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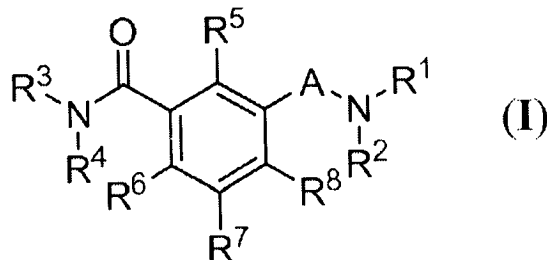
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(54) Title: NOVEL ANTIVIRAL AGENTS AGAINST HBV INFECTION



(57) Abstract: The present invention is directed toward novel compounds and novel methods of use of said compounds of the formula (I), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions. (Formula (I)) Including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are defined herein.

NOVEL ANTIVIRAL AGENTS AGAINST HBV INFECTION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of United States Application No. 61/746,552, filed December 27, 2012, which is incorporated herein by reference in its entirety for all purposes.

GOVERNMENT RIGHTS

[0002] This invention was made with government support under Grant Nos. R43AI098200 R43AI104066 awarded by the NIH's National Institute of Allergy and Infectious Diseases (NIAID). The government has certain rights in the invention.

FIELD OF INVENTION

[0003] The present invention describes compounds and methods useful as pregenomic RNA encapsidation inhibitors, useful for the treatment of Hepatitis B virus (HBV) infection and related conditions.

BACKGROUND OF THE INVENTION

[0004] Hepatitis B virus (HBV) infection remains a major public health problem. Currently, an estimated 350 million people worldwide and 1.4 million in the US are chronically infected with HBV (McMahon, 2005). Approximately one-third of these individuals will die from serious liver diseases, such as cirrhosis and hepatocellular carcinoma, if left untreated (Lee, 1997; Lok, 2004).

[0005] Seven drugs are currently available for the management of chronic hepatitis B, which include two formulations of alpha-interferon (standard and pegylated) and five nucleos(t)ide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) that inhibit HBV DNA polymerase (Keeffe et al., 2008). At present, the preferred first-line treatment choices are entecavir, tenofovir or peg-interferon alfa-2a. However, even with the first-line treatment options, peg-interferon alfa-2a is effective in achieving certain serological milestones in only one-third of treated patients and frequently associated with severe side effects (Janssen et al., 2005; Lau et al., 2005; Perrillo, 2009). Entecavir and tenofovir are highly potent HBV inhibitors, but a long-term or possibly life-time treatment is required to continuously suppress HBV replication, which may eventually fail due to emergence of drug resistant viruses (Dienstag, 2009). Hence, there is a pressing need for the

introduction of novel, safe and effective therapies for chronic hepatitis B, which is listed by National Institute of Allergy and Infectious Diseases (NIAID) as a High Priority Area of Interest.

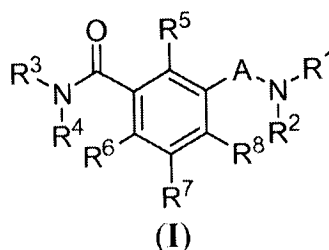
[0006] HBV is a noncytopathic, liver tropic DNA virus belonging to Hepadnaviridae family. Pregenomic (pg) RNA is the template for reverse transcriptional replication of HBV DNA and its encapsidation, together with viral DNA polymerase, into nucleocapsid is essential for the subsequent viral DNA synthesis. Inhibition of pregenomic RNA (pg) encapsidation would block HBV replication and provide a new therapeutic approach to the treatment of HBV. A similar approach would also lead to new therapeutic approaches to other viruses.

[0007] Clinically, inhibition of pregenomic RNA (pg) encapsidation, or more generally of inhibition of nucleocapsid assembly, offers the following therapeutic advantages: First, inhibition of pregenomic RNA (pg) encapsidation will complement the current medications by providing an additional option for a subpopulation of patients that do not tolerate or benefit from the current medications (Akbar et al., 2009; Liaw, 2009; Peters, 2009; Wiegand, van Bommel, and Berg). Second, based on their distinct antiviral mechanism, inhibition of pregenomic RNA (pg) encapsidation will be effective against HBV variants that are resistant to the currently available DNA polymerase inhibitors (Zoulim and Locarnini, 2009). Third, like the Highly Active Antiretroviral Therapy (HAART) for human immunodeficiency virus (HIV) infection (Este and Cihlar), combination therapy of the inhibitors of pregenomic RNA (pg) encapsidation with DNA polymerase inhibitors should synergistically suppress HBV replication and prevent the emergence of drug resistance and thus offers a safer and more effective treatment for chronic hepatitis B infection.

[0008] There is a long-felt need for new antiviral drugs that are both disease-modifying and effective in treating patients that are infected with hepatitis B virus, and other viruses, or preventing the onset thereof in patients at risk of getting the associated disease(s). There is also a clear and present need for new antiviral drugs that are both disease modifying and effective in treating patients that are infected with drug resistant hepatitis B virus, and other viruses. The present invention addresses the need for new antiviral drugs that are both disease-modifying and effective in treating patients that are infected with hepatitis B virus, and other viruses. Administration of these therapeutic agents to an infected patient, either as monotherapy or in combination with other treatments or ancillary treatments, will lead to significantly improved prognosis, diminished progression of the disease, and enhanced seroconversion rates.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention is directed toward novel compounds and novel methods of use of said compounds of the formula (I), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions.



