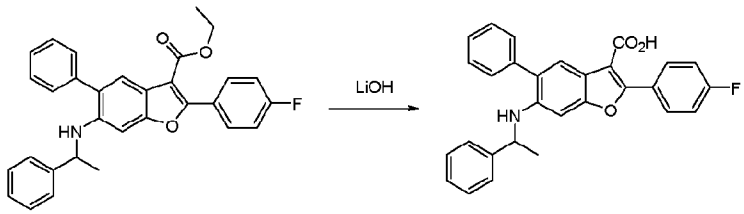
Step 4: ethyl 2-(4-fluorophenyl)-5-phenyl-6-[(1-phenylethyl)amino]-1-benzofuran-3-carboxylate



A mixture of the product of Step 3 (400 mg, 1.06 mmol), (1-bromoethyl) benzene (197 mg, 1.06 mmol) and Cs_2CO_3 (7.8 g, 24 mmol) in dry DMF (100 mL) was stirred at 140°C for 4 hours. After the mixture was concentrated, the residue was diluted with DCM, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC to give the product (200 mg, yield: 39%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90~7.88 (m, 2H), 7.62 (s, 1H), 7.47~7.45 (m, 2H), 7.45~7.44 (m, 1H), 7.26~7.25 (m, 5H), 7.18~7.17 (m, 2H), 7.04~7.03 (m, 2H), 6.45 (s, 1H), 4. 42~4.41 (m, 1H), 4 28~4.26 (q, J = 8.0 Hz, 2H), 1.36~1.34 (d, J = 8.0 Hz, 3H), 1.26~1.24 (t, J = 8.0 Hz, 3H). MS $(M+H)^+$: 480.

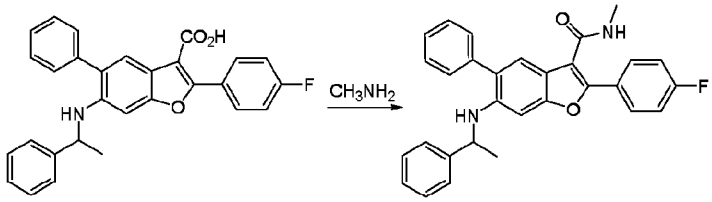
Step 5: 2-(4-fluorophenyl)-5-phenyl-6-[(1-phenylethyl)amino]-1-benzofuran-3-carboxylic acid



The product (110 mg, yield: 58.4%) was prepared in an analogous manner to Example 13 using the general procedure in Example 13, Step 4. The crude product was used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93~7.89 (m, 2H), 7.70 (s, 1H), 7.46~7.45 (m, 4H), 7.42~7.40 (m, 1H), 7.38~7.35 (m, 4H), 7.07~7.03 (m, 3H), 6.50 (s, 1H), 4.44~4.39 (m, 1H), 1.37~1.36 (d, J = 4.0 Hz, 3H). MS $(M+H)^+$: 452.

Step 6: 2-(4-fluorophenyl)-N-methyl-5-phenyl-6-[(1-phenylethyl)amino]-1-benzofuran-3-carboxamide

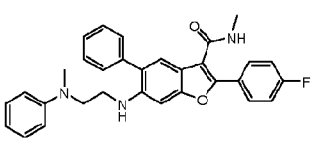


Example 69 (20 mg, yield: 48.6%) was prepared according to the general procedure in Example 1, Step 6.

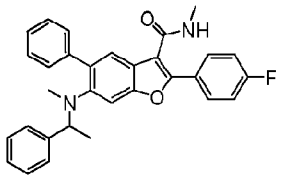
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82~7.78 (m, 2H), 7.45~7.44 (m, 4H), 7.36~7.35(m, 2H), 7.27~7.25 (m, 4H), 7.18~7.16 (m, 2H), 7.05~7.01 (m, 2H), 6.48 (s, 1H), 5.72 (s, 1H), 4.44~4.39 (m, 1H), 2.89~2.87 (s, 3H), 1.37~1.35 (d, J = 8.0 Hz, 3H). MS $(M+H)^+$: 465.

Example 70: 2-(4-fluorophenyl)-*N*-methyl-6-({2-[methyl(phenyl)amino]ethyl}amino)-5-phenyl-1-benzofuran-3-carboxamide

Example 70 was prepared according to the general procedures of Example 69.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
70		2-(4-fluorophenyl)-*N*-methyl-6-({2-[methyl(phenyl)amino]ethyl}amino)-5-phenyl-1-benzofuran-3-carboxamide	7.91~8.08 (m, 2H), 7.65 (s, 1H), 7.25~7.35 (m, 5H), 7.10~7.15 (m, 4H), 6.71 (s, 1H), 6.60~6.70 (m, 3H), 4.25~4.31 (m, 2H), 3.41~3.50 (m, 2H), 2.75 (s, 3H), 1.30~1.33 (t, J = 12.0 Hz, 3H).	494

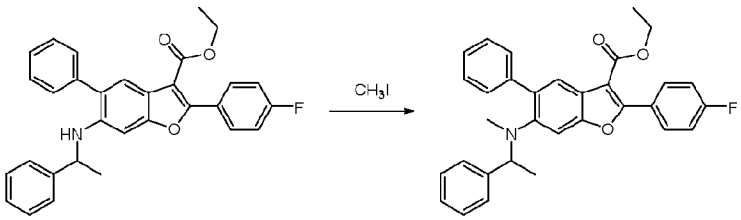
Example 71: 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(1-phenylethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-4

Steps 1-4 were performed in accordance with Example 69, Steps 1-4.

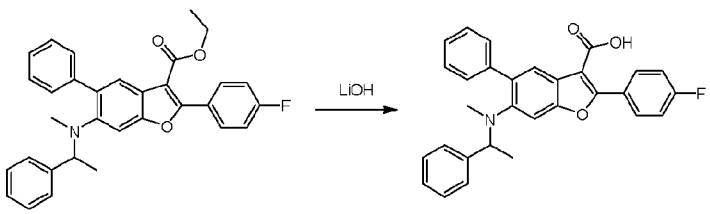
Step 5: ethyl 2-(4-fluorophenyl)-6-[methyl(1-phenylethyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



The product of Step 4 (62 mg, 0.13 mmol), CH_3I (29 mg, 0.20 mmol), K_2CO_3 (37 mg, 0.27 mmol) in DMF (2 mL) was stirred at 90°C for 16 hours. The mixture was quenched with water, diluted with DCM, dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by prep-TLC to give pure compound product (49 mg, yield: 77.7%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90~7.88 (m, 2H), 7.62 (s, 1H), 7.47~7.45 (m, 2H), 7.45~7.44 (m, 1H), 7.26~7.25 (m, 5H), 7.18~7.17 (m, 2H), 7.04~7.03 (m, 2H), 6.45 (s, 1H), 4.33~4.28 (q, J = 2.0 Hz, 2H), 4.17~4.12 (m, 1H), 2.50 (s, 3H), 1.32~1.27 (t, J = 2.0 Hz, 3H), 1.32~1.34 (d, J = 0.8 Hz, 3H). MS $(M+H)^+$: 494.

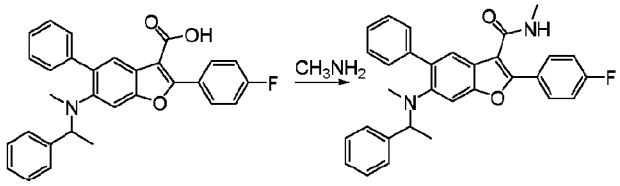
Step 6: 2-(4-fluorophenyl)-6-[methyl(1-phenylethyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



The carboxylic acid (75 mg, yield: 90 %) was prepared in an analogous manner to Example 13 using the general procedure in Example 13, Step 4. The carboxylic acid was used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90~7.88 (m, 2H), 7.62 (s, 1H), 7.47~7.45 (m, 2H), 7.45~7.44 (m, 1H), 7.26~7.25 (m, 5H), 7.18~7.17 (m, 2H), 7.04~7.03 (m, 2H), 6.45 (s, 1H), 4. 17~4.12 (m, 1H), 2.50 (s, 3H), 1.32~1.34 (d, J = 0.8 Hz, 3H). MS $(M+H)^+$: 466.

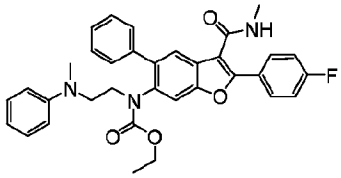
Step 7: 2-(4-fluorophenyl)-N-methyl-6-[methyl(1-phenylethyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



The product (30 mg, yield: 38.9%) was prepared according to the general procedure in Example 1, Step 6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86~7.83 (m, 2H), 7.66 (s, 1H), 7.50~7.45 (m, 4H), 7.34~7.33 (m, 2H), 7.25~7.20 (m, 2H), 7.17~7.13 (m, 2H), 6.95~6.93 (m, 2H), 6.96 (s, 1H), 4.55 (m, 1H), 2.93 (s, 3H), 2.85 (s, 3H), 1.35 (s, 3H). MS $(M+H)^+$: 479.

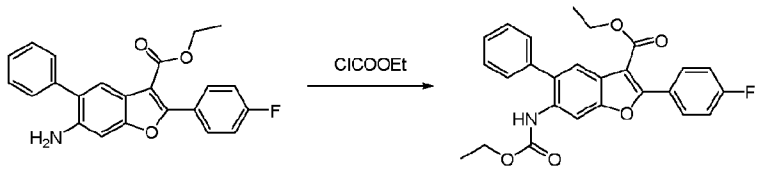
Example 72: ethyl [2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl]{2-[methyl(phenyl)amino]ethyl}carbamate



Steps 1-3

Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

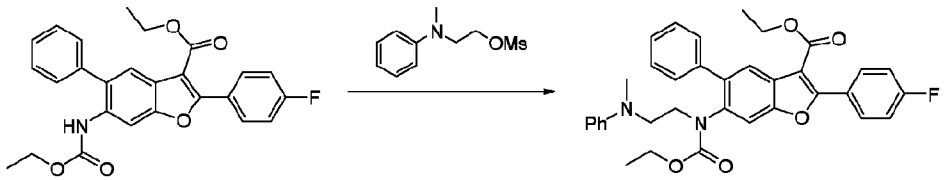
Step 4: ethyl 6-[(ethoxycarbonyl)amino]-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylate



A mixture of the product of Step 3 (64 mg, 0.17 mmol), EtOOCCl (22 mg, 0.21 mmol), Py (23 mg, 0.31 mmol) in DCM (3 mL) was stirred at RT for 2 hours. The mixture was quenched with H_2O, diluted with DCM, dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by prep-TLC to give pure carbamate (63 mg, yield: 83.3%) as a white solid.

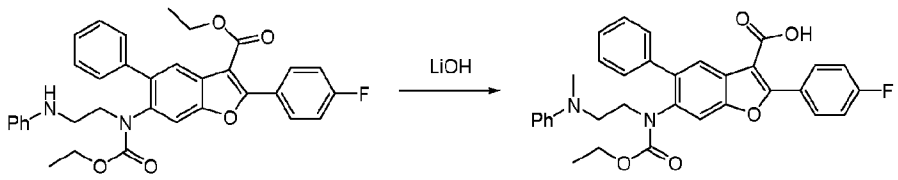
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02~8.00 (m, 2H), 7.78 (s, 1H), 7.49~7.47 (m, 2H), 7.45~7.34 (m, 3H), 7.14~7.09 (m, 2H), 6.67 (m, 1H), 4.34~4.30 (q, J = 1.6 Hz, 2H), 4.16~4.11 (q, J = 2.0 Hz, 2H), 2.18~2.14 (t, J = 1.6 Hz, 3H), 2.13~1.98 (t, J = 2.0 Hz, 3H). MS $(M+H)^+$: 448.

Step 5: ethyl 6-[(ethoxycarbonyl){2-[methyl(phenyl)amino]ethyl}amino]-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylate



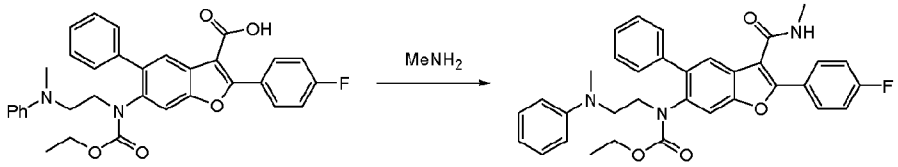
The product of Step 4 (474 mg, 1.06 mmol), 2-(methyl(phenyl)amino)ethyl methanesulfonate (243 mg, 1.06 mmol) and Cs_2CO_3 (7.8 g, 24 mmol) in dry DMF (100 mL) was stirred at 140°C for 4 hours. After the mixture was concentrated, the residue was diluted with DCM, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC to give the desired amino carbamate (335 mg, yield: 54.6%). MS $(M+H)^+$: 581.

Step 6: 6-[(ethoxycarbonyl){2-[methyl(phenyl)amino]ethyl}amino]-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylic acid



The product of Step 5 (25 mg, yield: 90%) was prepared in an analogous manner to Example 13 using the general procedure in Example 13, Step 4. The carboxylic acid was used directly in the next step without further purification.

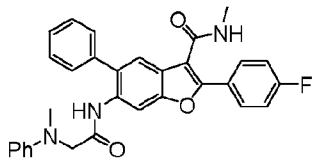
Step 7: ethyl [2-(4-fluorophenyl)-3-(methylcarbamoyl)-5-phenyl-1-benzofuran-6-yl]{2-[methyl(phenyl)amino]ethyl}carbamate



Example 72 (15 mg, yield: 48.7%) was prepared according to the general procedure in Example 1, Step 6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89~7.87 (m, 2H), 7.65 (s, 1H), 7.40~7.36 (m, 2H), 7.32~7.20 (m, 6H), 7.19~7.18 (m, 3H), 7.15~7.10 (m, 2H), 6.09 (m, 1H), 4.09~4.04 (m, 2H), 3.35~3.36 (m, 2H), 3.19~3.07 (m, 2H), 2.97~2.89 (m, 6H), 1.21~1.10 (m, 3H). MS $(M+H)^+$: 566.

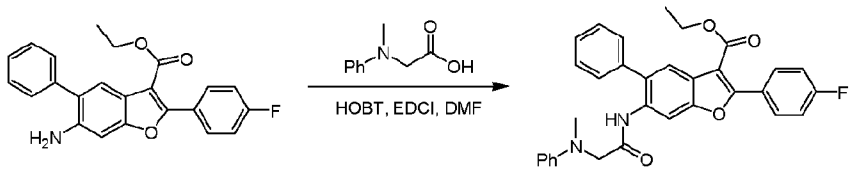
Example 73: 2-(4-fluorophenyl)-*N*-methyl-6-[(*N*-methyl-*N*-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-2

Steps 1-2 were performed in accordance with Example 1, Steps 1-2.

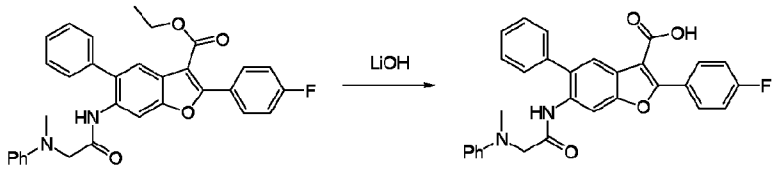
Step 3: ethyl 2-(4-fluorophenyl)-6-[(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



The amide (75 mg, yield: 50%) was prepared from the product of Step 2 according to the general procedure in Example 1, Step 6.

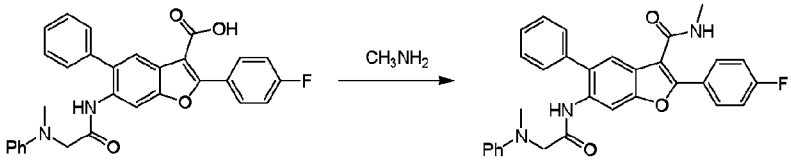
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.41~8.48 (m, 2H), 8.01~8.09 (m, 2H), 7.78 (s, 1H), 7.01~7.15 (m, 8H), 6.71~6.75 (m, 1H), 6.50 (t, J = 12.0 Hz, 2H), 4.31~4.35 (m, 2H), 3.24 (s, 3H), 2.61 (m, 2H), 1.30~1.33 (t, J = 12.0 Hz, 3H). MS $(M+H)^+$: 523.

Step 4: 2-(4-fluorophenyl)-6-[(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



The carboxylic acid (50 mg, yield: 75%) was prepared in an analogous manner to Example 13 using the general procedure in Example 13, Step 4. The carboxylic acid was used in the next step without further purification.

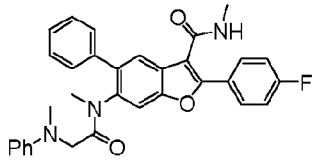
Step 5: 2-(4-fluorophenyl)-N-methyl-6-[(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



The amide (35 mg, yield: 78%) was prepared according to the general procedure in Example 1, Step 6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 3H), 8.71 (s, 3H), 7.81~7.89 (m, 2H), 7.55 (s, 1H), 7.23~7.25 (m, 5H), 7.01~7.12 (m, 2H), 6.71~6.75 (m, 1H), 6.50 (d, J = 12.0 Hz, 2H), 5.71~5.75 (m, 2H), 3.78 (s, 3H), 2.58 (s, 3H). MS $(M+H)^+$: 508.

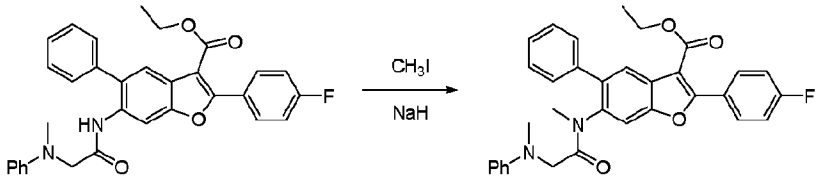
Example 74: 2-(4-fluorophenyl)-N-methyl-6-[methyl(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-3

Steps 1-3 were performed in accordance with Example 73, Steps 1-3.

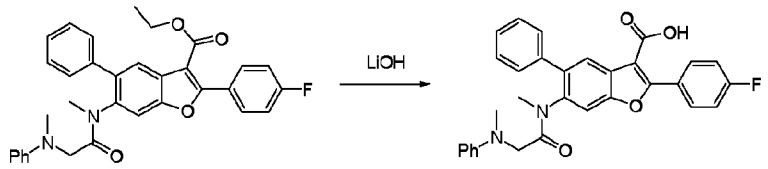
Step 4: ethyl 2-(4-fluorophenyl)-6-[methyl(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



The alkylated amide (90 mg, yield: 90%) was prepared in an analogous manner to the compound prepared in Example 1, Step 4.

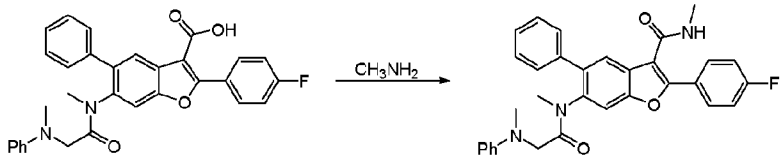
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.01~8.05 (m, 2H), 7.36~7.45 (m, 6H), 7.13~7.18 (m, 2H), 6.96~7.02 (m, 2H), 6.53~6.61 (m, 1H), 6.53~6.61 (t, J = 4.0 Hz, 2H), 4.31~4.39 (m, 2H), 3.58~3.66 (m, 2H), 3.24 (s, 3H), 2.70 (s, 3H), 1.30~1.33 (t, J = 12.0 Hz, 3H). MS $(M+H)^+$: 537.

Step 5: 2-(4-fluorophenyl)-6-[methyl(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



The carboxylic acid (85 mg, yield: 95%) was prepared in an analogous manner to Example 13 using the general procedure in Example 13, Step 4. The carboxylic acid was used in the next step without further purification.

Step 6: 2-(4-fluorophenyl)-N-methyl-6-[methyl(N-methyl-N-phenylglycyl)amino]-5-phenyl-1-benzofuran-3-carboxamide

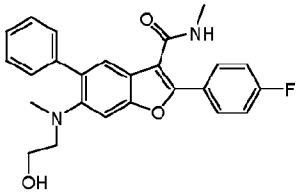
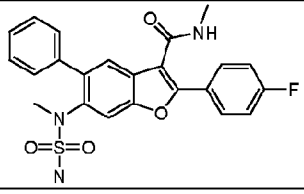


The amide was prepared in an analogous manner to Example 1, Step 6 (25 mg, yield: 68%).