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R¹ may also alternatively or additionally optionally include optionally substituted C₁₋₆ haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R² is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl; R² may also alternatively or additionally optionally include optionally substituted C₃₋₇ cycloalkyl or optionally substituted heterocyclic; or

R¹ and R² are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms; and

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted

alkylheteroaryl; in some embodiments, R^3 may also comprise an optionally substituted C_{1-6} linear alkyl;

R^4 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

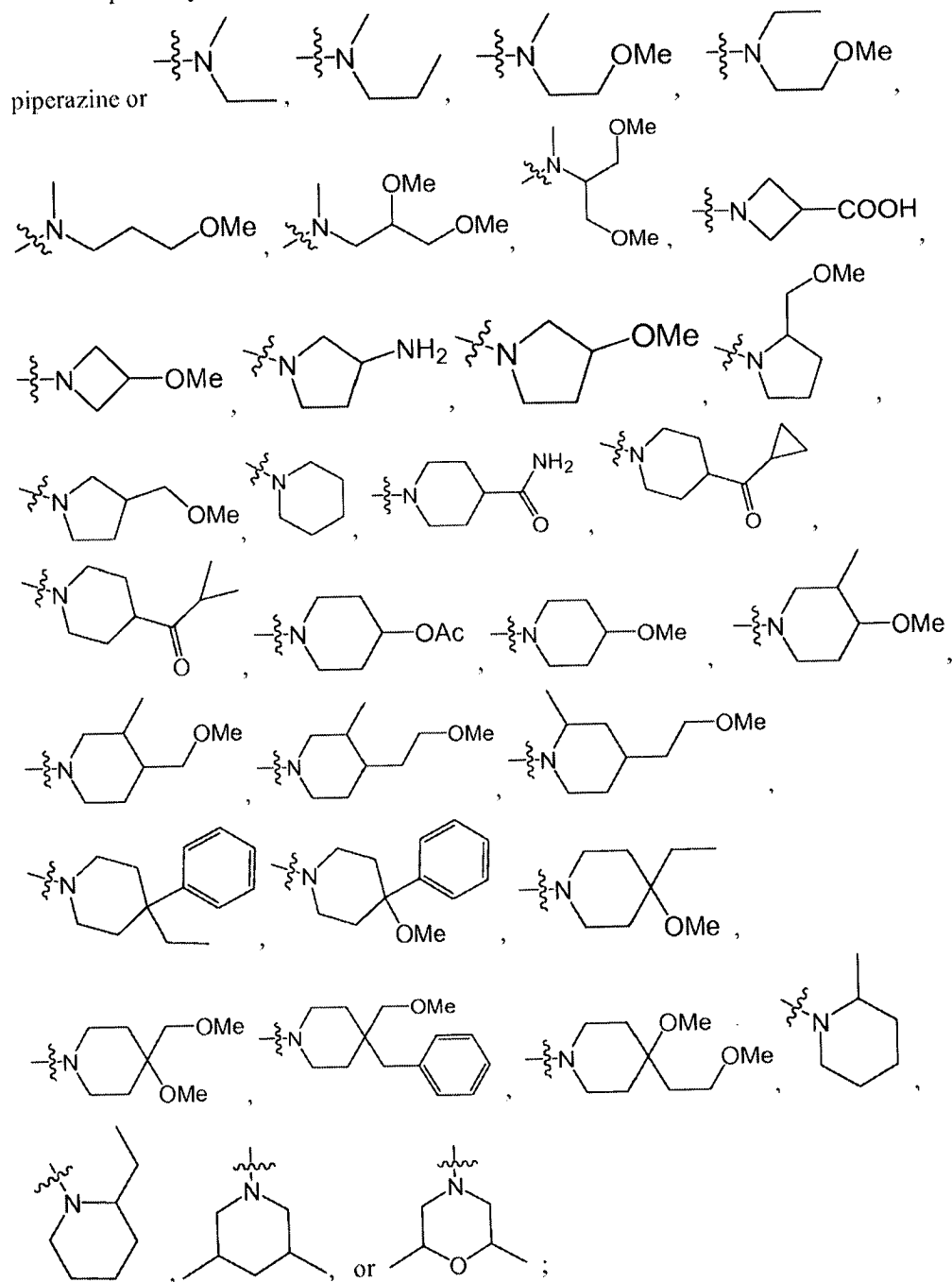
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms; and

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; R^9 may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

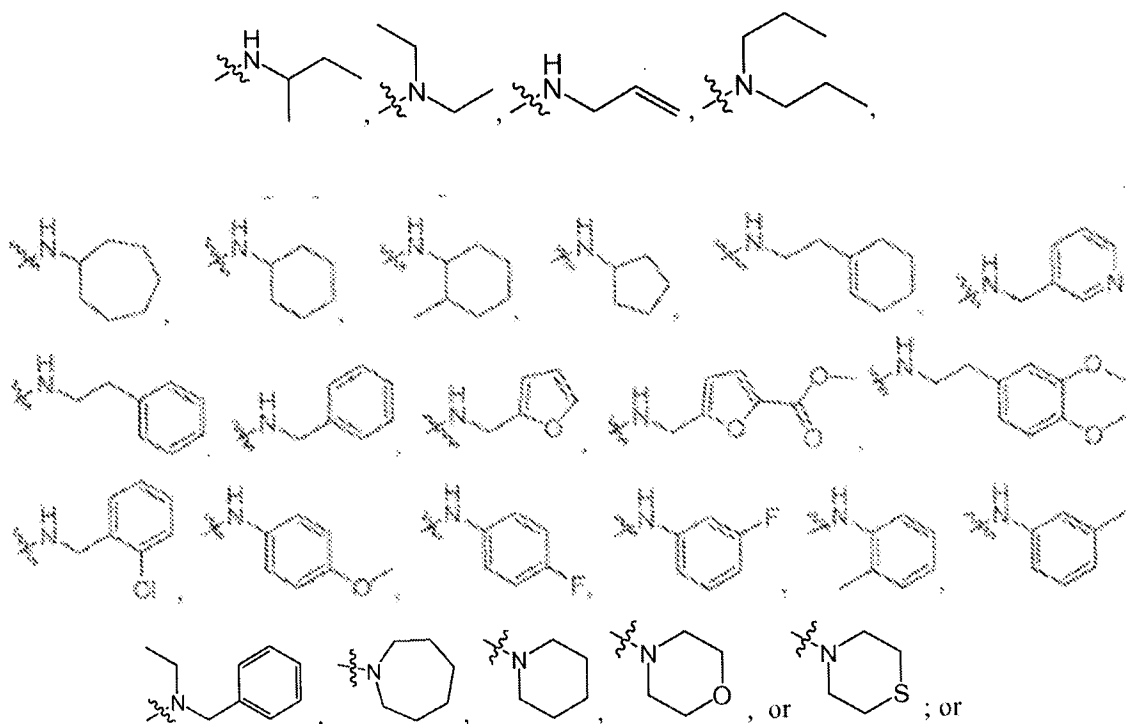
[0010] provided that when A is SO_2 ; R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring, then none of the following (a) through (d) apply:

- (a) R^3 is an optionally substituted phenyl and R^1 or R^2 , either individually or when taken together, contain a hydroxyl group, or

(b) R^3 is an optionally substituted alkyl or phenyl, and $N(R^1)(R^2)$ is an optionally substituted



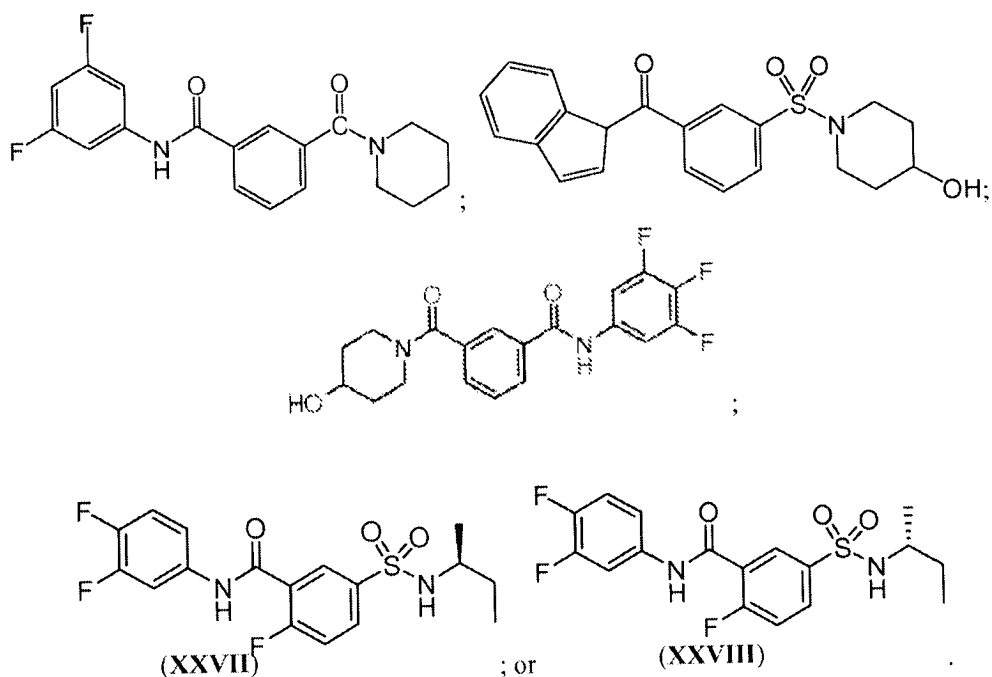
(c) R^3 is optionally substituted alkyl, aryl, or alkaryl and $N(R^1)(R^2)$ is



(d) either R^3 or R^4 is an unsubstituted or monosubstituted aryl, or an unsubstituted or monosubstituted alkaryl, or unsubstituted or monosubstituted heteroaryl and R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocyclic ring structure with 6 to 12 atoms; or

[0011] provided that the compound is not 3-[[[(dicyclopropylmethyl)amino]sulfonyl]-N-(4-isopropoxyphenyl)benzamide; or 3-[[[2-(1H-benzimidazol-2-yl)propyl]amino]sulfonyl]-N-(4-isopropoxyphenyl)benzamide; or 3-[(cyclohexylamino)sulfonyl]-N-(4-isopropylphenyl)benzamide; or 3-(anilinosulfonyl)-N-(4-isopropylphenyl)benzamide; or 5-[[3-[(4-methoxyphenyl)amino]carbonyl]phenyl)sulfonyl]amino]pentanoic acid; or 3-[(*tert*-butylamino)sulfonyl]-N-(4-methoxyphenyl)benzamide; or (3S)-1-[[3-[[5-isopropoxy-pyridin-2-yl]amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or (3R)-1-[[3-[[5-isopropoxy-pyridin-2-yl]amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or 3-(piperidin-1-ylsulfonyl)-N-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide; or N-(5-bromo-3-methoxypyridin-2-yl)-3-

(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenylpyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenoxy-pyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-[3-methoxy-5-(phenylthio)pyridin-2-yl]-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(5-ethyl-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-vinylpyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or



[0012] Some embodiments of the compounds of formula (I) also exclude those compounds when A is SO₂; R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R² and R⁸ taken together with the atoms to which they are bound do not to form an optionally substituted ring, R³ is optionally substituted alkyl, aryl, or alkaryl and N(R¹)(R²) is an optionally substituted piperidine.

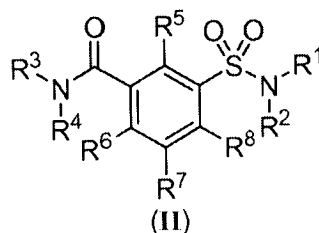
[0013] The embodiments of the present invention include compounds of formula (I) where

A is SO₂;

R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

R^2 and R^8 taken together with the atoms to which they are bound do not form an optionally substituted ring;

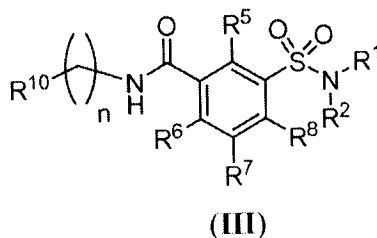
thereby providing compounds having formula (II),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0014] In some embodiments, R^1 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^8 are as defined below.