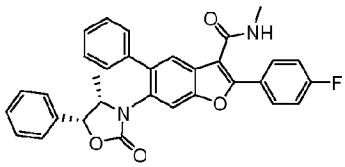
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89~7.91 (m, 2H), 7.86 (s, 1H), 7.39~7.42 (m, 4H), 7.34~7.38 (m, 2H), 7.13~7.18 (m, 2H), 7.00~7.09 (m, 2H), 6.55~6.57 (m, 1H), 6.16 (d, J = 4.0 Hz, 2H), 5.71~5.73 (m, 1H), 3.48~3.56 (m, 2H), 3.24 (s, 3H), 2.94 (d, J = 8.0 Hz, 3H), 2.69 (s, 3H). MS $(M+H)^+$: 522.

Examples 75-76

Examples 75 and 76 were prepared according to the general procedures of Example 74.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
75		2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methyl) amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.84~7.88 (m, 2H), 7.70 (s, 1H), 7.62 (s, 1H), 7.33~7.41 (m, 5H), 7.13~7.19 (m, 2H), 5.93 (br, 1H), 3.60 (s, 2H), 3.38 (s, 2H), 2.97 (s, 3H), 2.91 (d, J = 4.8 Hz, 3H).	419
76		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(sulfamoyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.84 ~7.88 (m, 2H), 7.32~7.43 (m, 6H), 7.07~7.19 (m, 2H), 6.85 (s, 1H), 5.89 (br, 1H), 2.92 (d, J = 4.8 Hz, 3H), 2.79 (s, 3H).	454

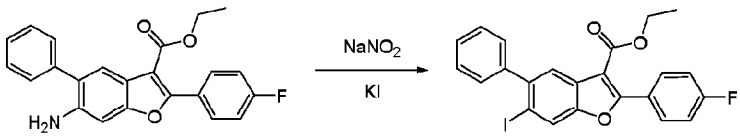
Example 77: 2-(4-fluorophenyl)-*N*-methyl-6-[(4*S*,5*R*)-4-methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-3

Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

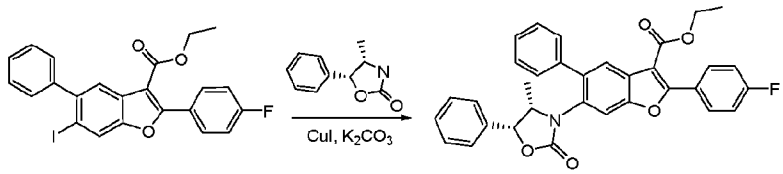
Step 4: ethyl 2-(4-fluorophenyl)-6-iodo-5-phenyl-1-benzofuran-3-carboxylate



A solution of the product of Step 3 (100 mg, 0.27 mmol) in 30% H_2SO_4 aqueous solution was cooled at 0°C. Then the solution of $NaNO_2$ in 1 mL H_2O was added dropwise to amine solution over a period of 1 minute with keeping the temperature at 0°C. The resulting mixture was stirred for an additional 30 minutes at 0°C. An aqueous solution of KI was added dropwise over 5 minutes. The reaction mixture was stirred for 3 hours at RT, giving a dark brown solution. The solution was extracted with EtOAc. The organic layer was washed with Na_2SO_3 solution and concentrated to give the crude iodide (40 mg, yield: 31%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.06~8.10 (m, 2H), 7.99 (s, 1H), 7.38~7.48 (m, 5H), 7.17~7.22 (m, 2H), 4.39 (q, J = 7.2 Hz, 2H), 1.35(t, J = 7.2 Hz, 3H). MS $(M+H)^+$: 487.

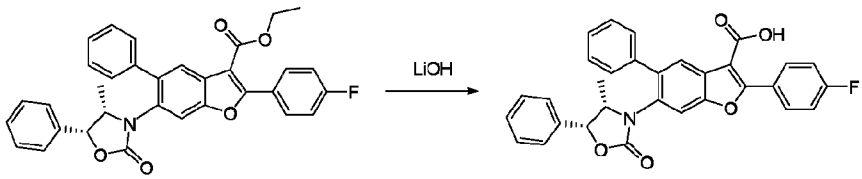
Step 5: ethyl 2-(4-fluorophenyl)-6-[(4S,5R)-4-methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-5-phenyl-1-benzofuran-3-carboxylate



The iodide (30 mg, 0.06 mmol), (4S, 5R)-4-methyl-5-phenyloxazolidin-2-one (17 mg, 0.9 mmol), CuI (15 mg, 0.08 mmol) and K_2CO_3 (20 mg, 0.14 mmol) in dry nitrobenzene (1 mL) was heated to 180°C for 6 hours. When TLC showed the reaction was completed, H_2O was added to the mixture and the aqueous phase was extracted by EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC to give the *N*-aryl oxizolidinone (10 mg, yield: 30%).

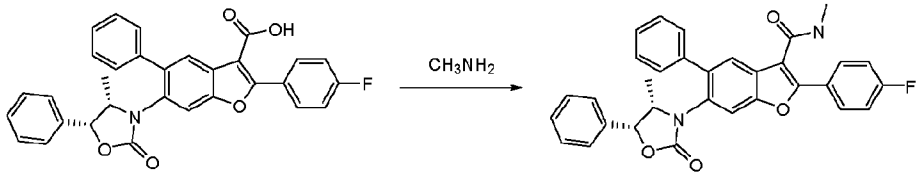
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.02 (m, 3H), 7.99 (s, 1H), 7.39~7.55 (m, 5H), 7.07~7.27 (m, 7H), 5.26 (d, J = 8.0 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.61 (br s, 1H), 1.31 (t, J = 7.2 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H). MS $(M+H)^+$: 536.

Step 6: 2-(4-fluorophenyl)-6-[(4S,5R)-4-methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-5-phenyl-1-benzofuran-3-carboxylic acid



To a stirred solution of ester (40 mg, 0.07 mmol) in dioxane/H_2O (1:1, 2 mL) was added LiOH (20 mg, 0.48 mmol), and the mixture was stirred at 100°C for 3 hours. The mixture was concentrated *in vacuo*. The residue was dissolved in H_2O, 1N HCl was added until pH to 3, and the mixture was extracted with EtOAc. The organic solvent was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated. The solvent was removed by distillation to provide the crude carboxylic acid (35 mg, yield: 92%). It was used for the next step without further purification.

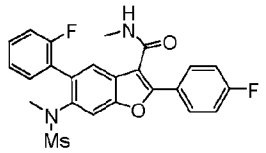
Step 7: 2-(4-fluorophenyl)-N-methyl-6-[(4S,5R)-4-methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-5-phenyl-1-benzofuran-3-carboxamide



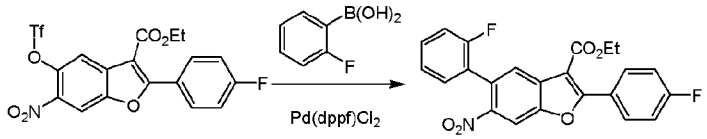
A solution of carboxylic acid (35 mg, 0.07 mmol), HOBT (40 mg, 0.30 mmol) and EDCI (50 mg, 0.32 mmol) in dry DMF (2 mL) was stirred at RT. After 30 minutes, Et_3N (0.2 mL) and CH_3NH_2 (HCl salt, 40 mg, 0.59 mmol) was added to the mixture, and the mixture was stirred overnight. After the solvent was removed, H_2O was added, and the mixture was extracted with EtOAc. The combined organic layer was washed with H_2O, brine and concentrated. The residue was purified by prep-TLC to give the product of Example 77 (20 mg, yield: 56%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86~7.89 (m, 2H), 7.74 (s, 1H), 7.52 (s, 1H), 7.40~7.42 (m, 5H), 7.25~7.26 (m, 3H), 7.06~7.14 (m, 4H), 5.84 (br s, 1H), 5.25 (d, J = 8.0 Hz, 1H), 3.62 (br s, 1H), 2.91 (d, J = 4.8 Hz, 3H), 0.44 (d, J = 6.8 Hz, 3H). MS $(M+H)^+$: 521.

Example 78: 5-(2-fluorophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



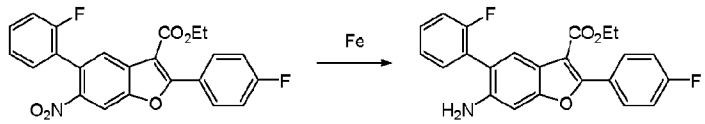
Step 1: ethyl 5-(2-fluorophenyl)-2-(4-fluorophenyl)-6-nitro-1-benzofuran-3-carboxylate



2-Fluorophenylboronic acid (obtained according to procedure in WO 2004/041201 A2; 283 mg, 2.10 mmol) and $K_3PO_4 \cdot 3H_2O$ (556 mg, 2.10 mmol) were added to a suspension of triflate (described in Example 1) (500 mg, 1.05 mmol) in dry DMF (2 mL) under N_2. Then $Pd(dppf)Cl_2$ (5 mg, 0.08 mmol) was added to the mixture under N_2. The reaction mixture was heated to 80°C for 6 hours. The mixture was cooled, diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column to give pure aryl fluoride (250 mg, yield: 55%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 8.00~8.01 (m, 3H), 7.31~7.35 (m, 2H), 7.20~7.22 (m, 3H), 7.03~7.05 (m, 1H), 4.30~4.36 (dd, J = 8.0 Hz, 2H), 1.27~1.31 (m, 3H). MS $(M+H)^+$: 424.

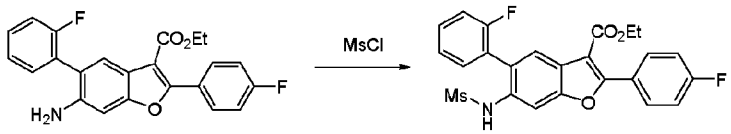
Step 2: ethyl 6-amino-5-(2-fluorophenyl)-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate



A mixture of nitro arene (250 mg, 0.59 mmol), Fe (264 mg, 4.70 mmol) and NH_4Cl (475 mg, 8.85 mmol) in H_2O/MeOH/THF (2 mL/2 mL/2 mL) was refluxed for 3 hours. Then, H_2O was added to quench the reaction, which was filtered and extracted with EtOAc, washed with brine and dried over Na_2SO_4. The solvent was removed by distillation. After purification by column, the desired aninline was obtained (180 mg, yield: 77%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94~7.97 (m, 2H), 7.74 (s, 1H), 7.32~7.35 (m, 2H), 7.05~7.20 (m, 4H), 6.67 (s, 1H), 4.26~4.30 (dd, J = 8.0 Hz, 2H), 1.18~1.27 (m, 3H). MS $(M+H)^+$: 394.

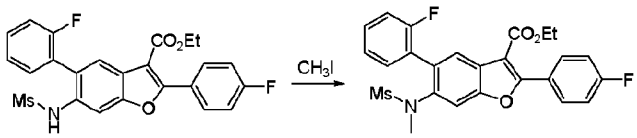
Step 3: ethyl 5-(2-fluorophenyl)-2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



MsCl (65 mg, 0.60 mmol) was added to a solution of aniline (180 mg, 0.50 mmol) and pyridine (79 mg, 1.00 mmol) in dry DCM (2 mL). The reaction mixture was stirred overnight at RT. After diluted with H_2O and extracted with DCM, the mixture was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by prep-TLC to give sulfonamide (150 mg, yield: 75%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94~7.97 (m, 2H), 7.74 (s, 1H), 7.71 (s, 1H), 7.32~7.35 (m, 2H), 7.05~7.20 (m, 4H), 4.26~4.30 (dd, J = 8.0 Hz, 2H), 2.95 (s, 3H), 1.18~1.27 (m, 3H). MS $(M+H)^+$: 472.

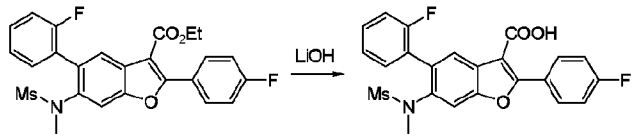
Step 4: ethyl 5-(2-fluorophenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



KI (4 mg, 0.02 mmol), K_2CO_3 (60 mg, 0.40 mmol), and CH_3I (113 mg, 0.80 mmol) were added to a solution of sulfonamide (100 mg, 0.20 mmol) in dry DMF (5 mL) under N_2. The mixture was heated to 80°C overnight. The mixture was cooled, diluted with H_2O, and extracted with EtOAc; the organic solvent was washed with brine, dried over Na_2SO_4 and filtered; and the solvent was evaporated under reduced pressure. The crude was purified by prep-TLC and the desired alkyl sulfonamide was obtained (90 mg, yield: 87%).

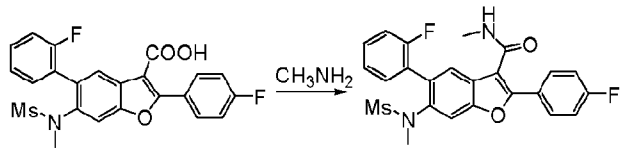
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.03~8.05 (m, 2H), 8.01 (s, 1H), 7.63 (s, 1H), 7.37~7.44 (m, 2H), 7.12~7.27 (m, 4H), 4.34~4.40 (dd, J = 8.0 Hz, 2H), 3.23 (s, 3H), 2.48 (s, 3H), 1.34~1.36 (m, 3H). MS $(M+H)^+$: 486.

Step 5: 5-(2-fluorophenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylic acid



The ester (90 mg, 0.20 mmol) was dissolved in 1,4-dioxane (2 mL) and H_2O (2 mL). Then LiOH (84 mg, 2.00 mmol) was added to the solution, and the mixture was refluxed for 2 hours. After acidified with HCl (1 N) and extracted with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the carboxylic acid (80 mg, yield: 90%). It was used for the next step without further purification.

Step 6: 5-(2-fluorophenyl)-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



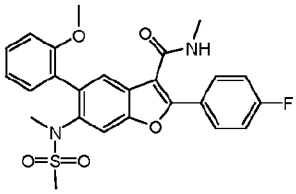
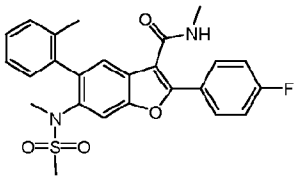
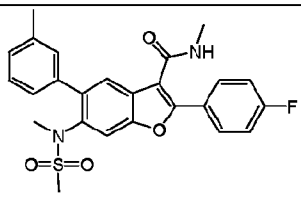
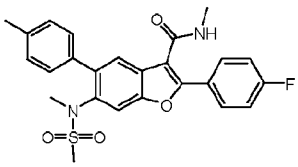
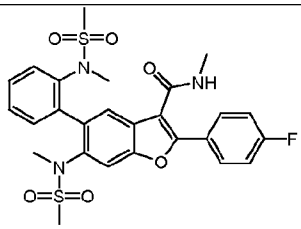
The carboxylic acid (75 mg, 0.16 mmol), HOBT (37 mg, 0.24 mmol) and EDCI (77 mg, 0.40 mmol) were dissolved in dry DMF (2 mL). The resulting solution was stirred for 30 minutes. Then, methanamine HCl salt (43 mg, 0.64 mmol) and Et_3N (73 mg, 0.72 mmol) was added to the mixture. After stirred overnight, the mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered

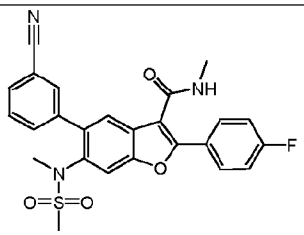
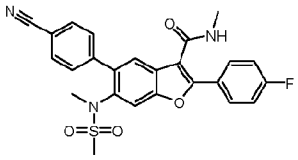
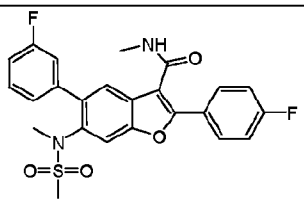
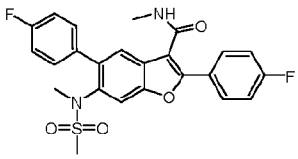
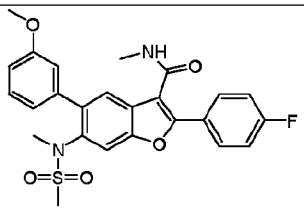
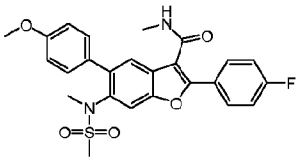
and evaporated. The crude product was purified by prep-TLC to give pure Example 78 (35 mg, yield: 47%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88~7.92 (m, 2H), 7.74 (s, 1H), 7.60 (s, 1H), 7.34~7.40 (m, 2H), 7.10~7.24 (m, 4H), 5.92 (s, 1H), 3.20 (s, 3H), 2.94~2.95 (d, J = 4.0 Hz, 3H), 2.47 (s, 3H). MS $(M+H)^+$: 471

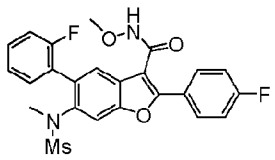
Examples 79-89

Examples 79-89 were prepared according to the general procedures of Example 78.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
79		2-(4-fluorophenyl)-5-(2-methoxyphenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-1-benzofuran-3-carboxamide	7.88~7.91 (m, 2H), 7.62 (s, 1H), 7.53 (s, 1H), 7.28~7.32 (m, 1H), 7.23 (d, J = 4.0 Hz, 1H), 7.09~7.13 (m, 2H), 6.97~6.99 (t, J =8.0 Hz, 1H), 6.88~6.90 (t, J =8.0 Hz, 1H), 5.79~5.80 (m, 1H), 3.69 (s, 3H), 3.11 (s, 3H), 2.89~2.91(d, J = 8.0 Hz, 3H), 2.34 (s, 3H).	483
80		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-5-(2-methylphenyl)-1-benzofuran-3-carboxamide	7.91 (t, J =4.2 Hz, 2H), 7.63 (d, J =3.6 Hz, 1H), 7.57 (d, J =4.0 Hz, 1H), 7.13~7.27 (m, 6H), 5.92 (s, 1H), 3.11 (d, J =2.8 Hz, 3H), 2.92 (s, 3H), 2.36 (d, J =2.4 Hz, 3H), 2.16 (d, J =3.2 Hz, 3H).	467
81		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-5-(3-methylphenyl)-1-benzofuran-3-carboxamide	7.85 ~7.88 (m, 2H), 7.68 (s, 1H), 7.53 (s, 1H) 7.25 (t, J = 7.6 Hz, 1H), δ 7.10 ~7.18 (m, 5H), 5.79 (s, 1H), 3.07 (s, 3H), 2.91 (d, J = 4.8 Hz, 3H), 2.48 (s, 3H), 2.35 (s, 3H).	467
82		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-5-(4-methylphenyl)-1-benzofuran-3-carboxamide	7.94 ~7.97 (m, 2H), 7.74 (s, 1H), 7.58 (s, 1H), 7.32~7.34 (m, 2H), 7.24~7.26 (m, 2H), 7.16~7.19 (m, 2H), 5.86 (s, 1H), 3.14 (s, 3H), 2.97~2.98 (d, J = 4.0 Hz, 3H), 2.58 (s, 3H), 2.41 (s, 3H).	467
83		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-5-{2-[methyl (methylsulfonyl) amino]phenyl}-1-benzofuran-3-carboxamide	7.99 ~8.01 (m, 2H), 7.98 (s, 1H), 7.50~7.55 (m, 2H), 7.41~7.49 (m, 3H), 7.22~7.26 (m, 2H), 3.23 (s, 6H), 3.07 (s, 3H), 2.93 (d, J = 4.0 Hz, 6H), 2.74 (s, 3H).	560

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
84		5-(3-cyanophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.83 ~7.87 (m, 2H), 7.75 (s, 1H), 7.65~7.68 (m, 3H), 7.63 (s, 1H), 7.48~7.54 (m, 1H), 7.13~7.17 (m, 2H), 5.75~5.76 (m, 1H), 3.09 (s, 3H), 2.92 (d, *J* = 4.0 Hz, 3H), 2.68 (s, 3H).	478
85		5-(4-cyanophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.82 ~7.85 (m, 2H), 7.76 (s, 1H), 7.66~7.68 (m, 2H), 7.51~7.53 (m, 3H), 7.13~7.17 (m, 2H), 5.65 (s, 1H), 3.07 (s, 3H), 2.92 (s, 3H), 2.70 (s, 3H).	478
86		5-(3-fluorophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.94 ~7.98 (m, 2H), 7.83 (s, 1H), 7.64 (s, 1H), 7.42~7.47 (m, 1H), 7.10~7.26 (m, 5H), 5.87~5.88 (m, 1H), 3.19 (s, 3H), 3.03 (d, *J* = 5.2 Hz, 3H), 2.69 (s, 3H).	471
87		2,5-bis(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.84 ~7.88 (m, 2H), 7.71 (s, 1H), 7.33~7.37 (m, 2H), 7.05~7.19 (m, 5H), 5.75 (s, 1H), 3.05 (s, 3H), 2.91 (d, *J* = 4.0 Hz, 3H), 2.60 (s, 3H).	471
88		2-(4-fluorophenyl)-5-(3-methoxyphenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.91 ~7.95 (m, 2H), 7.76 (s, 1H), 7.57 (s, 1H), 7.31~7.35 (m, 1H), 7.16~7.20 (m, 2H), 6.99~7.01 (m, 2H), 6.90~6.93 (m, 1H), 5.85 (s, 1H), 3.83 (s, 3H), 3.11 (s, 3H), 2.97~2.98 (d, *J* = 4.0 Hz, 3H), 2.62 (s, 3H).	483
89		2-(4-fluorophenyl)-5-(4-methoxyphenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	7.91 ~7.89 (m, 2H), 7.87 (s, 1H), 7.53 (s, 1H), 7.32~7.29 (m, 2H), 7.19~7.10 (m, 2H), 6.93~6.90 (m, 2H), 5.75 (s, 1H), 3.80 (s, 3H), 3.09 (s, 3H), 2.93 (s, 3H), 2.53 (s, 3H).	483

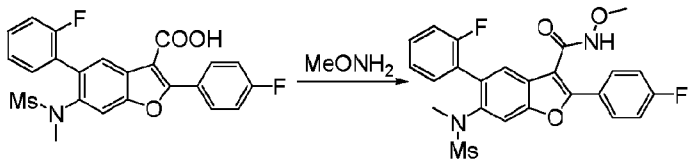
Example 90: 5-(2-fluorophenyl)-2-(4-fluorophenyl)-*N*-methoxy-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Steps 1-5

Steps 1-5 were performed in accordance with Example 78, Steps 1-5.