[0015] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , thereby providing compounds having formula (III),



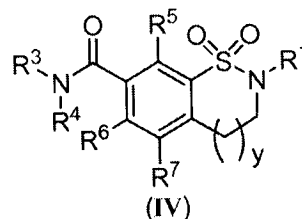
including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof,
wherein:

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and

n is 0 or 1.

[0016] In some embodiments, R^1 , R^2 , and R^5 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 , R^2 , and R^5 through R^8 are as defined below. In some embodiments, R^2 and R^8 taken together with the atoms to which they are bound do not form an optionally substituted carbocyclic or heterocyclic ring.

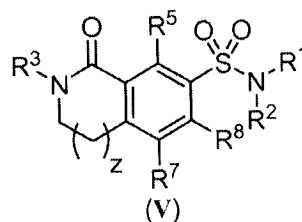
[0017] The embodiments of the present invention include compounds of formula (I) specifically having formula (IV),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: y is 0 or 1. In some embodiments, y is 2.

[0018] In some embodiments, R^1 and R^3 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 and R^3 through R^8 are as defined below. In some embodiments, R^4 and R^6 taken together with the atoms to which they are bound do not form an optionally substituted carbocyclic or heterocyclic ring.

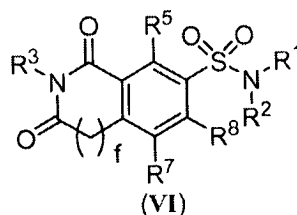
[0019] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , having formula (V),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: z is 0 or 1.

[0020] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below. In some embodiments, R^2 and R^8 taken together with the atoms to which they are bound do not form an optionally substituted carbocyclic or heterocyclic ring.

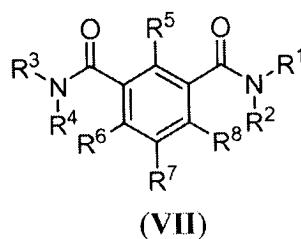
[0021] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , having formula (VI),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: *f* is 0 or 1.

[0022] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below. In some embodiments, R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring.

[0023] The embodiments of the present invention include compounds of formula (I) where A is CO, having formula (VII),

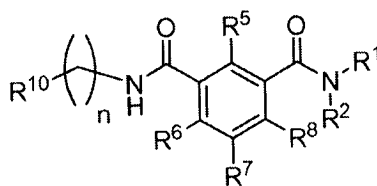


including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0024] In some embodiments, R^1 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^8 are as defined below.

[0025] In some embodiments of the compounds of Formula (VII), R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring; and R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring;

[0026] The embodiments of the present invention include compounds of formula (I) where A is CO, thereby providing compounds having formula (VIII),



(VIII)

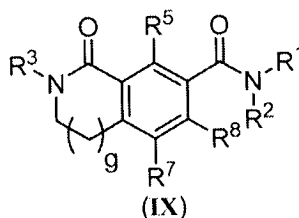
including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and

n is 0 or 1.

[0027] In some embodiments, R^1 through R^2 and R^5 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^2 and R^5 through R^8 are as defined below.

[0028] The embodiments of the present invention include compounds of formula (I) where A is CO, having formula (IX):

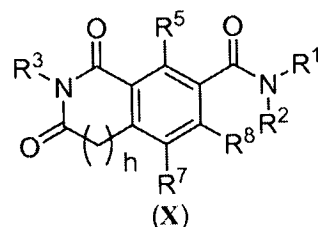


(IX)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: g is 0 or 1.

[0029] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below. In some embodiments, R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring; and

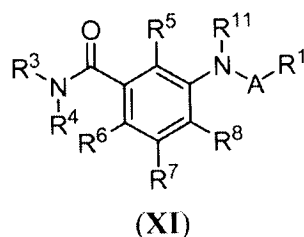
[0030] The embodiments of the present invention include compounds of formula (I) where A is CO, having formula (X),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: h is 0 or 1.

[0031] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below.

[0032] The embodiments of the present invention include compounds having formula (XI), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

A is selected from a group consisting of SO_2 and CO ;

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted C_{1-6} haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine,

optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl; in some embodiments, R³ may also comprise an optionally substituted C₁₋₆ linear alkyl;

R⁴ is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁶ may also alternatively or additionally optionally include cyano or N(R⁹)₂; or

R⁴ and R⁶ are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

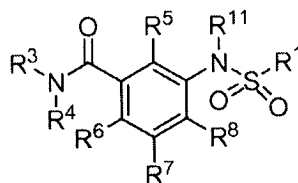
R⁷ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁷ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁸ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁸ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁹ is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl; R⁹ may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

R¹¹ is selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl.

[0033] The embodiments of the present invention also include compounds having formula (XII),

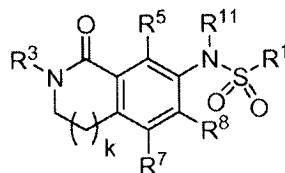


(XII)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0034] In some embodiments, R^1 , R^3 through R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 through R^8 and R^{11} are as defined below.

[0035] The embodiments of the present invention include compounds having formula (XIII),

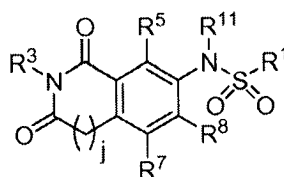


(XIII)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: k is 0 or 1.

[0036] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other independent embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

[0037] The embodiments of the present invention include compounds having formula (XIV),

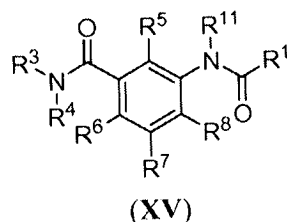


(XIV)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: j is 0 or 1.