Step 6: 5-(2-fluorophenyl)-2-(4-fluorophenyl)-N-methoxy-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide

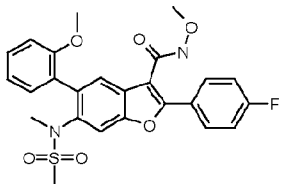
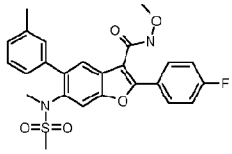
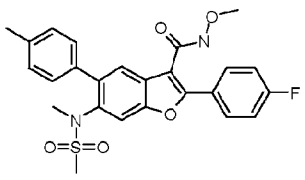


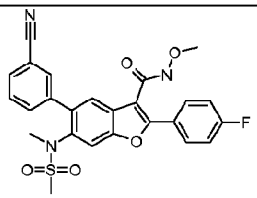
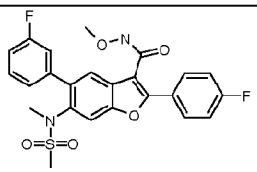
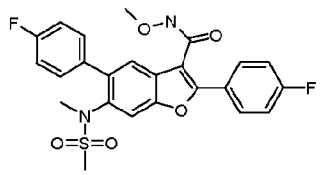
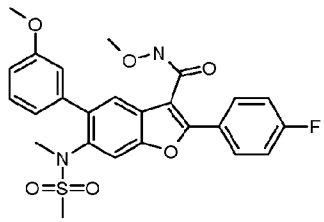
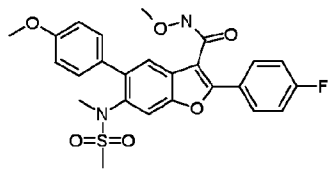
Example 90 was prepared using conditions analogous to the coupling reaction described in Example 7, Step 6 (40 mg, yield: 51%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.90~7.93 (m, 2H), 7.74 (s, 1H), 7.62 (s, 1H), 7.36~7.38 (m, 2H), 7.13~7.25 (m, 4H), 3.83 (s, 3H), 3.21 (s, 3H), 2.46 (s, 3H). MS $(M+H)^+$: 487.

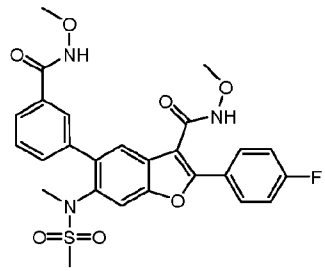
Examples 91-98

Examples 91-98 were prepared according to the general procedures of Example 90.

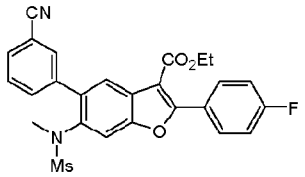
Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
91		2-(4-fluorophenyl)-*N*-methoxy-5-(2-methoxyphenyl)-6-[methyl (methylsulfonyl)amino] -1-benzofuran-3-carboxamide	7.56 (s, 1H), 7.81~7.85 (m, 2H), 7.62 (s, 1H), 7.55 (s, 1H), 7.30~7.35 (m, 1H), 7.21~7.24 (m, 1H), 7.10~7.18 (m, 1H), 6.95~7.01 (m, 1H), 6.89~6.91 (d, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.11 (s, 3H), 2.34 (s, 3H).	450
92		2-(4-fluorophenyl)-*N*-methoxy-6-[methyl (methylsulfonyl)amino] -5-(3-methylphenyl)-1-benzofuran-3-carboxamide	8.36 (s, 1H), 7.94 ~7.98 (m, 2H), 7.75 (s, 1H), 7.62 (s, 1H) 7.33 (t, *J* = 7.6 Hz, 1H), 7.18 ~7.26 (m, 5H), 3.87 (s, 3H), 3.15 (s, 3H), 2.53 (s, 3H), 2.42 (s, 3H).	483
93		2-(4-fluorophenyl)-*N*-methoxy-6-[methyl (methylsulfonyl)amino] -5-(4-methylphenyl)-1-benzofuran-3-carboxamide	8.39 (s, 1H), 7.92~7.96 (m, 2H), 7.72 (s, 1H), 7.59 (s, 1H), 7.30~7.32 (m, 2H), 7.24~7.25 (m, 2H), 7.16~7.21 (m, 2H), 3.84 (s, 3H), 3.13 (s, 3H), 2.56 (s, 3H), 2.40 (s, 3H).	483

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
94		5-(3-cyanophenyl)-2-(4-fluorophenyl)-*N*-methoxy-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.37 (s, 1H), 7.84~7.88 (m, 2H), 7.72 (s, 1H), 7.62~7.68 (m, 3H), 7.56 (s, 1H),.7.48~7.54 (m, 1H), 7.13~7.17 (m, 2H), 3.80 (s, 3H), 3.09 (s, 3H), 2.68 (s, 3H).	494
95		5-(3-fluorophenyl)-2-(4-fluorophenyl)-*N*-methoxy-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.29 (s, 1H), 7.91~7.95 (m, 2H), 7.76 (s, 1H), 7.61 (s, 1H), 7.38~7.44 (m, 1H), 7.07~7.23 (m, 5H), 3.85 (s, 3H), 3.14 (s, 3H), 2.63 (s, 3H).	487
96		2,5-bis(4-fluorophenyl)-*N*-methoxy-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.25 (s, 1H), 7.85~7.89 (m, 2H), 7.69 (s, 1H), 7.54 (s, 1H), 7.33~7.37 (m, 2H), 7.06~7.17 (m, 4H), 3.80 (s, 3H), 3.07 (d, *J* = 4.0 Hz, 3H), 2.59 (s, 3H).	487
97		2-(4-fluorophenyl)-*N*-methoxy-5-(3-methoxyphenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.49 (s, 1H), 7.89~7.93 (m, 2H), 7.72 (s, 1H), 7.57 (s, 1H), 7.31~7.35 (m, 1H), 7.15~7.19 (m, 2H), 6.97~6.99 (m, 2H), 6.91~6.93 (m, 1H), 3.83 (s, 6H), 3.10 (s, 3H), 2.60 (s, 3H).	499
98		2-(4-fluorophenyl)-*N*-methoxy-5-(4-methoxyphenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.29 (s, 1H), 7.91~7.89 (m, 2H), 7.87 (s, 1H), 7.53 (s, 1H), 7.32~7.29 (m, 2H), 7.19~7.10(m, 2H), 6.93~6.90 (m, 2H), 3.80 (s, 3H), 3.09 (s, 3H), 2.93 (s, 3H), 2.53 (s, 3H).	499

Example 99: 2-(4-fluorophenyl)-*N*-methoxy-5-[3-(methoxycarbamoyl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide

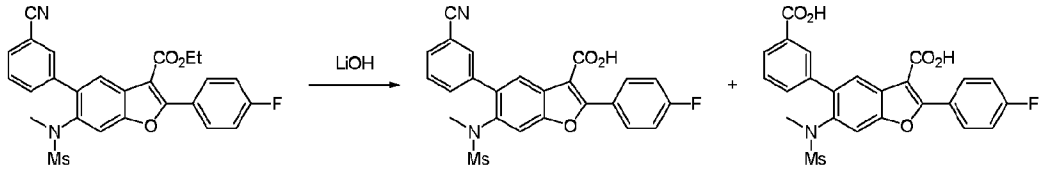


Steps 1-4: ethyl 5-(3-cyanophenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



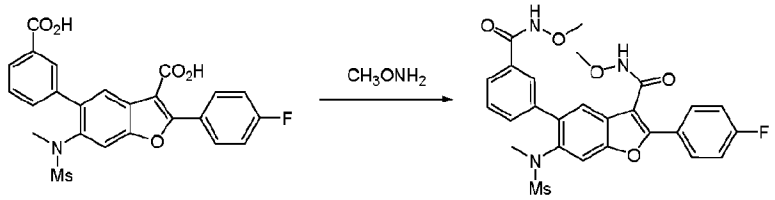
Steps 1-4 were performed in an analogous manner to Example 1, Steps 1-4.

Step 5: 5-(3-cyanophenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylic acid and 5-(3-carboxyphenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylic acid



The ester (450 mg, 0.92 mmol) was dissolved in dioxane (5 mL). Then LiOH (96 mg, 4 mmol) was added to the solution, and the mixture was stirred at RT overnight. After acidifing with HCl (1 N) and extracting with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the cyano carboxylic acid (300 mg, yield: 50%) and dicarboxylic acid (100 mg, yield: 30%). The crude mixture was used for the next step without further purification.

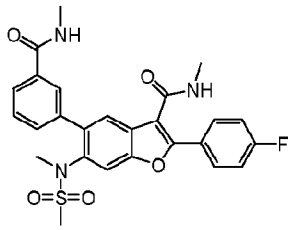
Step 6: 2-(4-fluorophenyl)-N-methoxy-5-[3-(methoxycarbamoyl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Example 99 was prepared using condition analogous to the coupling reaction described in Example 7, Step 6 (55 mg, yield: 73%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.49~9.54 (m, 1H), 8.39 (s, 1H), 7.86~7.89 (m, 2H), 7.83~7.85 (m, 2H), 7.79 (s, 1H), 7.45~7.51 (m, 3H), 7.13~7.17 (m, 2H), 3.81~3.82 (m, 6H), 2.99 (s, 3H), 2.78 (s, 3H). MS $(M+H)^+$: 542.

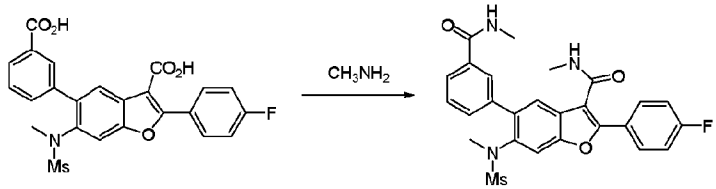
Example 100: 2-(4-fluorophenyl)-*N*-methyl-5-[3-(methylcarbamoyl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Steps 1-5: 5-(3-carboxyphenyl)-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylic acid

Steps 1-5 were performed according to the general procedures in Example 99, Steps 1-5.

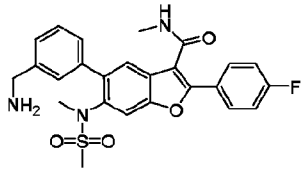
Step 6: 2-(4-fluorophenyl)-N-methyl-5-[3-(methylcarbamoyl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



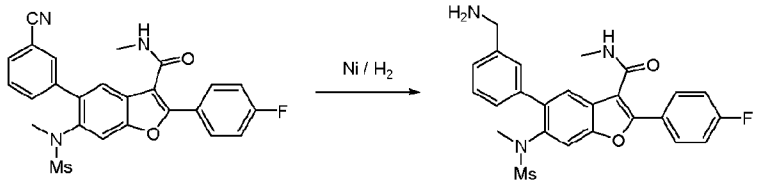
Example 100 was prepared according to the general procedure in Example 1, Step 6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86~7.89 (m, 2H), 7.78~7.81 (m, 2H), 7.44~7.51 (m, 3H), 7.12~7.16 (t, J = 12.0 Hz, 2H), 6.72~6.73 (m, 1H), 5.81~5.82 (m, 1H), 2.92~2.95 (m, 6H), 2.90 (s, 3H), 2.84 (s, 3H). MS $(M+H)^+$: 510.

Example 101: 5-[3-(aminomethyl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



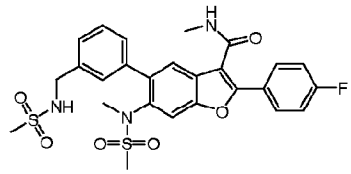
Step 1: 5-[3-(aminomethyl)phenyl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Raney-Ni (100 mg) and ammonia (conc. 0.5 mL) were added to a solution of the compound of Example 84 (58 mg, 0.13 mmol) in MeOH (20 mL). And then the mixture was degassed and stirred under 30 psi of H_2 overnight at RT. After filtered through CELITE, the filtrate was concentrated to give the desired benzylic amine (50 mg, yield: 85%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79~7.82 (m, 2H), 7.57 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.06~7.10 (t, J = 16.0 Hz, 2H), 6.58~6.59 (m, 3H), 3.98 (s, 2H), 2.93 (s, 3H), 2.71 (d, J = 4.0 Hz, 3H), 2.49 (s, 3H). MS $(M+H)^+$: 482.

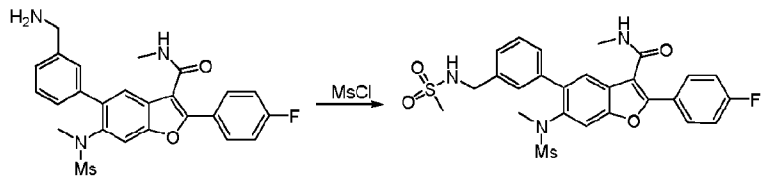
Example 102: 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-(3-{[(methylsulfonyl)amino]methyl}phenyl)-1-benzofuran-3-carboxamide



Steps 1-2

Steps 1-2 were performed according to the general procedures in Example 1, Steps 1-2.

Step 3: 2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-(3-{[(methylsulfonyl)amino]methyl}phenyl)-1-benzofuran-3-carboxamide



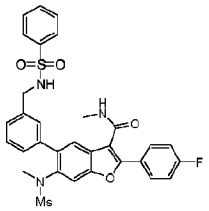
Example 102 was prepared in an analogous manner to the sulfonamide synthesis described in Example 1, Step 3 (20 mg, yield: 60%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85~7.88 (m, 2H), 7.76 (s, 1H), 7.52 (s, 1H), 7.46 (s, 1H), 7.36~7.38 (m, 1H), 7.28~7.32 (m, 2H), 7.12~7.16 (m, 2H), 5.78~5.79 (m, 1H),

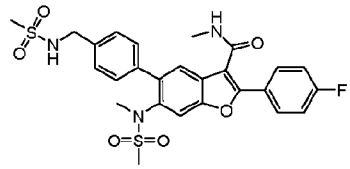
4.95~4.96 (m, 1H), 4.31 (d, J = 8.0 Hz, 2H), 2.91~2.93 (m, 6H), 2.86 (s, 3H), 2.79 (s, 3H). MS $(M+H)^+$: 560.

Example 103

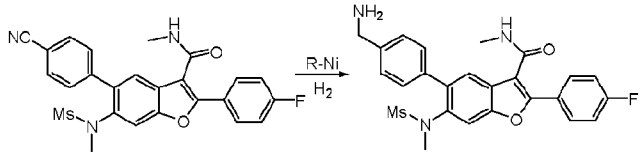
Example 103 was prepared according to the general procedures of Example 102.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
103		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-(3-{[(phenylsulfonyl)amino]methyl}phenyl)-1-benzofuran-3-carboxamide	7.82~7.85 (m, 4H), 7.68 (s, 1H), 7.48~7.52 (m, 4H), 7.46 (s, 1H), 7.41~7.44 (m, 2H), 7.11~7.30 (m, 3H), 5.82~5.87 (m, 1H), 5.15 ~5.18 (m, 1H), 4.09~4.10 (m, 2H), 2.90~2.93 (m, 6H), 2.71 (s, 3H).	622

Example 104: 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1-benzofuran-3-carboxamide



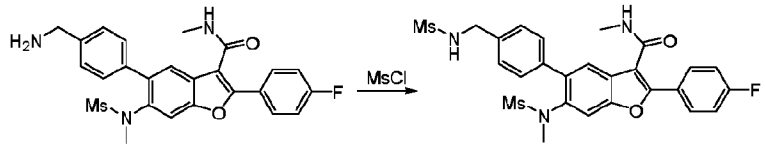
Step 1: 5-[4-(aminomethyl)phenyl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



To a solution of the compound of Example 85 (400 mg, 83.8 mmol) in MeOH (10 mL), and Raney-Ni (30 mg) was added. The reaction was degassed and then was shaken under 30 psi H_2 overnight. The reaction mixture was filtered, washed with MeOH. The solvent was evaporated to give the desired benzylic amine (350 mg, yield: 87%).

^{1}H-NMR (400 MHz, $CDCl_3$) 7.82~7.85 (m, 2H), 7.47~7.52 (m, 3H), 7.45 (s, 1H), 7.31~7.37 (m, 2H), 6.99~7.11 (m, 2H), 6.41 (s, 1H), 4.12 (s, 2H), 2.88 (s, 3H), 2.72 (d, J = 4.0 Hz, 3H), 2.52 (s, 3H). MS $(M+H)^+$: 482.

Step 2: 2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1-benzofuran-3-carboxamide

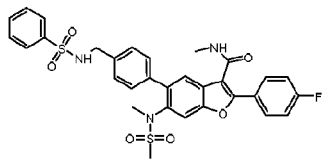
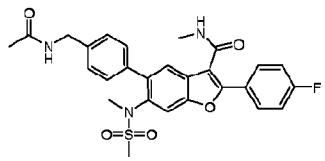
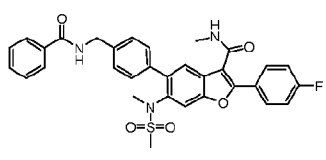


Example 104 was prepared in an analogous manner to the sulfonamide prepared in Example 1, Step 3 (20 mg, yield: 60%).

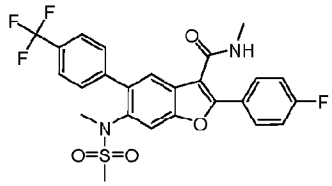
^{1}H-NMR (400 MHz, $CDCl_3$) 7.85~7.88 (m, 2H), 7.69 (s, 1H), 7.51 (s, 1H), 7.37 (s, 4H), 7.14~7.19 (m, 2H), 4.21 (s, 2H), 3.04 (s, 3H), 2.83 (s, 3H), 2.75 (s, 3H) 2.70 (s, 3H). MS $(M+H)^+$: 560.

Examples 105-107

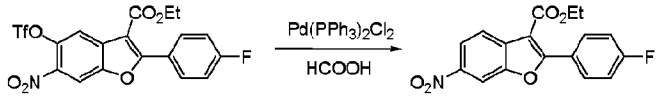
Examples 105-107 were prepared according to the general procedures of Example 104.