[0038] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

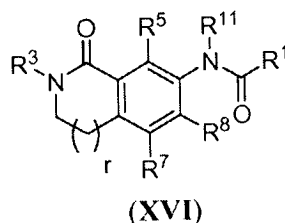
[0039] The embodiments of the present invention include compounds having formula (XV),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0040] In some embodiments, R^1 , R^3 through R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 through R^8 and R^{11} are as defined below.

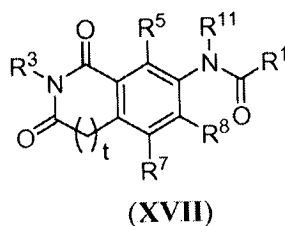
[0041] The embodiments of the present invention include compounds having formula (XVI),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof
wherein: r is 0 or 1.

[0042] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

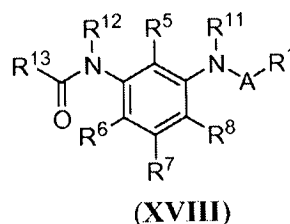
[0043] The embodiments of the present invention include compounds having formula (XVII),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof
wherein: t is 0 or 1.

[0044] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

[0045] The embodiments of the present invention include compounds having formula (XVIII), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R¹ may also alternatively or additionally optionally include optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and OR⁹; R⁶ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁷ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and OR⁹; R⁷ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

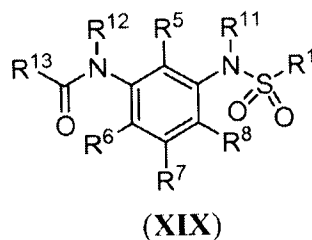
R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} ; R^9 may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{11} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl;

R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

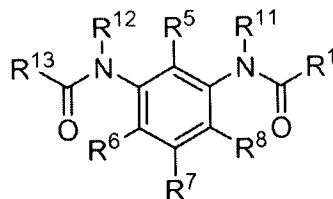
[0046] The embodiments of the present invention include compounds having formula (XIX),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0047] In some embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined for the compound of formula (XVIII). In other embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined below.

[0048] The embodiments of the present invention include compounds having formula (XX),

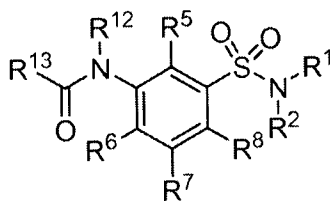


(XX)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0049] In some embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined for the compound of formula (XVIII). In other embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined below.

[0050] The embodiments of the present invention include compounds having formula (XXI), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



(XXI)

including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy- C_{1-6} -alkoxide, $-SO_2-C_{1-6}$ alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R^2 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl; R^2 may also alternatively or additionally optionally include optionally substituted C_{3-7} cycloalkyl or optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{1-6} haloalkyl; R^9 may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

[0051] The present invention further relates to compositions comprising:
an effective amount of one or more compounds according to the present invention and an excipient.

[0052] The present invention also relates to a method for treating or preventing diseases that involve nucleocapsid assembly, especially but not exclusively, including pregenomic RNA

encapsidation, including, for example, HBV infection, said method comprising administering to a subject an effective amount of a compound or composition according to the present invention.

[0053] The present invention yet further relates to a method for treating or preventing diseases that involve nucleocapsid assembly, especially but not exclusively, including pregenomic RNA encapsidation, including, for example, HBV infection, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0054] The present invention also relates to a method for treating or preventing disease or conditions associated with HBV infection, and diseases that involve nucleocapsid assembly, especially but not exclusively, including pregenomic RNA encapsidation. Said methods comprise administering to a subject an effective amount of a compound or composition according to the present invention.

[0055] The present invention yet further relates to a method for treating or preventing disease or conditions associated with HBV infection, and diseases that involve nucleocapsid assembly, especially but not exclusively, including pregenomic RNA encapsidation, wherein said method comprises administering to a subject a composition comprising an effective amount of one or more compounds according to the present invention and an excipient.

[0056] These, and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (°C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0057] Without intending to be bound by the correctness or incorrectness of any particular theory, the compounds of the present invention are believed to operate by the inhibition of nucleocapsid assembly, generally, and by inhibiting the formation of viral genomic RNA/DNA-containing capsids (i.e., pregenomic RNA encapsidation inhibitors of HBV), specifically. The term “pregenomic RNA encapsidation inhibitors of HBV” refer to a class of compounds that interfere with the association of a viral nucleic acid and its capsid proteins specifically related to that virus. By

interfering with capsid formation, this mechanism provides an effective strategy to suppress viral replication, generally, and with HBV specifically. While the language used in this application is largely directed to the treatment of HBV, possibly by inhibiting the association of hepdnaviral pre-genomic RNA and capsid, the same strategy of interfering with the association of the essential RNA or DNA of other viruses and their capsids would also be effective antiviral strategies using the compounds described herein, e.g., HIV. That is, in each case where the compound or treatment refers specifically to the treatment of HBV, additional embodiments provide that other viruses may also be treated by the application of the compounds described herein, for example by repressing viral replication and morphogenesis by interfering with capsid formation; by interfering with the association of nucleic acids with capsid; by interfering with association of RNA with capsid protein; interfering with pregenomic RNA association and capsid; and by interfering with nucleic acid capsid association, particularly by interfering with formation of the hepadna and HBV capsid formation.

[0058] The pregenomic RNA encapsidation inhibitors of the present invention are capable of treating and preventing diseases associated with pregenomic RNA encapsidation, for example HBV infection. Pregenomic (pg) RNA is the template for reverse transcriptional replication of HBV DNA and its encapsidation, together with viral DNA polymerase, into nucleocapsid is essential for the subsequent viral DNA synthesis. Without wishing to be limited by theory, it is believed that inhibition of pregenomic RNA encapsidation can ameliorate, abate, or otherwise cause to be controlled, diseases associated with pregenomic RNA encapsidation, for example HBV infection. Pregenomic RNA encapsidation inhibitors of the present invention address the clear and unmet need to identify novel and safe antiviral agents for the treatment of HBV infection that are chemically and mechanistically distinct from HBV antiviral drugs in current clinical use.