Example	Structure		^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
105		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl)amino] -5-(4- {[(phenylsulfonyl) amino]methyl}phenyl)-1-benzofuran-3-carboxamide	7.84~7.88 (m, 4H), 7.68 (s, 1H), 7.47~7.56 (m, 4H), 7.30~7.32 (m, 2H), 7.15~7.23 (m, 2H), 7.11~7.19 (m, 2H), 5.76 (s, 1H), 4.69 (s, 1H), 4.14 (d, *J* = 4.0 Hz, 2H), 3.04 (s, 3H), 2.88 (d, *J* = 8.0 Hz, 3H), 2.81 (s, 3H).	622
106		5-{4- [(acetylamino)methyl] phenyl}-2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl)amino] -1-benzofuran-3-carboxamide	7.84~7.87 (m, 2H), 7.66 (s, 1H), 7.492 (s, 1H), 7.32~7.34 (m, 2H), 7.25~7.27 (m, 2H), 7.09~7.13 (m, 2H), 5.94 (s, 1H), 4.39 (d, *J* = 8.0 Hz, 2H), 3.05 (s, 3H), 2.89 (d, *J* = 8.0 Hz, 3H), 2.57 (s, 3H), 1.96 (s, 3H).	524
107		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl)amino] -5-(4- {[(phenylcarbonyl) amino]methyl}phenyl)-1-benzofuran-3-carboxamide	7.86~7.88 (m, 2H), 7.74~7.75 (m, 2H), 7.67 (s, 1H), 7.50 (s, 1H), 7.37~7.46 (m, 7H), 7.09~7.14 (m, 2H), 6.54 (s, 1H), 5.87 (s, 1H), 4.62 (d, *J* = 8.0 Hz, 2H), 3.06 (s, 3H), 2.89 (d, *J* = 4.0 Hz, 3H), 2.56 (s, 3H).	586

Example 108: 2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-[4-(trifluoromethyl)phenyl]-1-benzofuran-3-carboxamide



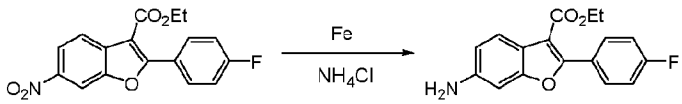
Step 1: ethyl 2-(4-fluorophenyl)-6-nitro-1-benzofuran-3-carboxylate



HCOOH (2.4 g, 71.23 mmol), Bu_3N (11.6 g, 85.47 mmol) and $Pd(PPh_3)_2Cl_2$ (197 mg, 0.28 mmol) were added to a solution of triflate (obtained according to procedure in WO 2004/041201 A2, 9 g, 28.49 mmol) in DMF (90 mL). The mixture was heated to 110°C under N_2 protection. After stirred for 0.5 hour, the mixture was diluted with H_2O and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated. The crude product was purified by column to give pure nitro arene (4.78 g, yield: 51%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 2 Hz, 1H), 8.20~8.23 (m, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.03~8.07 (m, 2H), 7.13~7.18 (m, 2H), 4.36~4.41 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H). MS $(M+H)^+$: 330.

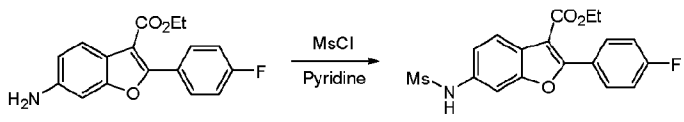
Step 2: ethyl 6-amino-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate



A mixture of the product of Step 1 (4.78 g, 14.5 mmol), Fe (4.06 g, 72.6 mmol) and NH_4Cl (6.20 g, 116 mmol) in H_2O/MeOH/THF (50 mL /50 mL /50 mL) was refluxed for 4 hours. Then, H_2O was added to quench the reaction, and the mixture was extracted with EtOAc. After washing with brine and dried, the solvent was removed by distillation. The pure aniline was obtained (3.47 g, yield: 80%) by prep-TLC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94~7.98 (m, 2H), 7.73 (d, J = 8 Hz, 1H), 7.08 (t, J = 8.8 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 6.8 Hz, 1H), 4.30~4.35 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H). MS $(M+H)^+$: 300.

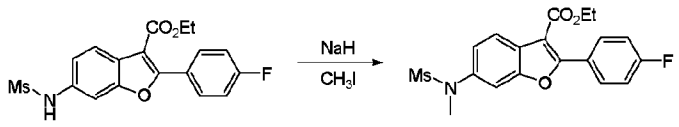
Step 3: ethyl 2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



MsCl (122 mg, 1.06 mmol) was added to a solution of aniline (200 mg, 0.67 mmol) and pyridine (107 mg, 1.35 mmol) in dry DCM (2 mL). After stirred overnight at RT, the mixture was diluted with H_2O and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated. The crude product was purified by prep-TLC to give the desired sulfonamide (200 mg, yield: 78.5%).

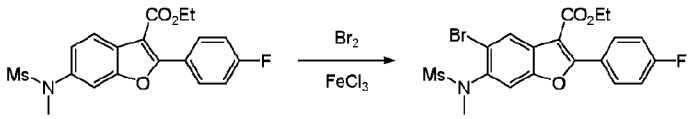
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97~8.06 (m, 3H), 7.53~7.54 (m, 1H), 7.11~7.19 (m, 3H), 6.74 (s, 1H), 4.30~4.35 (m, 2H), 3.93 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). MS $(M+H)^+$: 378.

Step 4: ethyl 2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



NaH (60 % in oil, 111 mg, 2.78 mmol) and CH_3I (395 mg, 2.78 mmol) were added to a solution of sulfonamide (211 mg, 0.56 mmol) in dry DMF (4 mL) under N_2. After stirred overnight at RT, ice cold diluted AcOH was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was used for the next step without further purification (210 mg, yield: 96%).

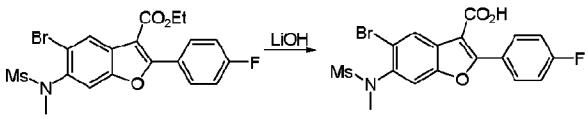
Step 5: ethyl 5-bromo-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylate



A stirred solution of sulfonamide (500 mg, 1.3 mmol) and $FeCl_3$ (210 mg, 0.78 mmol) in dry CCl_4 (5 mL) was added Br_2 (210 mg, 1.3 mmol) in dry CCl_4 (2 mL). The mixture was allowed to stir at 50°C for 4 hours. The mixture was cooled, diluted with H_2O, and extracted with DCM; the organic solvent was washed with brine, dried over Na_2SO_4 and filtered; and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography to give aryl bromide (240 mg, yield: 30%).

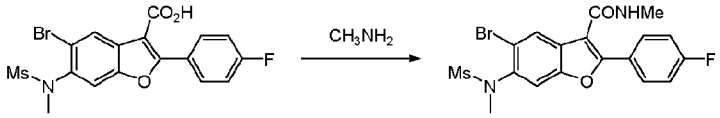
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.91~8.05 (m, 2H), 7.62 (s, 1H), 7.02~7.15 (m, 2H), 4.32~4.46 (m, 2H), 3.37 (s, 3H), 3.02 (s, 3H), 1.35 (t, J = 4.4 Hz, 3H). MS $(M+H)^+$: 470.

Step 6: 5-bromo-2-(4-fluorophenyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxylic acid



The ester (210 mg, yield: 80%) was hydrolysed in an analogous manner to the general procedure of Example 78, Step 5. The carboxylic acid was used in the next step without further purification.

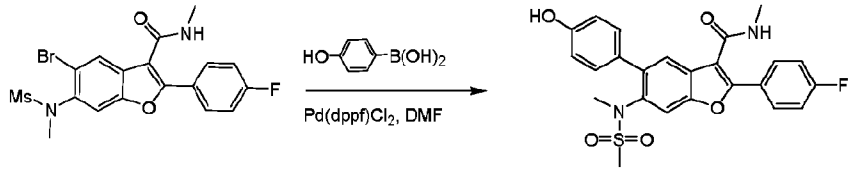
Step 7: 5-bromo-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



The amide was prepared according to the general procedure in Example 1, Step 6 (180 mg, yield: 75%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.81~7.85 (m, 2H), 7.63 (s, 1H), 7.12~7.19 (m, 2H), 5.71 (br, 1H), 3.27 (s, 3H), 3.02 (s, 3H), 2.93 (d, J = 4.4 Hz, 3H). MS $(M+H)^+$: 455.

Step 8: 2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-5-[4-(trifluoromethyl)phenyl]-1-benzofuran-3-carboxamide

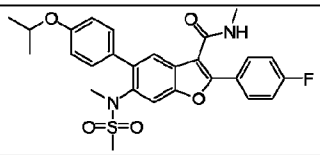
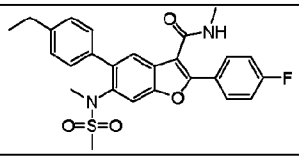
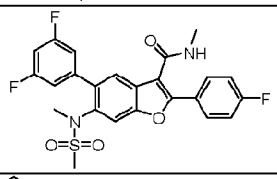
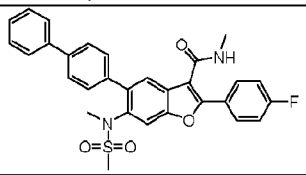
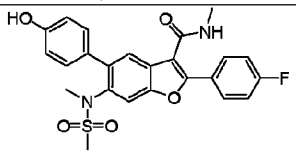
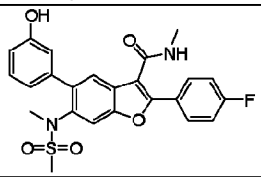
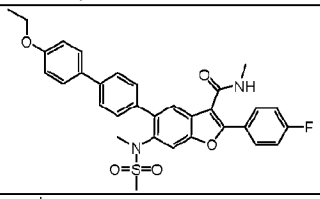
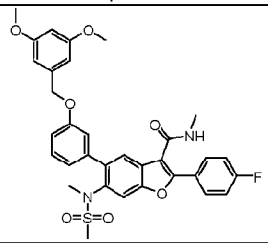


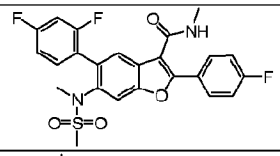
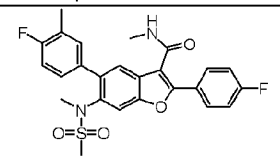
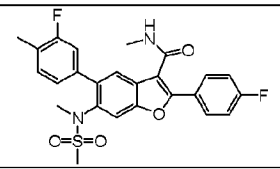
To a solution of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (30 mg, 0.066 mmol) in DMF (2 mL) were added 4-hydroxy-phenyl boronic acid (21 mg, 0.13 mmol) and $K_3PO_4 \cdot 3H_2O$ (36.5 mg, 0.13 mmol). Then, $Pd(dppf)Cl_2$ (3.4 mg, 0.004 mmol) was added under N_2. The resulting mixture was heated to 90°C for 12 hours. The mixture was cooled to RT, then filtered and purified by prep-HPLC to give 2-(4-fluorophenyl)-5-(4-hydroxyphenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide. (4.8 mg, Yield; 15.5%).

MS $(M+H)^+$: 469.

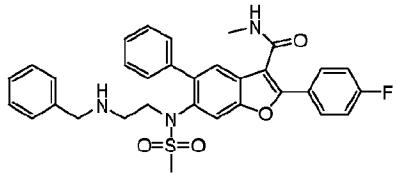
Examples 109-122

Examples 109-122 were prepared according to the general procedures of Example 108.

Example	Structure	Name	MS $(M+H)^+$
109		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-[4-(propan-2-yloxy)phenyl]-1-benzofuran-3-carboxamide	511
110		5-(4-ethylphenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	481
111		5-(3,5-difluorophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	489
112		5-(biphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	529
113		2-(4-fluorophenyl)-5-(4-hydroxyphenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	469
114		2-(4-fluorophenyl)-5-(3-hydroxyphenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	469
115		5-(4'-ethoxybiphenyl-4-yl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	573
118		5-{3-[(3,5-dimethoxybenzyl)oxy]phenyl}-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	619

Example	Structure	Name	MS $(M+H)^+$
119		5-(2,4-difluorophenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	489
121		5-(4-fluoro-3-methylphenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	485
122		5-(3-fluoro-4-methylphenyl)-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	485

Example 123: 6-{[2-(benzylamino)ethyl](methylsulfonyl)amino}-2-(4-fluorophenyl)-N-methyl-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-4

Steps 1-4 were performed in an analogous manner to Example 1, Steps 1-4.

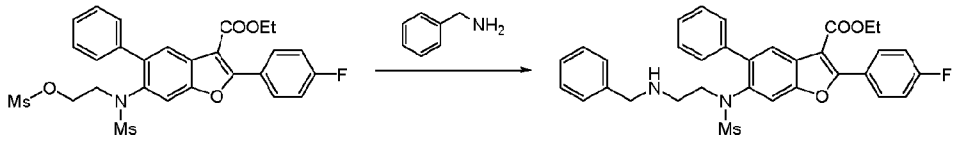
Step 5: ethyl 2-(4-fluorophenyl)-6-[(methylsulfonyl){2-[(methylsulfonyl)oxy]ethyl}amino]-5-phenyl-1-benzofuran-3-carboxylate

MsCl (0.2 mL, 3.0 mmol) was added to a solution of alcohol (1 g, 2.0 mmol) and Et_3N (0.6 mL, 4.0 mmol) in dry DCM (10 mL), in a manner similar to that of Example 1, Step 4. The reaction mixture was stirred overnight at RT. After dilution with H_2O and extraction with DCM, the mixture was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column to give the mesylate (800 mg, yield: 75%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.03 (m, 2H), 7.99 (s, 1H), 7.57 (s, 1H), 7.48~7.50 (m, 2H), 7.35~7.43 (m, 3H), 7.11~7.16 (m, 2H), 4.30~4.35 (dd, J = 8.0 Hz, 2H),

4.02~4.05 (m, 2H), 3.21~3.83 (m, 2H), 2.98 (s, 3H), 2.90 (s, 3H), 1.27~1.30 (m, 3H). MS $(M+H)^+$: 576.

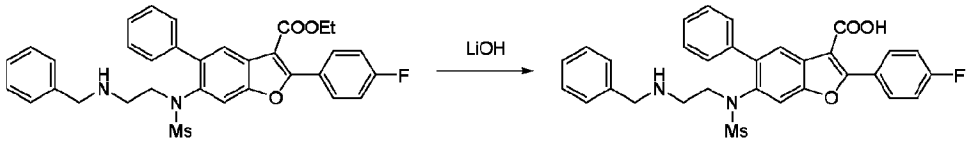
Step 6: ethyl 6-{[2-(benzylamino)ethyl](methylsulfonyl)amino}-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylate



Benzylamine (0.5 mL, 0.27 mmol)) was added to a solution of mesylate (50 mg, 0.09 mmol) in Et_3N (1 mL) and MeCN (1 mL). The reaction mixture was stirred overnight at 60°C. After dilution with H_2O and extraction with EtOAc, the mixture was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by prep-TLC to give the benzylic amine (30 mg, yield: 58%).

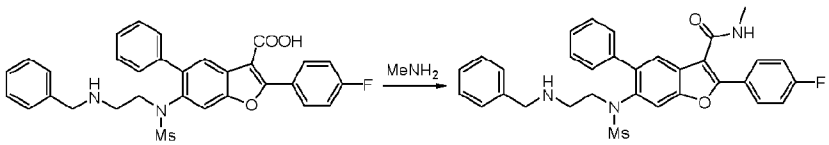
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.03 (m, 2H), 7.99 (s, 1H), 7.57 (s, 1H), 7.48~7.50 (m, 2H), 7.35~7.43 (m, 7H), 7.11~7.16 (m, 3H), 4.30~4.35 (dd, J = 8.0 Hz, 2H), 4.02~4.05 (m, 2H), 3.21~3.83 (m, 2H), 2.98 (s, 3H), 2.32 (d, J = 8.0 Hz, 2H), 1.27~1.30 (m, 3H). MS $(M+H)^+$: 587.

Step 7: 6-{[2-(benzylamino)ethyl](methylsulfonyl)amino}-2-(4-fluorophenyl)-5-phenyl-1-benzofuran-3-carboxylic acid



The ester (30 mg, 0.05 mmol) was dissolved in 1,4-dioxane (1 mL) and H_2O (1 mL). Then LiOH (21 mg, 0.5 mmol) was added to the solution, and the mixture was refluxed for 2 hours. After being acidified with HCl (1 N) and extracted with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the carboxylic acid (22 mg, yield: 79%). The acid was used in the next step without further purification.

Step 8: 6-{[2-(benzylamino)ethyl](methylsulfonyl)amino}-2-(4-fluorophenyl)-N-methyl-5-phenyl-1-benzofuran-3-carboxamide

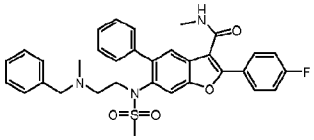
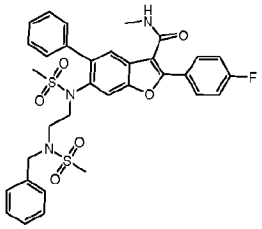
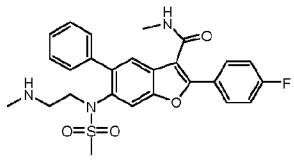


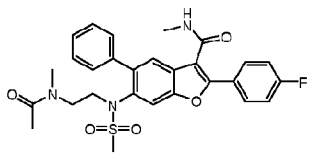
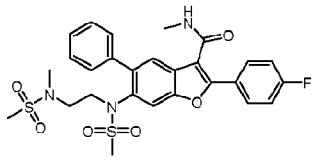
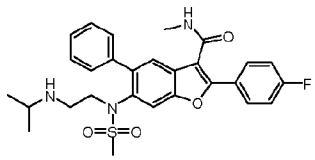
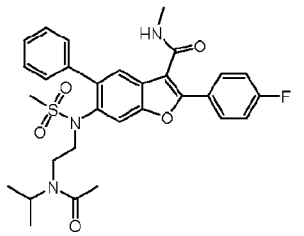
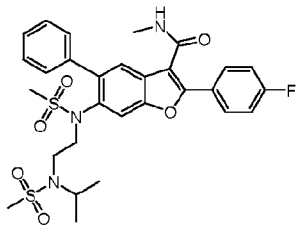
Carboxylic acid (22 mg, 0.04 mmol), HOBT (10 mg, 0.06 mmol) and EDCI (19 mg, 0.10 mmol) were dissolved in dry DMF (1 mL). The resulting solution was stirred for 30 minutes. Then, methanamine HCl salt (11 mg, 0.16 mmol) and Et_3N (18 mg, 0.18 mmol) was added to the mixture. After stirred overnight, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep-HPLC to give pure amide (Example 124) (20 mg, yield: 70%).

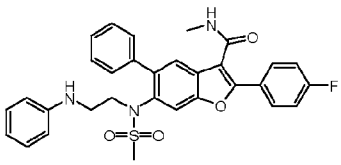
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87~7.88 (m, 2H), 7.68 (s, 1H), 7.44 (s, 1H), 7.38~7.42 (m, 2H), 7.23~7.25 (m, 6H), 7.13~7.19 (m, 4H), 5.87 (s, 1H), 3.58~3.61 (m, 2H), 3.51~3.52 (m, 2H), 3.06 (s, 3H), 2.91 (s, 3H), 2.53~2.59 (m, 2H). MS $(M+H)^+$: 572.