[0059] Clinically, the pregenomic RNA encapsidation inhibitors of the present invention complement the current medications by providing an additional option for a subpopulation of patients that do not tolerate or benefit from the current medications (Akbar et al., 2009; Liaw, 2009; Peters, 2009; Wiegand, van Bommel, and Berg). In addition, the pregenomic RNA encapsidation inhibitors of the present invention may be effective on HBV variants that are resistant to the currently available DNA polymerase inhibitors (Zoulim and Locarnini, 2009). Further, combination therapies of the pregenomic RNA encapsidation inhibitors of the present invention with DNA polymerase inhibitors may synergistically suppress HBV replication and prevent the emergence of drug resistance, offering a safer and more effective treatment for chronic hepatitis B (Billioud *et al.*, 2011).

[0060] The present invention may be understood more readily by reference to the following description taken in connection with the accompanying Figures and Examples, all of which form a part of this disclosure. It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and / or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of any claimed invention. Similarly, unless specifically otherwise stated, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the invention herein is not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement. Throughout this text, it is recognized that the descriptions refer both to the compounds and compositions, as well as the methods of making, formulating, and treating using the compounds and compositions themselves, and vice versa.

[0061] In the present disclosure the singular forms “a,” “an,” and “the” include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to “a material” is a reference to at least one of such materials and equivalents thereof known to those skilled in the art, and so forth.

[0062] When a value is expressed as an approximation by use of the descriptor “about,” it will be understood that the particular value forms another embodiment. In general, use of the term “about” indicates approximations that can vary depending on the desired properties sought to be obtained by the disclosed subject matter and is to be interpreted in the specific context in which it is used, based on its function. The person skilled in the art will be able to interpret this as a matter of routine. In some cases, the number of significant figures used for a particular value may be one non-limiting method of determining the extent of the word “about.” In other cases, the gradations used in a series of values may be used to determine the intended range available to the term “about” for each value. Where present, all ranges are inclusive and combinable. That is, references to values stated in ranges include every value within that range.

[0063] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or specifically excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for

brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. Finally, while an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself, combinable with others.

[0064] The transitional terms “comprising,” “consisting essentially of,” and “consisting” are intended to connote their generally in accepted meanings in the patent vernacular; that is, (i) “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) “consisting of” excludes any element, step, or ingredient not specified in the claim; and (iii) “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. Embodiments described in terms of the phrase “comprising” (or its equivalents), also provide, as embodiments, those which are independently described in terms of “consisting of” and “consisting essentially of.” For those embodiments provided in terms of “consisting essentially of,” the basic and novel characteristic(s) is the facile operability of the methods (or the systems used in such methods or the compositions derived therefrom) in treating the conditions described herein.

[0065] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as “A, B, or C” is to be interpreted as including the embodiments, “A,” “B,” “C,” “A or B,” “A or C,” “B or C,” or “A, B, or C.” Similarly, a subscript description for carbons or ring structures, such as C₁₋₆ alkyl, is understood to include each individual element of that list, and every combination of that list, as a separate embodiment, for example C₁-alkyl, C₂-alkyl, C₃-alkyl, C₄-alkyl, C₅-alkyl, C₆-alkyl, C₁₋₂-alkyl, C₁₋₃-alkyl, C₁₋₄-alkyl, C₁₋₅-alkyl, C₁₋₆-alkyl, C₂₋₃-alkyl, C₂₋₄-alkyl, C₂₋₅-alkyl, C₂₋₆-alkyl, C₃₋₄-alkyl, C₃₋₅-alkyl, C₃₋₆-alkyl, C₄₋₅-alkyl, C₄₋₆-alkyl, and C₅₋₆-alkyl,

[0066] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are described herein.

[0067] As used herein, the terms “treating” or “treatment” of a disease or disorder refers to the application or administration of a therapeutic agent, i.e., a compound of the invention (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (e.g., for diagnosis or ex vivo applications), who has HBV infection, a symptom of HBV infection or the potential to develop HBV infection, with the purpose of controlling the progression (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof) of the disease, or ameliorating the effects of the disease. In another embodiment, the terms refer to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treating” or “treatment” refers to delaying the onset of the disease or disorder, or even preventing the same.

[0068] The terms “preventing” or “prevention” are intended to connote the ability of the treatment or compound to reduce the risk of a disease or condition described herein. In other embodiments, these terms may also refer to a reduction in risk of acquiring a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject not yet exposed to or predisposed to the disease, and not yet experiencing or displaying symptoms of the disease).

[0069] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present teachings also consist essentially of, or consist of, the recited components, and that the processes of the present teachings also consist essentially of, or consist of, the recited processing steps.

[0070] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components and can be selected from a group consisting of two or more of the recited elements or components.

[0071] The use of the singular herein includes the plural (and vice versa) unless specifically stated otherwise. In addition, where the use of the term “about” is before a quantitative value, the present teachings also include the specific quantitative value itself, unless specifically stated otherwise.

[0072] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present teachings remain operable. Moreover, two or more steps or actions can be conducted simultaneously

[0073] As used herein, the term "halogen" shall mean chlorine, bromine, fluorine and iodine.