Examples 124-132

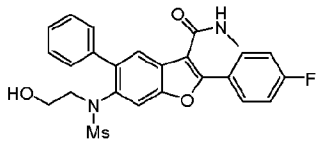
Examples 124-132 were prepared according to the general procedures of Example 123.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
124		6-[{2-[benzyl(methyl) amino]ethyl} (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.88~7.91 (m, 2H), 7.73 (s, 1H), 7.45 (s, 1H), 7.38~7.42 (m, 2H), 7.34~7.36 (m, 6H), 7.12~7.17 (m, 4H), 5.84 (s, 1H), 3.70~3.81 (m, 4H), 2.88~2.93 (m, 8H), 2.43 (s, 3H).	586
125		6-[{2-[benzyl (methylsulfonyl) amino]ethyl} (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.86~7.89 (m, 2H), 7.65 (s, 1H), 7.41 (s, 1H), 7.31~7.34 (m, 5H), 7.19~7.21 (m, 3H), 7.12~7.16 (m, 4H), 5.84 (s, 1H), 4.16~4.18 (m, 2H), 3.28~3.33 (m, 2H), 3.11~3.14 (m, 2H), 2.95 (s, 3H), 2.66 (s, 3H), 2.63 (s, 3H).	650
126		2-(4-fluorophenyl)-*N*-methyl-6-{[2-(methylamino)ethyl] (methylsulfonyl) amino}-5-phenyl-1-benzofuran-3-carboxamide	7.78~7.92 (m, 2H), 7.70 (s, 1H), 7.57 (s, 1H), 7.41~7.55 (m, 4H), 7.35~7.39 (m, 1H), 7.13~7.16 (m, 2H), 6.06 (s, 1H), 3.43~3.52 (m, 2H), 3.24~3.27 (m, 2H), 2.95 (s, 3H), 2.86 (s, 3H), 2.76 (s, 3H).	496

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
127		6-[{2-[acetyl(methyl) amino]ethyl} (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	7.95~7.98 (m, 2H), 7.84 (s, 1H), 7.76 (s, 1H), 7.43~7.46 (m, 5H), 7.18~7.22 (m, 2H), 5.83 (s, 1H), 3.56~3.65 (m, 2H), 3.49~3.52 (m, 2H), 2.98 (s, 3H), 2.95 (s, 3H), 2.88 (s, 3H), 1.97 (s, 3H).	538
128		2-(4-fluorophenyl)-*N*-methyl-6-[{2-[methyl (methylsulfonyl) amino]ethyl} (methylsulfonyl) amino]-5-phenyl-1-benzofuran-3-carboxamide	7.95~7.99 (m, 2H), 7.79 (s, 1H), 7.75 (s, 1H), 7.57~7.59 (m, 2H), 7.44~7.47 (m, 3H), 7.17~7.22 (m, 2H), 5.84 (s, 1H), 3.76~3.80 (m, 2H), 3.30~3.34 (m, 2H), 3.14 (s, 3H), 3.09 (s, 3H), 2.84 (s, 3H), 2.73 (s, 3H).	574
129		2-(4-fluorophenyl)-*N*-methyl-6-{(methylsulfonyl)[2-(propan-2-ylamino)ethyl] amino}-5-phenyl-1-benzofuran-3-carboxamide	7.95~8.10 (m, 2H), 7.91 (s, 1H), 7.36~7.40 (m, 3H), 7.15~7.26 (m, 3H), 6.96~7.01 (m, 2H), 5.95 (s, 1H), 3.99~4.03 (m, 2H), 3.05 (s, 3H), 2.93 (s, 3H), 2.84~2.86 (m, 2H), 2.59~2.60 (m, 1H), 1.17~1.17 (m, 6H).	524
130		6-[{2-[acetyl (propan-2-yl) amino]ethyl} (methylsulfonyl) amino]-2-(4-fluorophenyl)-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide	8.05~8.09 (m, 2H), 8.04 (s, 1H), 7.61 (s, 1H), 7.37~7.49 (m, 5H), 7.17~7.21 (m, 2H), 6.03 (s, 1H), 3.85~3.91 (m, 1H), 3.41~3.46 (m, 2H), 3.22~3.29 (m, 2H), 3.13 (s, 3H), 2.87 (s, 3H), 2.03 (s, 3H), 0.87~1.06 (m, 6H).	566
131		2-(4-fluorophenyl)-*N*-methyl-6-[(methylsulfonyl){2-[(methylsulfonyl) (propan-2-yl)amino]ethyl} amino]-5-phenyl-1-benzofuran-3-carboxamide	7.94~7.98 (m, 2H), 7.80 (s, 1H), 7.59 (s, 1H), 7.50~7.52 (m, 2H), 7.42~7.47 (m, 3H), 7.18~7.23 (m, 2H), 5.85 (s, 1H), 3.91~3.98 (m, 1H), 3.48~3.54 (m, 2H), 2.98~2.99 (m, 2H), 2.84 (s, 3H), 2.72 (s, 3H), 2.61 (s, 3H), 1.04~1.06 (m, 6H).	602

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
132		2-(4-fluorophenyl)-*N*-methyl-6-{(methylsulfonyl)[2-(phenylamino)ethyl]amino}-5-phenyl-1-benzofuran-3-carboxamide	7.90~7.86 (m, 2H), 7.75 (s, 1H), 7.57 (s, 1H), 7.50~7.48 (m, 2H), 7.43~7.42 (m, 2H), 7.40~7.38 (m, 3H), 7.16~7.07 (m, 2H), 6.71~6.37 (m, 1H), 6.39~6.37 (m, 2H), 5.79 (s, 1H), 3.55~3.50 (m, 2H), 3.13~3.12 (m, 1H), 2.94 (s, 3H), 2.93~2.92 (m, 1H), 2.71 (s, 3H).	558

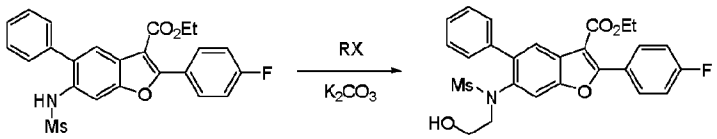
Example 133: 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-3

Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

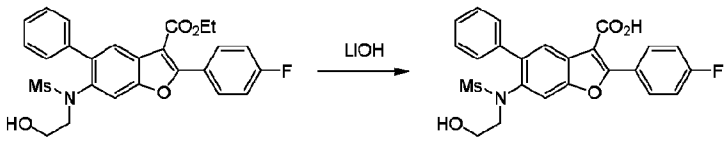
Step 4: ethyl 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



KI (6 mg, 0.036 mmol), K_2CO_3 (46 mg, 0.33 mmol), and 2-bromo ethanol (80 mg, 0.563 mmol) were added to a solution of ethyl 2-(4-fluorophenyl)-6-[(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate (50 mg, 0.131 mmol) in dry DMF under N_2 protection. The mixture was stirred at 60°C overnight. After dilution with H_2O and extraction with EtOAc, the organic solvent was washed with brine, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude was purified by prep-TLC to give the desired product of ethyl 2-(4-fluorophenyl)-6-[(2-hydroxyethyl) (methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate (60 mg, yield: 91%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00~8.03 (m, 3H), 7.61 (s, 1H), 7.51~7.52 (m, 2H), 7.35~7.44 (m, 3H), 7.11~7.16 (m, 2H), 4.30~4.36 (m, 2H), 3.21~3.56 (m, 4H), 2.91 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H).

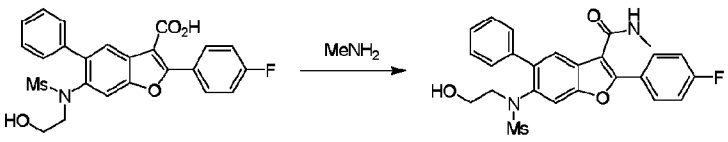
Step 5: 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid



To a solution of the product of Step 4 (60 mg, 0.12 mmol) in dioxane (1 mL) was added $LiOH \cdot H_2O$ (40 mg, 0.952 mmol) and H_2O (1 mL), and the resultant solution was stirred for 2 hours at 60°C. H_2O was added, and then 2N aqueous HCl was added to adjust pH = 4~5. After extraction with EtOAc, the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to provide the crude product. The crude was purified by prep-TLC. The desired product of 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylic acid was obtained (50 mg, yield: 88%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.99~8.03 (m, 2H), 7.62 (s, 1H), 7.48~7.49 (m, 2H), 7.38~7.43 (m, 3H), 7.11~7.15 (m, 2H), 3.19~3.59 (m, 4H), 2.90 (s, 3H).

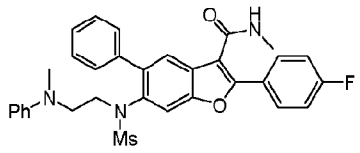
Step 6: 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-N-methyl-5-phenyl-1-benzofuran-3-carboxamide



The product of Step 5 (20 mg, 0.043 mmol), HOBT (12 mg, 0.08 mmol) and EDCI (26 mg, 0.13 mmol) were dissolved in dry DMF (1 mL). The resulting solution was stirred for 30 minutes. Then, methanamine (HCl salt, 7 mg, 0.22 mmol) and Et_3N (25 mg, 0.24 mmol) were added to the mixture. After stirring overnight, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep-TLC to give pure 2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-*N*-methyl-5-phenyl-1-benzofuran-3-carboxamide (10 mg, yield: 48%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86~7.90 (m, 2H), 7.72 (s, 1H), 7.59 (s, 1H), 7.47~7.50 (m, 2H), 7.32~7.40 (m, 3H), 7.10~7.16 (m, 2H), 5.80 (s, 1H), 3.28~3.47 (m, 4H), 2.90 (s, 6H).

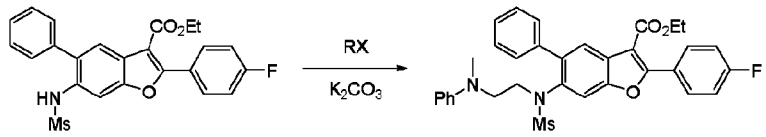
Example 134: 2-(4-fluorophenyl)-*N*-methyl-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



Steps 1-3

Steps 1-3 were performed in accordance with Example 1, Steps 1-3.

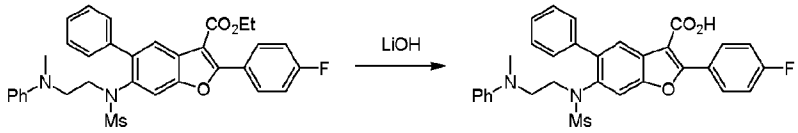
Step 4: ethyl 2-(4-fluorophenyl)-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate



Step 4 was performed in an an analogouos manner to Example 133, Step 4. The crude product was purified by prep-TLC to give pure ethyl 2-(4-fluorophenyl)-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxylate (60 mg, yield: 77%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06~8.10 (m, 3H), 7.59 (s, 1H), 7.49~7.51 (m, 2H), 7.39~7.46 (m, 3H), 7.14~7.22 (m, 4H), 6.66~6.70 (m, 1H), 6.54~6.56 (m, 2H), 4.37~4.42 (m, 2H), 3.23~3.67 (m, 4H), 2.81 (s, 3H), 2.75 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).

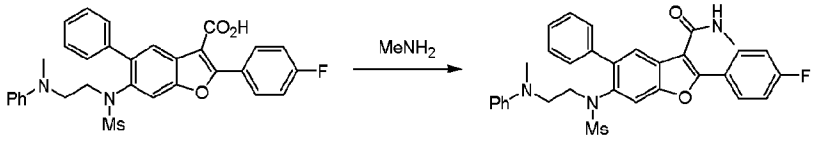
Step 5: 2-(4-fluorophenyl)-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl) amino5-phenyl-1-benzofuran-3-carboxylic acid



Step 5 was performed in an analogous manner to Example 133, Step 5. The crude product was purified by prep-TLC to give pure 2-(4-fluorophenyl)-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl) amino5-phenyl-1-benzofuran-3-carboxylic acid (50 mg, yield: 87%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80~7.89 (m, 3H), 7.50 (s, 1H), 7.07~7.42 (m, 10H), 6.97~7.01 (m, 2H), 3.41~3.67 (m, 4H), 2.94 (s, 3H), 2.71 (s, 3H).

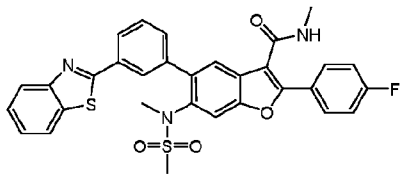
Step 6: 2-(4-fluorophenyl)-N-methyl-6-[{2-[methyl(phenyl)amino]ethyl}(methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide



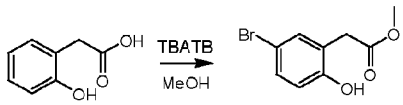
Step 6 was performed in an analogous manner to Example 133, Step 6. The crude product was purified by prep-TLC to give pure 2-(4-fluorophenyl)-*N*-methyl-6-[{2-[methyl(phenyl)amino]ethyl} (methylsulfonyl)amino]-5-phenyl-1-benzofuran-3-carboxamide (13 mg, yield: 42%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90~7.91 (m, 2H), 7.74 (s, 1H), 7.51 (s, 1H), 7.31~7.43 (m, 5H), 7.08~7.18 (m, 4H), 6.60~6.63 (m, 1H), 6.48~6.50 (m, 2H), 5.78 (s, 1H), 3.24~3.41 (m, 4H), 2.92 (d, *J* = 4.8 Hz, 3H), 2.74 (s, 3H), 2.70 (s, 3H).

Example 135: 5-(3-(benzo[d]thiazol-2-yl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxamide



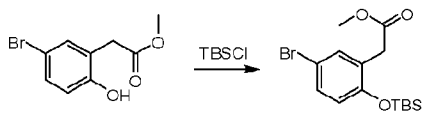
Step 1: Methyl 2-(5-bromo-2-hydroxyphenyl)acetate



2-(2-hydroxyphenyl)acetic acid (100 g, 0.66 mol) was dissolved in MeOH, and then TBATB (320 g, 0.66 mmol) was added to the solution. The resulting mixture was stirred at RT for 18 hours. After evaporation of solvent, the residue was dissolved in diethyl ether. The organic layer was washed with 1 N HCl, 2 M sodium bisulfate, H_2O and brine, dried and evaporated to yield methyl 2-(5-bromo-2-hydroxyphenyl)acetate (145 g, yield: 90%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.20~7.25 (m, 2H), 6.75~6.78 (m, 1H), 3.74 (s, 3H), 3.62 (s, 2H). MS $(M+H)^+$: 245.

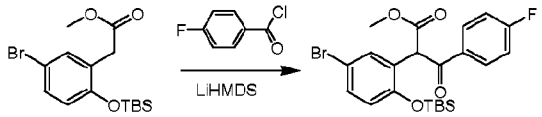
Step 2: Methyl 2-(5-bromo-2-(tert-butyldimethylsilyloxy)phenyl)acetate



To a stirred solution of the product of Step 1 (1 g, 4.1 mmol) in DCM (5 mL) was added imidazole (0.56 g, 8.23 mmol) and TBSCl (0.93 g, 6.17 mmol) at 0°C. After stirred overnight at RT, the reaction mixture was washed with H_2O, brine and concentrated *in vacuo*, the residue was purified by column chromatography to furnish the pure product of methyl 2-(5-bromo-2-(tert-butyldimethylsilyloxy)phenyl)acetate (1.4 g, yield: 95%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 2.4 Hz, 1H), 7.17 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.61 (s, 3H), 3.50 (s, 2H), 0.91 (s, 9H), 0.15 (s, 6H). MS $(M+H)^+$: 359.

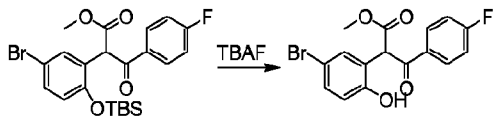
Step 3: Methyl 2-(5-bromo-2-(tert-butyldimethylsilyloxy)phenyl)-3-(4-fluorophenyl)-3-oxopropanoate



A solution of the product of Step 2 (500 mg, 1.4 mmol) in THF (10 mL) at -78°C was treated dropwise with lithium bis(trimethylsilyl)amide (1.7 mL, 1.7 mmol, 1 N in THF). After stirred 30 minutes, a solution of 4-fluorobenzoyl chloride (250 mg, 1.6 mmol) in THF was added dropwise. The reaction mixture was stirred at -78°C for 1 hour and at 0°C for another 1 hour. The mixture was quenched with 1 N HCl, THF was removed *in vacuo*, and the residue was extracted with EtOAc. The organic layer was concentrated and purified by column chromatography to afford the pure product of methyl 2-(5-bromo-2-(tert-butyldimethylsilyloxy)phenyl)-3-(4-fluorophenyl)-3-oxopropanoate (550 mg, yield: 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83~7.87 (m, 2H), 7.28 (d, J = 2.4 Hz, 1H), 7.16 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.93~6.98 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 5.86 (s, 1H), 3.65 (s, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H). MS $(M+H)^+$: 481.

Step 4: Methyl 2-(5-bromo-2-hydroxyphenyl)-3-(4-fluorophenyl)-3-oxopropanoate

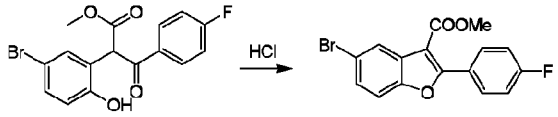


To a solution of the product of Step 3 (300 mg, 0.6 mmol) in THF (10 mL), TBAF (500 mg, 1.9 mmol) was added and the mixture was stirred at 0°C for 1 hour. After concentrated *in vacuo*, the mixture was suspended in H_2O and extracted with EtOAc. The organic layer was washed with H_2O, brine and concentrated. The residue was purified by

column chromatography to give the product of methyl 2-(5-bromo-2-hydroxyphenyl)-3-(4-fluorophenyl)-3-oxopropanoate (200 mg, yield: 87%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.33 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.07 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 5.93 (s, 1H), 3.77 (s, 3H). MS $(M+H)^+$: 367.

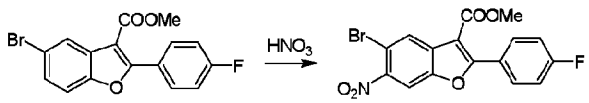
Step 5: Methyl 5-bromo-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate



To a solution of the product of Step 4 (100 mg, 0.3 mmol) in acetone (4 mL) was added concentrated HCl, and the mixture was heated under reflux for 30 minutes. Then, the reaction mixture was concentrated *in vacuo*, suspended in H_2O and extracted with EtOAc. The organic layer was washed with H_2O, brine and concentrated. The residue was purified by prep-TLC to give pure methyl 5-bromo-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate (70 mg, yield: 73%).

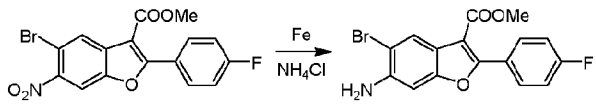
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.05 (m, 2H), 7.43 (m, 1H), 7.37 (m, 1H), 7.16 (m, 2H), 3.94 (s, 3H). MS $(M+H)^+$: 349.

Step 6: Methyl 5-bromo-2-(4-fluorophenyl)-6-nitro-1-benzofuran-3-carboxylate



To a solution of the product of Step 5 (0.5 g, 1.4 mmol) in $CHCl_3$ (4 mL), fuming HNO_3 (1 mL) was added dropwise at RT, and the mixture was stirred for 4 hours. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with $NaHCO_3$ and brine. The solvent was removed by concentration to provide the crude product of methyl 5-bromo-2-(4-fluorophenyl)-6-nitro-1-benzofuran-3-carboxylate (0.4 g, yield: 70%). It was used for the next step without further purification.

Step 7: Methyl 6-amino-5-bromo-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate



A mixture of the product of Step 6 (200 mg, 0.5 mmol), iron filings (200 mg, 3.58 mmol) and NH_4Cl (300 mg, 5.61 mmol) in MeOH:THF:H_2O (1:1:1, 20 mL) was stirred at reflux for 3 hours. After filtered and concentrated *in vacuo*, the residue was purified by column

chromatography to furnish the pure methyl 6-amino-5-bromo-2-(4-fluorophenyl)-1-benzofuran-3-carboxylate (150 mg, yield: 81%).

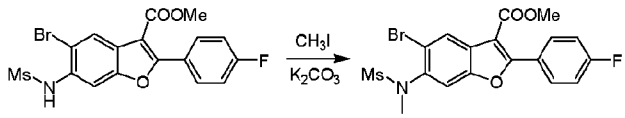
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.96 (m, 2H), 7.05~7.10 (m, 2H), 6.82 (s, 1H), 4.18 (br s, 2H), 3.86 (s, 3H). MS $(M+H)^+$: 364.

Step 8: Methyl 5-bromo-2-(4-fluorophenyl)-6-(methylsulfonamido)-1-benzofuran-3-carboxylate

MsCl (60 μL, 0.77 mmol) was added to a solution of the product of Step 7 (150 mg, 0.41 mmol) and pyridine (0.34 mL) in dry DCM (10 mL) at 0°C. After stirring overnight at RT, the mixture was diluted with water, and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*, and the residue was purified by prep-TLC to afford the pure product of methyl 5-bromo-2-(4-fluorophenyl)-6-(methylsulfonamido)-1-benzofuran-3-carboxylate (150 mg, yield: 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.99~8.03 (m, 2H), 7.83 (s, 1H), 7.11~7.16 (m, 2H), 6.82 (br s, 1H), 3.90 (s, 3H), 2.96 (s, 3H). MS $(M+H)^+$: 442.