[0074] As used herein, unless otherwise noted, "alkyl" and/or "aliphatic" whether used alone or as part of a substituent group refers to both straight and branched carbon chains having 1 to 20 carbon atoms or any number within this range, for example, 1 to 6 carbon atoms or 1 to 4 carbon atoms. Designated numbers of carbon atoms (e.g. C₁₋₆) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger alkyl-containing substituent. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like. Alkyl groups can be optionally substituted. Non-limiting examples of substituted alkyl groups include hydroxymethyl, chloromethyl, trifluoromethyl, aminomethyl, 1-chloroethyl, 2-hydroxyethyl, 1,2-difluoroethyl, 3-carboxypropyl, and the like. In substituent groups with multiple alkyl groups such as (C₁₋₆alkyl)₂amino, the alkyl groups may be the same or different. Optionally substituted alkyls include, as specific individual embodiments, haloalkyls and particularly partially fluorinated or perfluorinated alkyls, for example, -CH₂F, -CHF₂, and -CF₃.

[0075] As used herein, the terms "alkenyl" and "alkynyl" groups, whether used alone or as part of a substituent group, refer to straight and branched carbon chains having 2 or more carbon atoms, preferably 2 to 20, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. Alkenyl and alkynyl groups can be optionally substituted. Nonlimiting examples of alkenyl groups include ethenyl, 3-propenyl, 1-propenyl (*also* 2-methylethenyl), isopropenyl (*also* 2-methylethen-2-yl), buten-4-yl, and the like. Nonlimiting examples of substituted alkenyl groups include 2-chloroethenyl (*also* 2-chlorovinyl), 4-hydroxybuten-1-yl, 7-hydroxy-7-methyloct-4-en-2-yl, 7-hydroxy-7-methyloct-3,5-dien-2-yl, and the like. Nonlimiting examples of alkynyl groups include ethynyl, prop-2-ynyl (*also* propargyl), propyn-1-yl, and 2-methyl-hex-4-yn-1-yl. Nonlimiting examples of substituted alkynyl groups include, 5-hydroxy-5-methylhex-3-ynyl, 6-hydroxy-6-methylhept-3-yn-2-yl, 5-hydroxy-5-ethylhept-3-ynyl, and the like.

[0076] The terms "carboxyamino" and "carboxy-alkoxide" refers to structures – C(O)N(R¹⁵)₂ and –C(O)-OR¹⁵, respectively. Preferred "carboxyamino" and "carboxy-alkoxide" moieties of the present invention include those where R¹⁵ is, independently at each occurrence, H, C₁₋₆ alkyl,

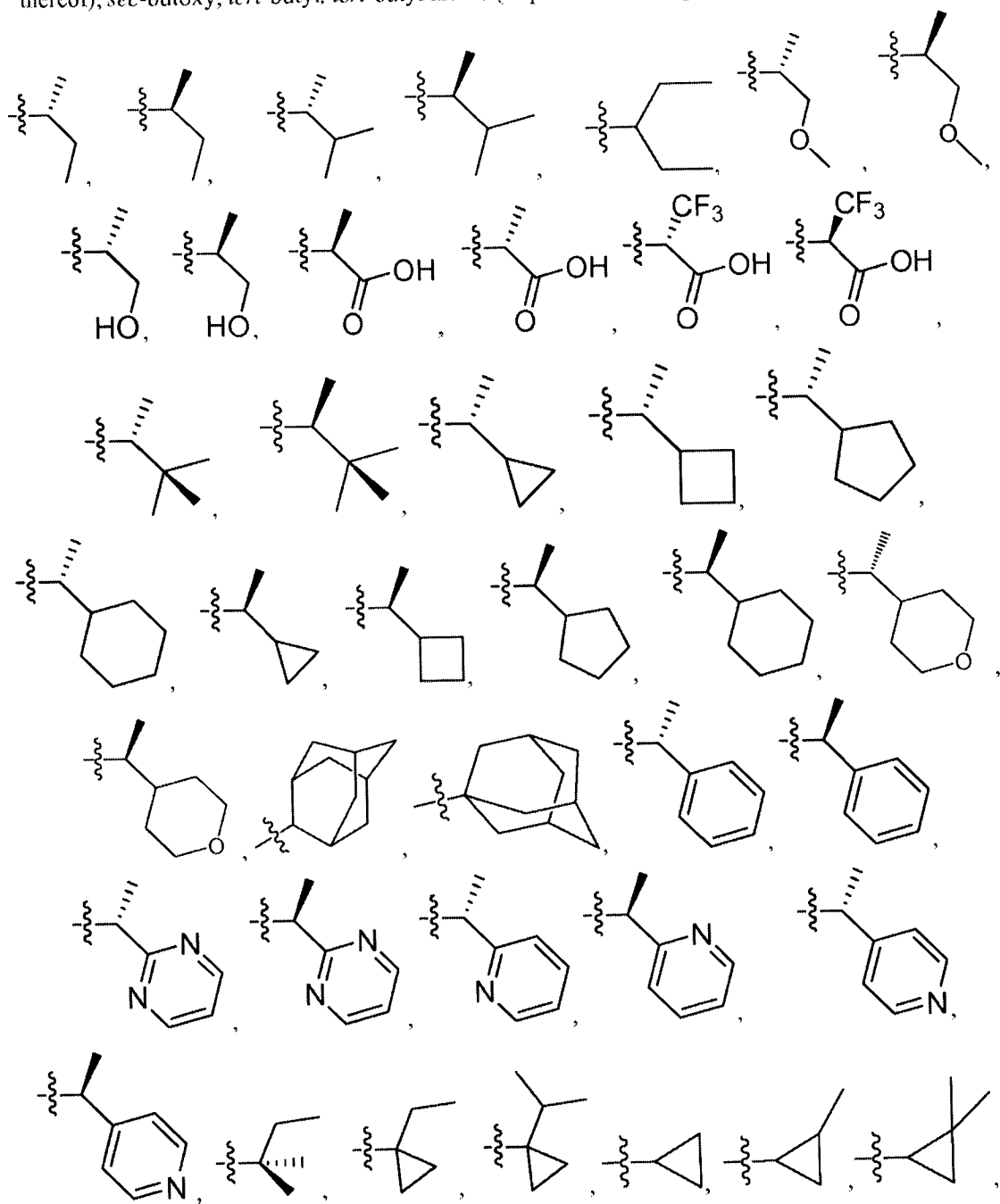
C₂₋₈ alkenyl, C₂₋₈ alkynyl, cycloalkyl (e.g., C₃₋₆ cycloalkyl), aryl, heterocyclyl, or heteroaryl. In but one example, -C(O)N(R¹⁵)₂ may be -C(O)N(CH₃)₂