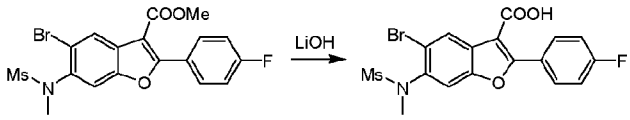
Step 9: Methyl 5-bromo-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxylate



CH_3I (0.8 mL, 12.85 mmol) was added to a mixture of the product of Step 8 (5.0 g, 11.31 mmol), K_2CO_3 (3.2 g, 23.15 mmol) and KI (1.9 mg, 11.45 mmol) in DMF (40 mL) under N_2 protection. The mixture was stirred at reflux overnight. After filtered and concentrated *in vacuo*, the residue was purified by column chromatography to give the product of methyl 5-bromo-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxylate (5 g, yield: 96%).

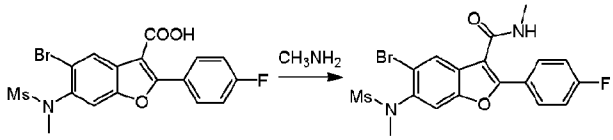
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.05~8.09 (m, 2H), 7.72 (s, 1H), 7.17~7.22 (m, 2H), 3.96 (s, 3H), 3.35 (s, 3H), 3.10 (s, 3H). MS $(M+H)^+$: 456.

Step 10: 5-bromo-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxylic acid



To a solution of the product of Step 9 (5 g, 0.11 mol) in dioxane / H_2O (1:1, 100 mL) was added LiOH·H_2O (4.6 g, 0.11 mol), and the mixture was stirred at 100°C for 2 hours. After concentration, the residue was dissolved in H_2O, 1 N HCl was added until pH reached 3, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed by distillation to provide the crude product of 5-bromo-2-(4-fluorophenyl)-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxylic acid (4.5 g, yield: 97%). It was used for the next step without further purification.

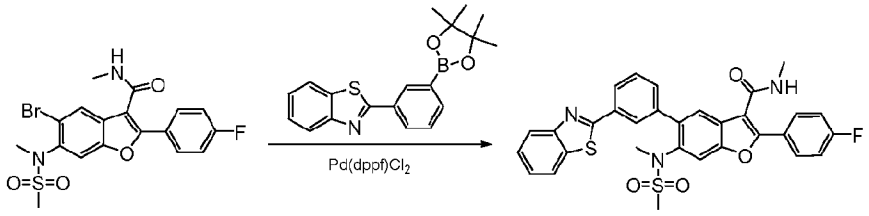
Step 11: 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxamide



A solution of the product of Step 10 (5 g, 11.31 mmol), HOBT (3.2 g, 23.7 mmol) and EDCI (5.0 g, 26.1 mmol) in dry DMF (100 mL) was stirred at RT. After 30 minutes, Et_3N (16 mL) and CH_3NH_2 (HCl salt, 3.7 g, 56.5 mmol) was added to the mixture, and the mixture was stirred overnight. After the solvent was removed, H_2O was added, and the mixture was extracted with EtOAc. The combined organic layer was washed with H_2O and brine and concentrated. The residue was purified by column chromatography to give the product of 5-bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxamide (4.8 g, yield: 93%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.88~7.92 (m, 2H), 7.70 (s, 1H), 7.18~7.23 (m, 2H), 5.78 (br s, 1H), 3.34 (s, 3H), 3.09 (s, 3H), 3.00 (d, J = 4.8 Hz, 3H). MS $(M+H)^+$: 455.

Step 12: 5-(3-(benzo[d]thiazol-2-yl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxamide

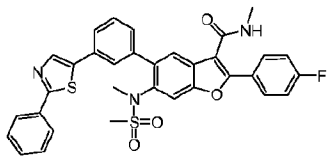
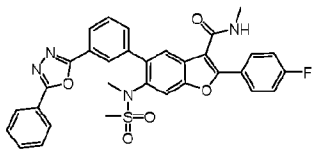


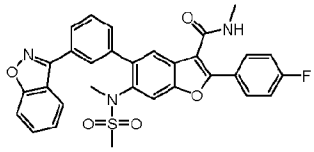
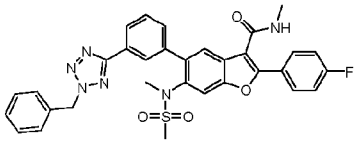
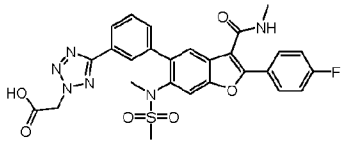
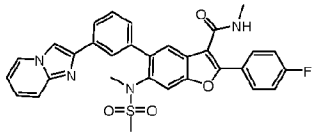
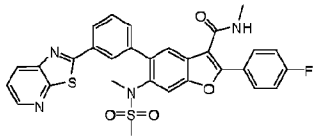
A mixture of $Pd(dppf)Cl_2$ (10 mg), the product of Step 11 (50 mg, 0.11 mmol), K_3PO_4 (60 mg, 0.28 mmol) and 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]thiazole (100 mg, 0.30 mmol) in DMF (2 mL) was stirred at 100°C under N_2 protection overnight. Then, the solvent was removed, and H_2O was added. After extracted with EtOAc, the combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by prep-HPLC to give the product of 5-(3-(benzo[d]thiazol-2-yl)phenyl)-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)-1-benzofuran-3-carboxamide (20 mg, yield: 31%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.12 (d, J = 7.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.91~7.96 (m, 3H), 7.86 (s, 1H), 7.58~7. 64 (m, 3H), 7.48~7.53 (m, 1H), 7.38~7.42 (m, 1H), 7.17~7.22 (m, 2H), 6.03 (br s, 1H), 3.17 (s, 3H), 2.99 (d, J = 4.8 Hz, 3H), 2.71 (s, 3H). MS $(M+H)^+$: 586.

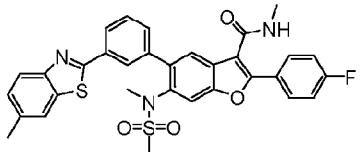
Examples 136-142

Examples 136-142 were prepared according to the general procedures of Example 135.

Example	Structure	Name	^{1}H-NMR (400 MHz)	MS $(M+H)^+$
136		2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-5-[3-(2-phenyl-1,3-thiazol-5-yl)phenyl]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.27 (s, 1H), 7.83~7.93 (m, 4H), 7.74 (s, 1H), 7.65 (s, 1H), 7.60~7.63 (m, 2H), 7.47~7.54 (m, 5H), 7.22 (t, J = 6.4 Hz, 2H), 6.00 (d, J = 4.4 Hz, 1H), 3.13 (s, 3H), 2.99 (d, J = 5.2 Hz, 3H), 2.75 (s, 3H).	612
137		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methyl sulfonyl)amino]-5-[3-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.17 (s, 1H), 8.08~8.12 (m, 3H), 7.86~7.90 (m, 2H), 7.82 (s, 1H), 7.55~7.64 (m, 3H), 7.45~7.49 (m, 3H), 7.12~7.17 (m, 2H), 5.84 (s, 1H), 3.11 (s, 3H), 2.93~2.94 (d, J = 4.4 Hz, 3H), 2.67 (s,3H).	597

Example	Structure	Name	^{1}H-NMR (400 MHz)	MS $(M+H)^+$
138		5-[3-(1,2-benzisoxazol-3-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.06 (s, 1H), 7.98~8.02 (m, 2H), 7.95~7.97 (m, 2H), 7.88 (s, 1H), 7.60~7.69 (m, 5H), 7.40 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 8.4 Hz, 2H), 5.88 (s, 1H), 3.21 (s, 3H), 3.00 (d, J = 4.8 Hz, 3H), 2.68 (s, 3H).	570
139		5-[3-(2-benzyl-2*H*-tetrazol-5-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.08~8.14 (m, 2H), 7.87~7.91(m, 2H), 7.77 (s, 1H), 7.58 (s, 1H), 7.49~7.51 (m, 2H), 7.30~7.38 (m, 5H), 7.14 (t, J = 8.8 Hz, 2H), 5.79 (d, J = 4.4 Hz, 1H), 5.23 (s, 2H), 3.09 (s, 3H), 2.92 (d, J = 4.8 Hz, 3H), 2.54 (s, 3H).	611
140		[5-(3-{2-(4-fluorophenyl)-3-(methylcarbamoyl)-6-[methyl(methylsulfonyl)amino]-1-benzofuran-5-yl}phenyl)-2*H*-tetrazol-2-yl]acetic acid	(MeOD) δ 8.25 (s, 1H), 8.17 (d, J = 6.4 Hz, 1H), 7.98~8.02 (m, 2H), 7.85 (s, 1H), 7.61~7.72 (m, 3H), 7.29 (t, J = 8.4 Hz, 2H), 5.62 (s, 2H), 3.21 (s, 3H), 2.95 (s, 3H), 2.82 (s, 3H).	579
141		2-(4-fluorophenyl)-5-[3-(imidazo[1,2-*a*]pyridin-2-yl)phenyl]-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.35 (d, J = 5.2 Hz, 1H), 8.06 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.86~7.89 (m, 2H), 7.66~7.73 (m, 3H), 7.50 (d, J = 7.2 Hz, 1H), 7.46 (s, 1H), 7.41 (t, J = 3.6 Hz, 1H), 7.24 (t, J = 6.0 Hz, 1H), 7.11 (t, J = 8.4 Hz, 2H), 6.98 (d, J = 3.6 Hz, 1H), 3.02 (s, 3H), 2.93 (d, J = 4.0 Hz, 3H), 2.86 (s, 3H).	569
142		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-[3-([1,3]thiazolo[5,4-*b*]pyridin-2-yl)phenyl]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.52 (s, 1H), 8.28~8.26 (d, J = 6.8 Hz, 1H), 8.26 (s, 1H), 8.18~8.12 (d, J = 4.8 Hz, 1H), 8.11~8.09 (m, 2H), 7.95 (s, 1H), 7.94~7.57 (m, 3H), 7.46~7.43 (m, 1H), 7.22~7.17 (t, J = 8.4 Hz, 2H), 5.89~5.88 (d, J = 4.0 Hz, 1H), 3.17 (s, 3H), 2.98~.2.97 (d, J = 4.8 Hz, 3H), 2.69 (s, 3H).	587

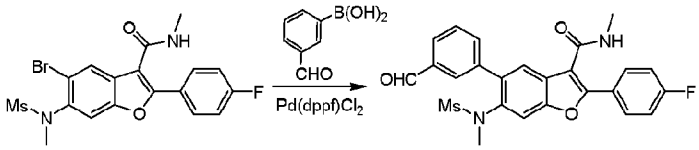
Example 143: 2-(4-fluorophenyl)-*N*-methyl-5-[3-(6-methyl-1,3-benzothiazol-2-yl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Steps 1-11

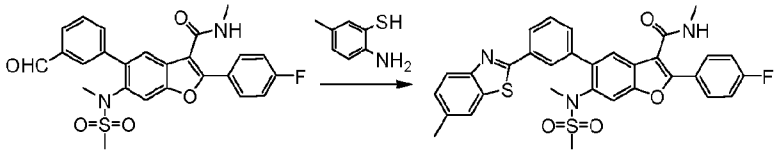
Steps 1-11 were performed in an analogous manner to Example 135, Steps 1-11.

Step 12: 2-(4-fluorophenyl)-5-(3-formylphenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



The aryl aldehyde (45 mg, yield: 73%) was prepared in an analogous manner to Example 136, Step 12.

Step 13: 2-(4-fluorophenyl)-N-methyl-5-[3-(6-methyl-1,3-benzothiazol-2-yl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide

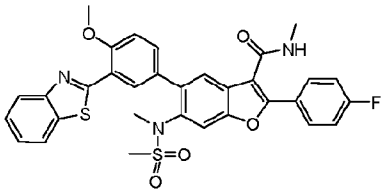
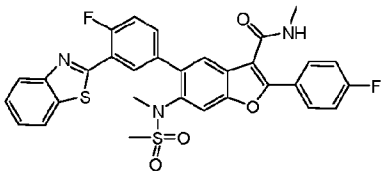
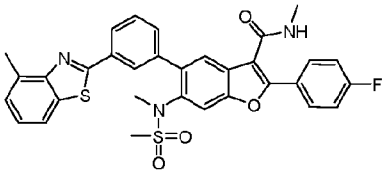
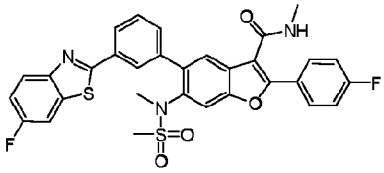


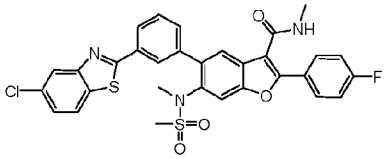
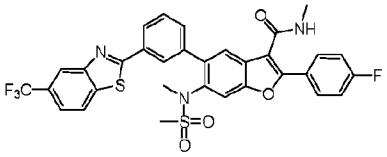
A mixture of 2-amino-5-methylbenzenethiol (50 mg, 0.10 mmol) and the aryl aldehyde (50 mg, 0.36 mmol) in DMSO was stirred at 200°C for 1 hour. After cooling, 20 mL H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed, and the crude product was purified by prep-TLC to give pure 2-(4-fluorophenyl)-*N*-methyl-5-[3-(6-methyl-1,3-benzothiazol-2-yl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (50 mg, yield: 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.12 (d, J = 6.8 Hz, 1H), 7.94~7.99 (m, 3H), 7.87 (s, 1H), 7.73 (s, 1H), 7.66 (s, 1H), 7.57~7.61 (m, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.19~7.24 (m, 2H), 6.05 (br s, 1H), 3.19 (s, 3H), 3.01 (d, J = 4.8 Hz, 3H), 2.72 (s, 3H), 2.53 (s, 3H). MS $(M+H)^+$: 600.

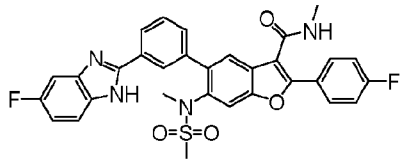
Examples 144-149

Examples 144-149 were prepared according to the general procedures of Example 143.

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
144		5-[3-(1,3-benzothiazol-2-yl)-4-methoxyphenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-1-benzofuran-3-carboxamide	8.56 (s, 1H), 7.97~7.99 (d, J = 8.0 Hz, 1H), 7.87~7.92 (m, 3H), 7.79 (s, 1H), 7.59~7.61 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.41~7.44 (m, 1H), 7.31~7.34 (m, 1H), 7.10~7.15 (m, 3H), 6.01 (s, 1H), 4.07 (s, 3H), 3.08~3.09 (d, J = 1.6 Hz, 3H), 2.93 (s, 3H), 2.75 (s, 3H).	616
145		5-[3-(1,3-benzothiazol-2-yl)-4-fluorophenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-1-benzofuran-3-carboxamide	8.41~8.43 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.91~7.94 (m, 3H), 7.79 (s, 1H), 7.57~7.61 (m, 2H), 7.45~7.49 (m, 1H), 7.37~7.41 (m, 1H), 7.28~7.32 (m, 1H), 7.15 (t, J = 8.8 Hz, 2H), 3.12 (s, 3H), 2.94 (s, 3H), 2.79 (s, 3H).	604
146		2-(4-fluorophenyl)-*N*-methyl-5-[3-(4-methyl-1,3-benzothiazol-2-yl)phenyl]-6-[methyl (methylsulfonyl) amino]-1-benzofuran-3-carboxamide	8.16 (s, 1H), 8.04~8.06 (m, 1H), 7.87~7.91 (m, 2H), 7.82 (s, 1H), 7.67 (t, J = 4.4 Hz, 1H), 7.60 (s, 1H), 7.51~7.53 (m, 2H), 7.22 (d, J = 5.2 Hz, 2H), 7.12~7.16 (m, 2H), 5.82 (d, J = 4.4 Hz, 1H), 3.12 (s, 3H), 2.93 (d, J = 4.8 Hz, 3H), 2.72 (s, 3H), 2.63 (s, 3H).	600
147		5-[3-(6-fluoro-1,3-benzothiazol-2-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl (methylsulfonyl) amino]-1-benzofuran-3-carboxamide	8.20 (s, 1H), 8.12 (d, J = 6.8 Hz, 1H), 8.02~8.05 (m, 1H), 7.97~8.00 (m, 2H), 7.91 (s, 1H), 7.68 (s, 1H), 7.66~7.60 (m, 3H), 7.24 (t, J = 8.8 Hz, 3H), 5.94 (d, J = 4.0 Hz, 1H), 3.20 (s, 3H), 3.03~3.02 (m, 3H), 2.75 (s, 3H).	604

Example	Structure	Name	^{1}H-NMR (400 MHz, $CDCl_3$) δ	MS $(M+H)^+$
148		5-[3-(5-chloro-1,3-benzothiazol-2-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	8.20 (s, 1H), 8.11~8.08 (m, 1H), 8.04~8.02 (d, J = 2.0 Hz, 1H), 7.96~7.92 (m, 2H), 7.86 (s, 1H), 7.82~7.79 (d, J = 8.4 Hz, 1H), 7.63~7.56 (m, 3H), 7.37~7.34 (m, 1H), 7.22~7.17 (m, 2H),. 5.88~5.86 (m, 1H), 3.15 (s, 3H), 2.98 (d, J = 5.2 Hz, 3H), 2.71 (s, 3H).	620
149		2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-5-{3-[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]phenyl}-1-benzofuran-3-carboxamide	8.31 (s, 1H), 8.21 (s, 1H), 8.20~8.11 (m, 1H), 8.02~8.00 (d, J = 8.4 Hz, 1H), 7.96~7.94 (m, 2H), 7.88 (s, 1H), 7.64~7.59 (m, 4H), 7.23~7.17 (m, 2H), 5.87~5.85 (m, 1H), 3.15 (s, 3H), 2.98 (d, J = 4.8 Hz, 3H), 2.73 (s, 3H).	654

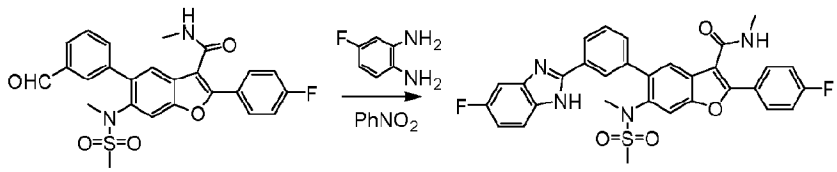
Example 150: 5-[3-(5-fluoro-1H-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



Steps 1-12

Steps 1-12 were performed in an analogous manner to Example 143, Steps 1-12.

Step 13: 5-[3-(5-fluoro-1H-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide



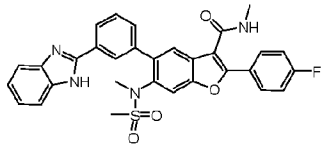
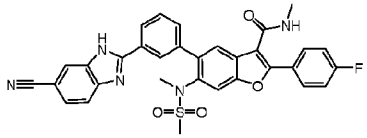
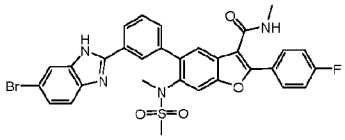
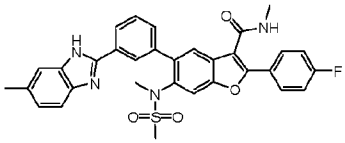
The aryl aldehyde of Example 143, Step 12 (100 mg, 0.21 mmol) and 4-fluorobenzene-1,2-diamine (32 mg, 0.25 mmol) were added in $PhNO_2$ (4 mL) and the mixture was heated to 120°C and stirred overnight. The mixture was concentrated, and H_2O (30 mL) was added. After extraction with EtOAc, the organic layer was washed with brine and concentrated.

The residue was purified by prep-HPLC to give pure 5-[3-(5-fluoro-1H-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-N-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide (30 mg, yield: 41.5%).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.00 (d, J = 6.8 Hz, 1H), 7.87 (m, 2H), 7.72 (s, 1H), 7.56~7.58 (m, 1H), 7.48~7.50 (m, 1H), 7.41(s,1H), 7.28~7.35 (m, 2H), 7.04~7.14 (m, 3H), 6.62~6.68 (m, 1H), 2.93~2.96 (m, 9H). MS $(M+H)^+$: 587.

Examples 151-154

Examples 151-154 were prepared according to the general procedures of Example 150.

Example	Structure	Name	^{1}H-NMR (400 MHz)	MS $(M+H)^+$
151		5-[3-(1*H*-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	(MeOD) δ 8.13 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.86 (t, J = 7.6 Hz, 3H), 7.82 (d, J = 7.6 Hz, 1H), 7.71~7.74 (m, 4H), 7.53 (t, J = 3.2 Hz, 2H), 7.20 (t, J = 8.4 Hz, 2H), 3.15 (s, 3H), 2.86 (s, 3H), 2.84 (s, 3H).	569
152		5-[3-(6-cyano-1*H*-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.18 (s, 1H), 8.11 (m, 1H), 7.92 (s, 1H), 7.81~7.86 (m, 3H), 7.67 (d, J = 8.4 Hz, 1H), 7.47~7.54 (m, 3H), 7.42 (s, 1H), 7.12~7.19 (m, 2H), 6.18 (br s, 1H), 3.06 (s, 3H), 2.95 (s, 3H), 2.87 (s, 3H).	594
153		5-[3-(6-bromo-1*H*-benzimidazol-2-yl)phenyl]-2-(4-fluorophenyl)-*N*-methyl-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.14 (s, 1H), 8.06 (d, J = 6.4 Hz, 1H), 7.91 (s, 2H), 7.72~7.63 (m, 2H), 7.33~7.47 (m, 5H), 7.18 (t, J = 8.0 Hz, 2H), 6.60 (s, 1H), 3.00 (s, 3H), 2.99 (s, 3H), 2.93 (s, 3H).	647
154		2-(4-fluorophenyl)-*N*-methyl-5-[3-(6-methyl-1*H*-benzimidazol-2-yl)phenyl]-6-[methyl(methylsulfonyl)amino]-1-benzofuran-3-carboxamide	($CDCl_3$) δ 8.09 (s, 1H), 7.95~7.97 (d, J = 7.6 Hz, 1H), 7.77~7.81 (m, 2H), 7.68 (s, 1H), 7.63~7.65 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.48~7.50 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.19~7.21 (d, J = 7.2 Hz, 1H), 7.04~7.09 (m, 2H), 3.04 (s, 3H), 2.81 (s, 3H), 2.75 (s, 3H), 2.40 (s, 3H).	583

Example 155: 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. EC_{50} determinations were calculated as a percentage of a DMSO control by fitting the data to a four-parameter fit function.

The activity table provided below illustrates the observed activity:

Example	Replicon 1b (nM)	Example	Replicon 1b (nM)
1	120	87	39
2	114	88	52
3	80	89	23
4	703	90	197
5	47	91	342
6	118	92	252
7	ND	93	54

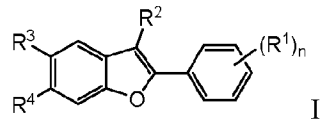
Example	Replicon 1b (nM)	Example	Replicon 1b (nM)
8	276	94	450
9	99	95	130
10	221	96	1228
11	ND	97	126
12	ND	98	72
13	84	99	623
14	ND	100	45
16	68	101	505
17	48	102	7
18	41	103	< 8
19	227	104	164
20	66	105	57
21	115	108	53
22	55	109	216
23	374	110	90
24	182	111	40
25	166	112	< 8
27	384	113	74
28	46	114	ND
29	412	117	ND
30	40	123	111
34	189	124	>10000
35	7	135	4
40	90	136	16
41	>2000	137	6
42	60	138	9
53	373	139	5
69	>3000	140	1191
70	329	141	3
71	>2500	142	1
72	2666	143	8
73	143	144	11
74	395	145	6
77	101	146	15
78	215	147	7
79	320	148	9

Example	Replicon 1b (nM)	Example	Replicon 1b (nM)
80	241	149	11
81	117	150	1
82	53	151	5
83	232	152	4
84	107	153	4
85	43	154	4
86	28		

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 structural formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from the group consisting of halogens;

n is 0, 1, 2 or 3;

R^2 is $C(O)NR^AR^B$;

R^A and R^B are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and $O(C_1$-C_6 alkyl);

R^3 is ArA, wherein ArA is an aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings, and

ii) 8-, 9- or 10-membered bicyclic rings, and

wherein said ArA is substituted by 0, 1, 2 or 3 substitutents R^C;

each R^C is independently selected from the group consisting of:

a) halogen,

b) OH

c) C_1-C_6 alkyl,

d) $O(C_1$-C_6 alkyl),

e) CN,

f) $(CH_2)_{0-3}$-ArB, wherein each ArB is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

g) $(CH_2)_{0-3}NR^DC(O)R^E$,

h) $(CH_2)_{0-3}NR^DSO_2R^E$,

i) $(CH_2)_{0-3}C(O)NR^DR^E$, and

j) $(CH_2)_{0-3}SO_2R^E$,

wherein each R^c c) C_1-C_6 alkyl, d) $O(C_1$-C_6 alkyl), and f) $(CH_2)_{0-3}$-ArB is substituted by 0, 1, 2 or 3 substituents R^F;

each R^D is independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

each R^E is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, OC_{1-6}alkyl and 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, wherein each R^E C_{1-6}alkyl, OC_{1-6}alkyl and 5- or 6-membered monocyclic rings is substituted by 0, 1, 2, 3 substituents independently selected from the group consisting of C_1-C_6 alkyl, $O(C_1$-C_6 alkyl), halogen and OH;

each R^F is independently selected from the group consisting of:

a) halogen,

b) C_1-C_6 alkyl,

c) $O(C_1$-C_6 alkyl),

d) CN,

e) NH_2,

f) $(CH_2)_{0-3}$-ArC, wherein each ArC is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein each R^F b) C_1-C_6 alkyl, c) $O(C_1$-C_6 alkyl), and f) $(CH_2)_{0-3}$-ArC is substituted by 0, 1, 2 or 3 substituents R^G;

each R^G is independently selected from the group consisting of halogen, CN, C_{1-6}alkyl, $O(C_1$-C_6 alkyl), CF_3 and C(O)OH;

R^4 is selected from the group consisting of NR^HR^I;

R^H is selected from the group consisting of:

a) hydrogen,

b) C_{1-6}alkyl,

c) $C(O)O(C_{1-6}$alkyl), and

d) SO_2R^J;

R^J is selected from the group consisting of C_{1-6}alkyl and NR^XR^Y, where R^X and R^Y are independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^I is selected from the group consisting of:

a) C_{1-6}alkyl,

b) C_{2-6}alkenyl,

c) C_{2-6}alkynyl,

d) $(CH_2)_{0-3}(C_{3-8}$cycloalkyl),

e) $(CH_2)_{0-3}(C_{3-8}$cycloalkenyl), and

f) $C(O)C_{1-6}$alkyl,

wherein R^I is substituted by 0, 1, 2, 3 or 4 R^K;

each R^K is independently selected from the group consisting of:

a) OR^L,

b) halogen,

c) CN,

d) NR^MR^N,

e) $OC(O)C_{1-6}$alkyl,

f) $C(O)OC_{1-6}$alkyl,

g) $(CH_2)_{0-3}$-ArD, wherein each ArD is an independently selected aromatic ring system selected from the group consisting of:

i) 5- or 6-membered monocyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

ii) 8-, 9- or 10-membered bicyclic rings with 0, 1, 2, 3 or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein each R^K e) $OC(O)C_{1-6}$alkyl, f) $C(O)OC_{1-6}$alkyl, and g) $(CH_2)_{0-3}$-ArD is substituted by 0, 1, 2 or 3 substituents R^O,

R^L is selected from the group consisting of hydrogen, C_{1-6}alkyl and phenyl;

R^M is selected from the group consisting of hydrogen, C_{1-6}alkyl and $(CH_2)_{0-3}$(phenyl);

R^N is selected from the group consisting of hydrogen, C_{1-6}alkyl, $SO_2(C_{1-6}alkyl)$ and $C(O)(C_{1-6}alkyl)$;

or R^M and R^N are taken together with the N to which they are attached to form a 5- to 7-membered ring substituted by 0, 1, 2 or 3 R^P;

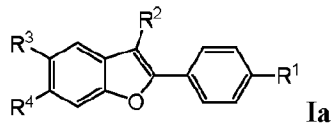
each R^O is independently selected from the group consisting of halogen, C_{1-6}alkyl, OC_{1-6}alkyl and $C(O)O(C_{1-6}alkyl)$;

each R^P is independently selected from the group consisting of halogen, C_{1-6}alkyl, OC_{1-6}alkyl, oxo and $C(O)O(C_{1-6}alkyl)$;

or R^H and R^I are taken together with the N to which they are attached to form a 5- to 7-membered ring.

2. The compound according to claim 1, wherein n is 1.

3. The compound according to any one of claims 1-2, wherein the compound is a compound of formula **Ia**:



Ia

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein R^1 is selected from the group consisting of fluorine, bromine and chlorine.

5. The compound according to any one of claims 1-4, wherein R^1 is fluorine.

6. The compound according to any one of claims 1-5, wherein R^A is hydrogen.

7. The compound according to any one of claims 1-6, wherein R^B is selected from the group consisting of $-CH_3$ and $-OCH_3$.

8. The compound according to any one of claims 1-7, wherein said ArA is phenyl.

9. The compound according to any one of claims 1-8, wherein each said R^C is independently selected from the group consisting of:

a) fluorine,

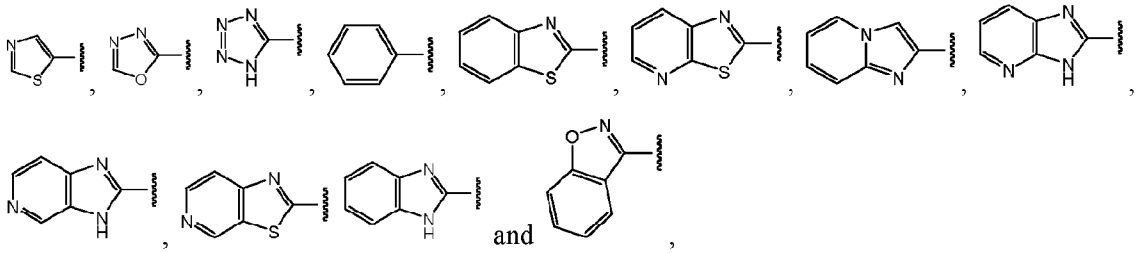
b) OH,

c) C_{1-3}alkyl,

d) OC_{1-3}alkyl,

e) CN,

f) $(CH_2)_{0-1}$-ArB, wherein ArB is independently selected from the group consisting of:



g) $(CH_2)_{0-1}N(CH_3)SO_2CH_3$,

h) $(CH_2)_{0-1}N(H)SO_2CH_3$,

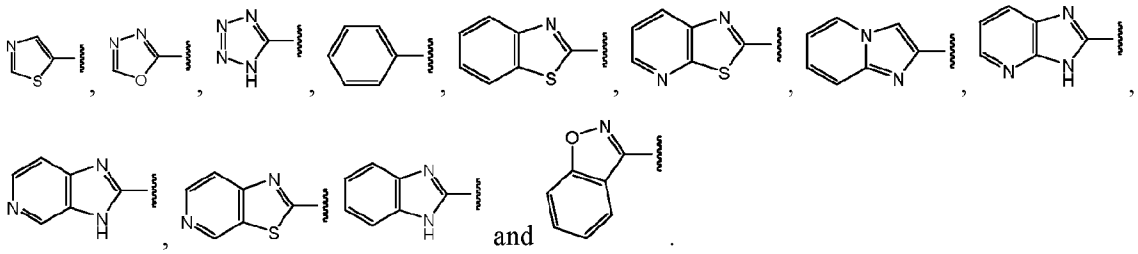
i) $(CH_2)_{0-1}N(CH_3)SO_2$phenyl,

j) $C(O)NHCH_3$,

k) $(CH_2)_{0-1}N(H)C(O)CH_3$, and

l) $(CH_2)_{0-1}N(H)C(O)$phenyl.

10. The compound according to any one of claims 1-9, wherein each said R^C is independently selected from the group consisting of



11. The compound according to any one of claims 1-10, wherein R^H is selected from hydrogen, CH_3 and SO_2CH_3.

12. The compound according to any one of claims 1-11, wherein R^H is SO_2CH_3.

13. The compound according to any one of claims 1-12, wherein R^I is selected from the group consisting of C_{1-6}alkyl and C_{2-6}alkenyl.

14. The compound according to any one of claims 1-13, wherein R^K is selected from the group consisting of

a) OR^L,

b) halogen,

c) CN,

d) NR^MR^N,

e) $OC(O)C_{1-6}$alkyl, and

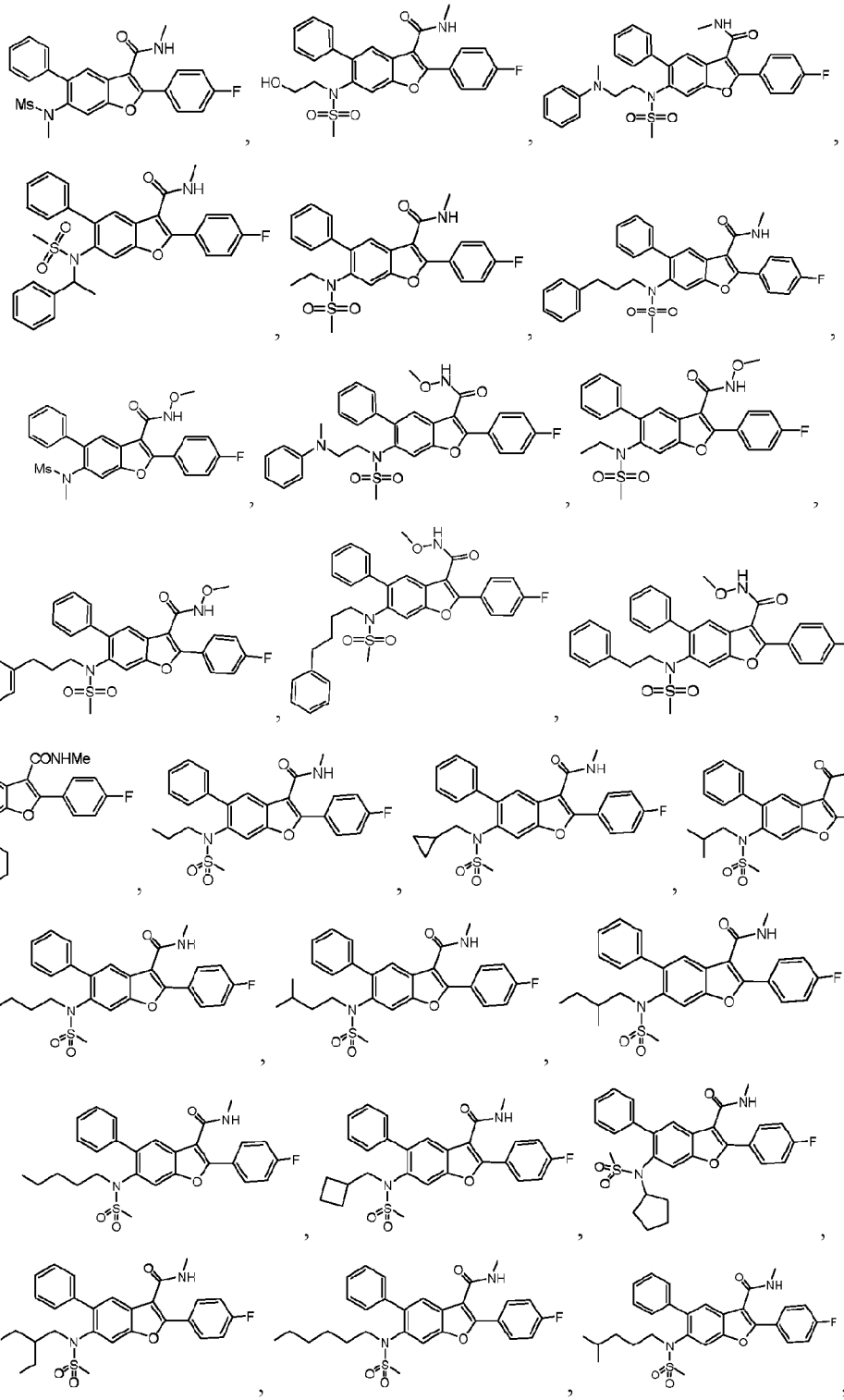
f) $C(O)OC_{1-6}$alkyl.

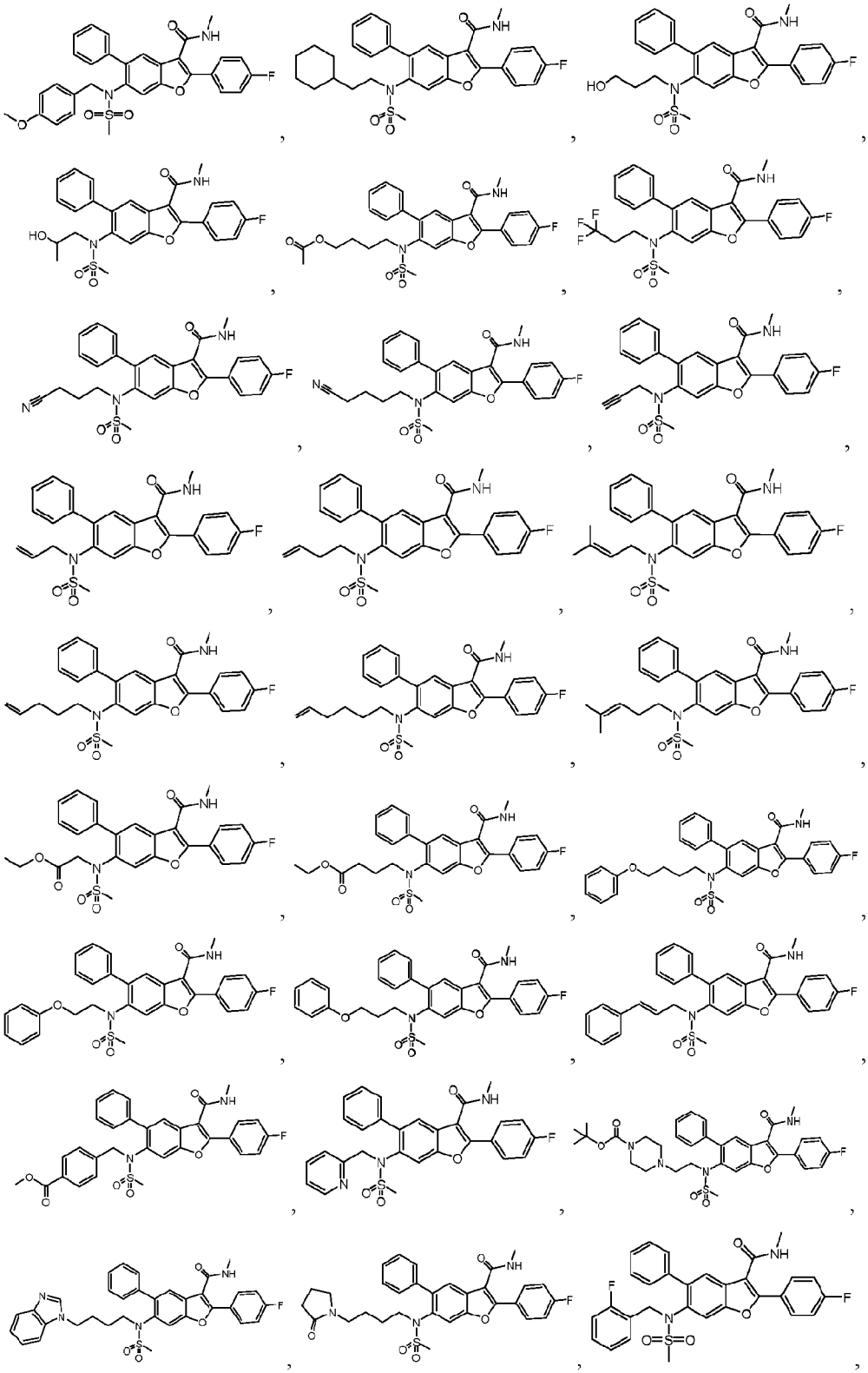
15. The compound according to any one of claims 1-14, wherein R^L is selected from the group consisting of C_{1-6}alkyl.

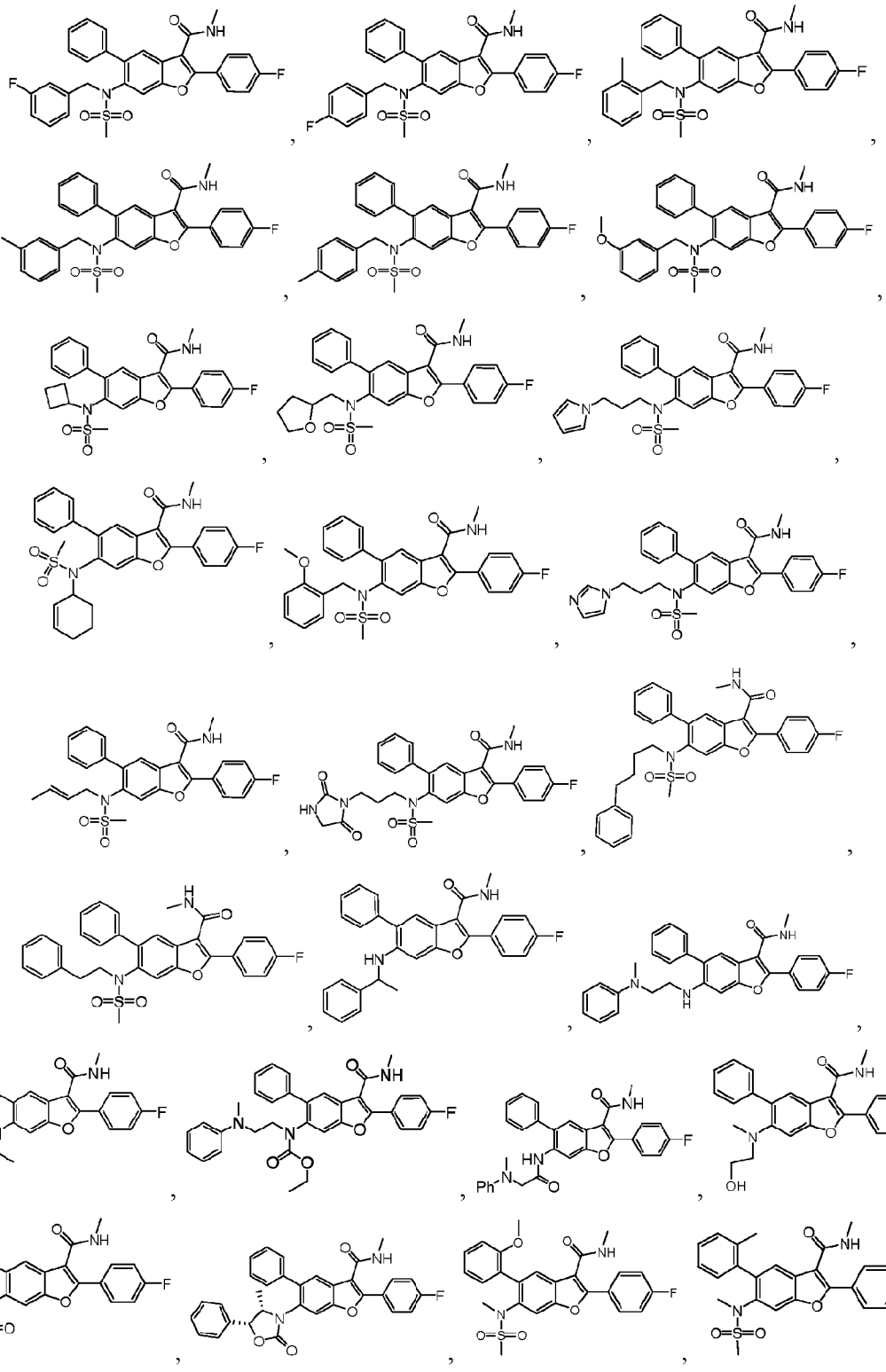
16. The compound according to any one of claims 1-15, wherein R^M is selected from the group consisting of hydrogen and C_{1-6}alkyl.

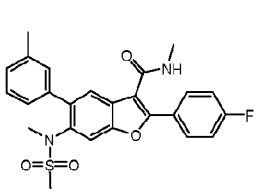
17. The compound according to any one of claims 1-16, wherein R^N is selected from the group consisting of C_{1-6}alkyl and $SO_2(C_{1-6}$alkyl).

18. A compound selected from the group consisting of





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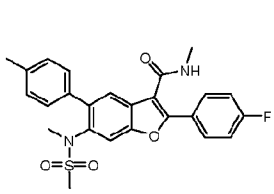
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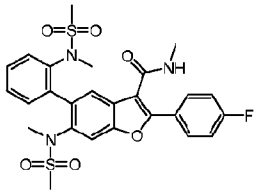
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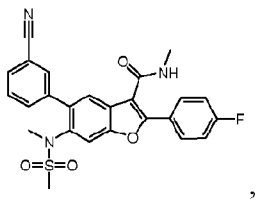
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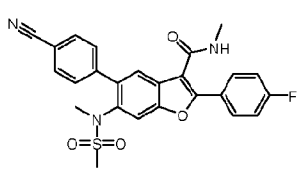
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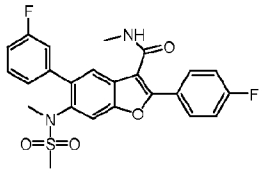
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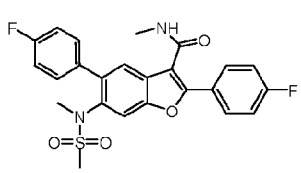
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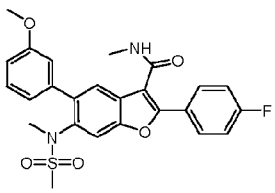
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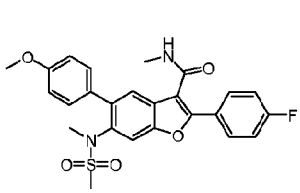
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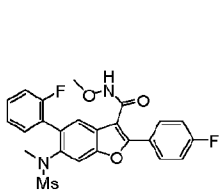
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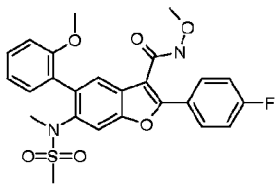
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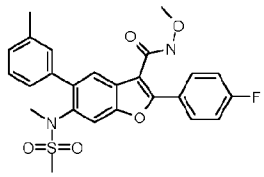
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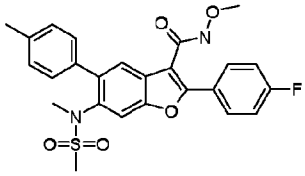
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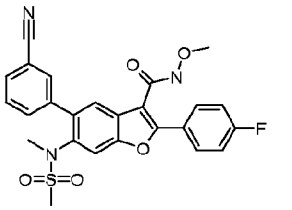
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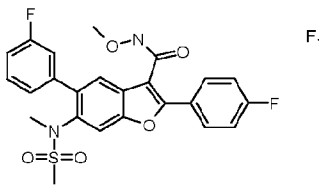
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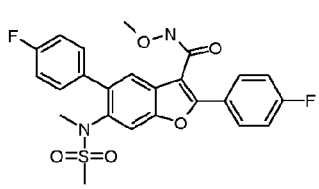
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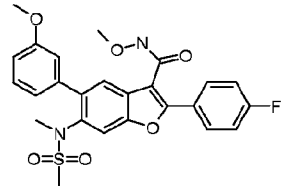
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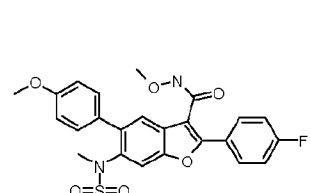
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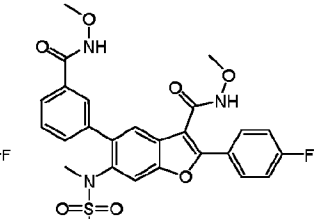
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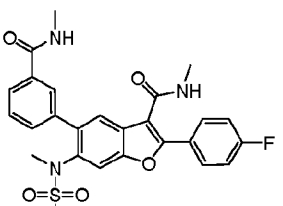
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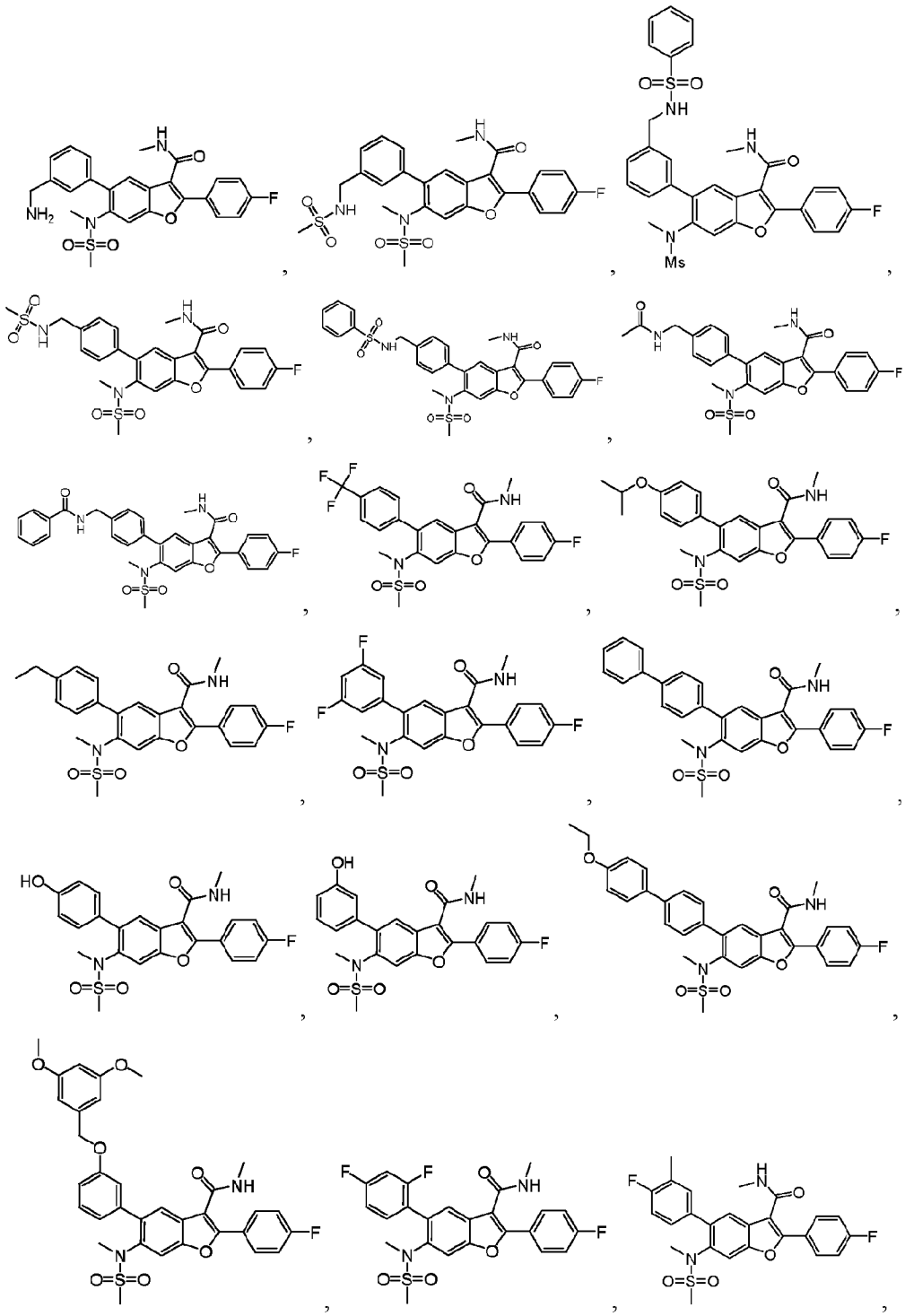

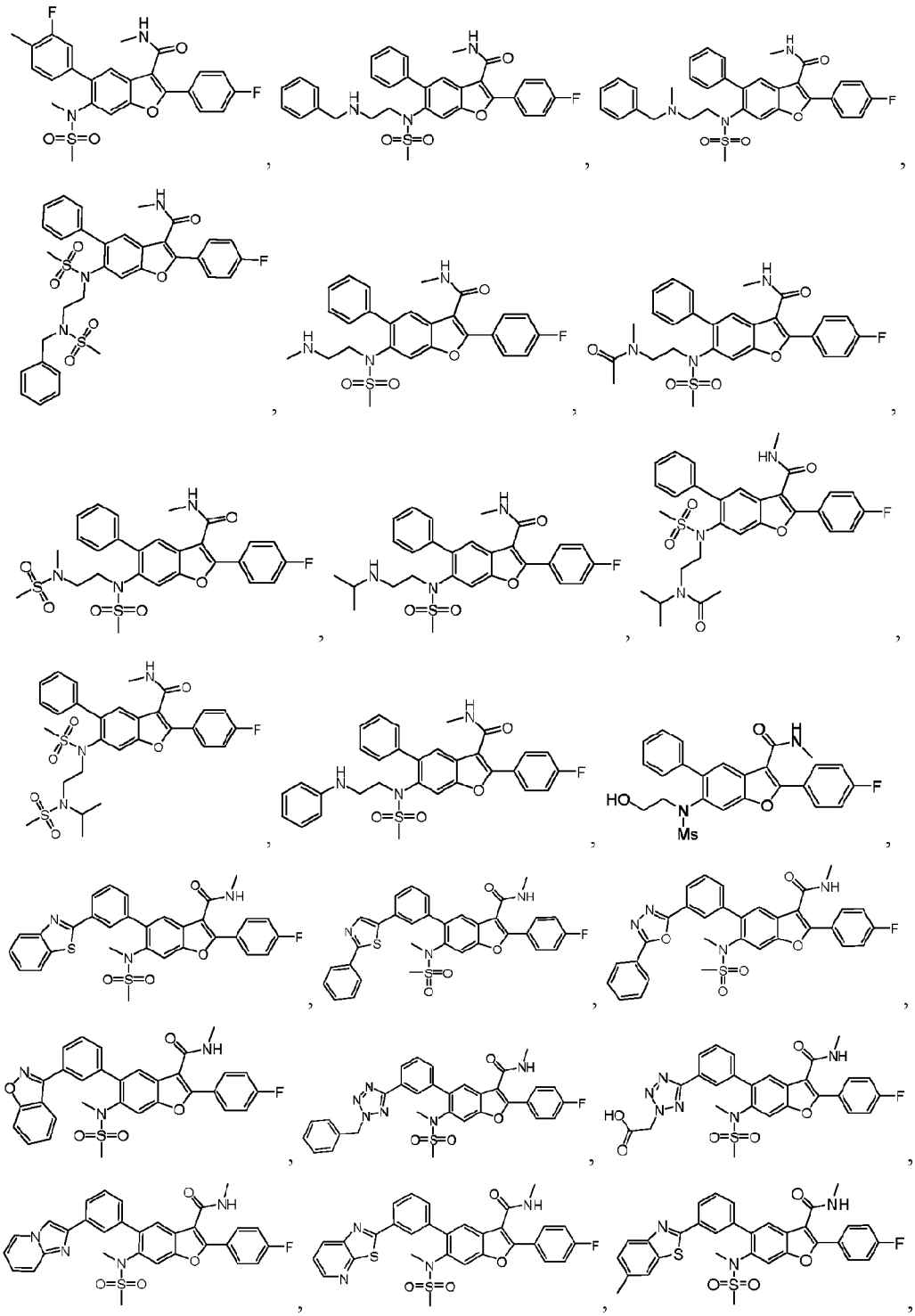

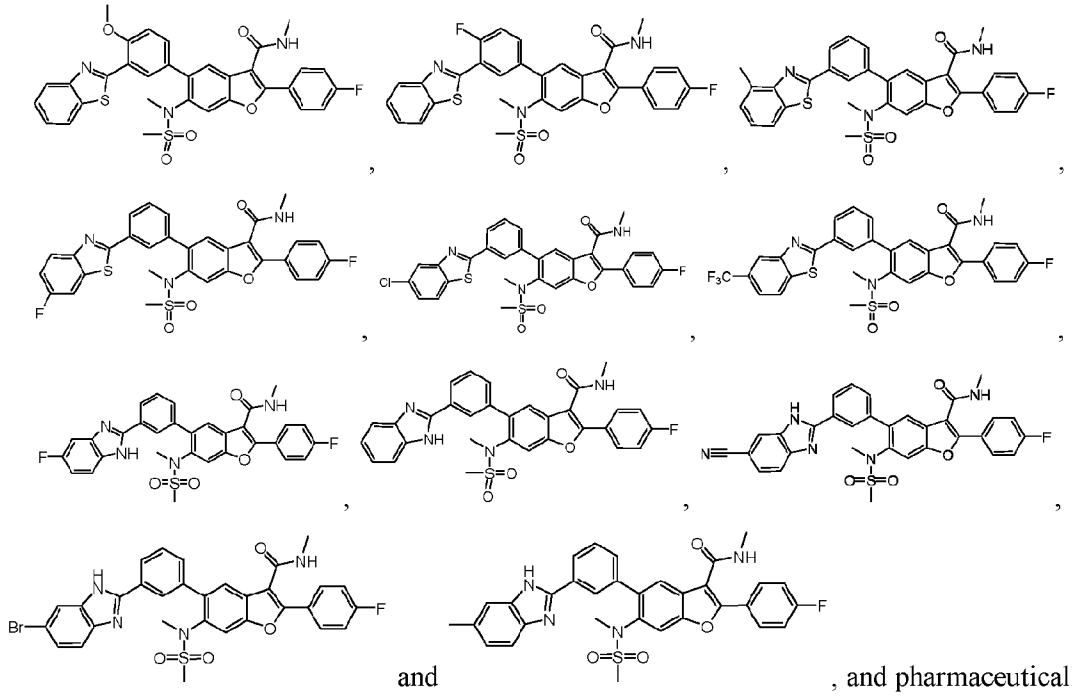

and , and pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1-18, and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition according to claim 19, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

21. The pharmaceutical composition according to claim 20, further comprising a second therapeutic agent selected from the group consisting of HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

22. A use of the compound according to any one of claims 1-18 in the preparation of a medicament for inhibiting HCV NS5B activity or for preventing and/or treating infection by HCV in a subject in need thereof.

23. A method of treating a patient infected with HCV comprising the step of administering an amount of the compound according to any one of claims 1-18 effective to prevent and/or treat infection by HCV in a subject in need thereof.

24. A method according to claim 24, further comprising the step of administering pegylated-interferon alpha and ribovirin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/070831

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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, A61P

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)

CPRS;CNKI;WPI;EPODOC;STN: hepatitis, HCV, benzofuran, carboxamide,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN1731993A(VIROPHARMA INC.), 8 Feb. 2006 (08.02.2006), See pages 15-23 and example 450 of description, claims 1-27	1-24

☐ 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
10 Nov. 2010(10.11.2010)	**09 Dec. 2010 (09.12.2010)**
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 HE, Xiangqiong Telephone No. (86-10)62084366

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/070831

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.: 23-24
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 23-24 are directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT). Nonetheless, the search has been carried out based on the use of the compounds in the manufacture of medicaments.

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/CN2010/070831

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN1731993A	08.02.2006	WO2004041201A2	21.05.2004
		US2004162318A1	19.08.2004
		AU2003290584A1	07.06.2004
		NO20052071A	23.05.2005
		BR0315937A	13.09.2005
		EP1581207A2	05.10.2005
		TW200418452A	01.10.2004
		MXPA05004608A	01.09.2005
		JP2006510736T	30.03.2006
		KR20050065661A	29.06.2005
		ZA200503501A	25.10.2006
		INDELNP200502291E	19.01.2007
		US7265152B2	04.09.2007
		US2007231318A1	04.10.2007
		AU2003290584B2	16.07.2009
		IN219490B	27.06.2008
		MX265539B	01.04.2009
		US2009281336A1	12.11.2009
		IL168282A	18.11.2009
		US7666863B2	23.02.2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/070831

CLSSIFICATION OF SUBJECT MATTER

C07D307/82 (2006.01) i
A61K31/343 (2006.01) n
A61P31/12 (2006.01) n