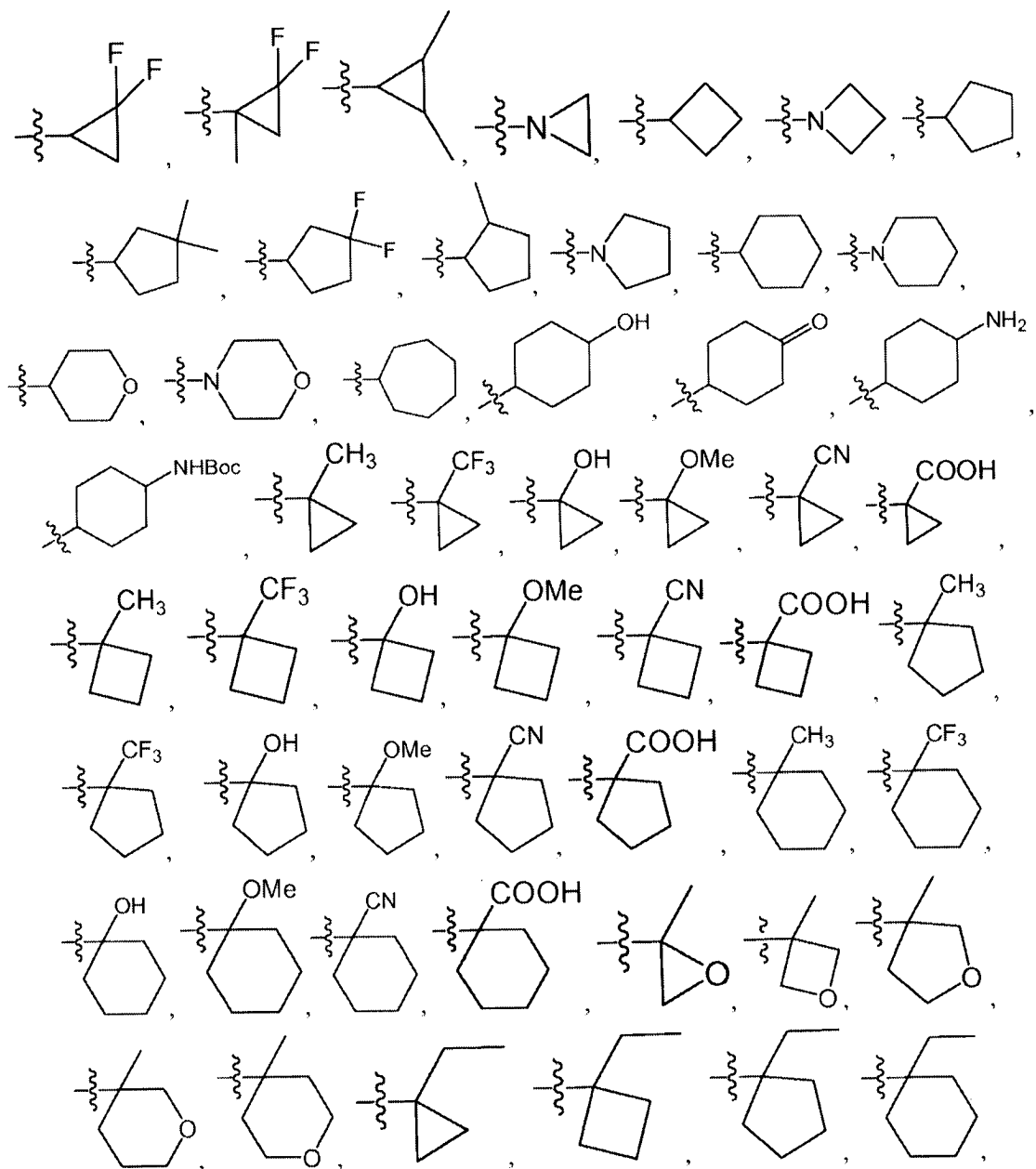
[0077] As used herein, “cycloalkyl,” whether used alone or as part of another group, refers to a non-aromatic carbon-containing ring including cyclized alkyl, alkenyl, and alkynyl groups, e.g., having from 3 to 14 ring carbon atoms, preferably from 3 to 7 or 3 to 6 ring carbon atoms, or even 3 to 4 ring carbon atoms, and optionally containing one or more (e.g., 1, 2, or 3) double or triple bond. Cycloalkyl groups can be monocyclic (e.g., cyclohexyl) or polycyclic (e.g., containing fused, bridged, and/or spiro ring systems), wherein the carbon atoms are located inside or outside of the ring system. Any suitable ring position of the cycloalkyl group can be covalently linked to the defined chemical structure. Cycloalkyl rings can be optionally substituted. Non-limiting examples of cycloalkyl groups include: cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, 2,3-dihydroxycyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctanyl, decalanyl, 2,5-dimethylcyclopentyl, 3,5-dichlorocyclohexyl, 4-hydroxycyclohexyl, 3,3,5-trimethylcyclohex-1-yl, octahydropentalenyl, octahydro-1*H*-indenyl, 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl, decahydroazulenyl; bicyclo[6.2.0]decanyl, decahydronaphthalenyl, and dodecahydro-1*H*-fluorenyl. The term “cycloalkyl” also includes carbocyclic rings which are bicyclic hydrocarbon rings, non-limiting examples of which include, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl.

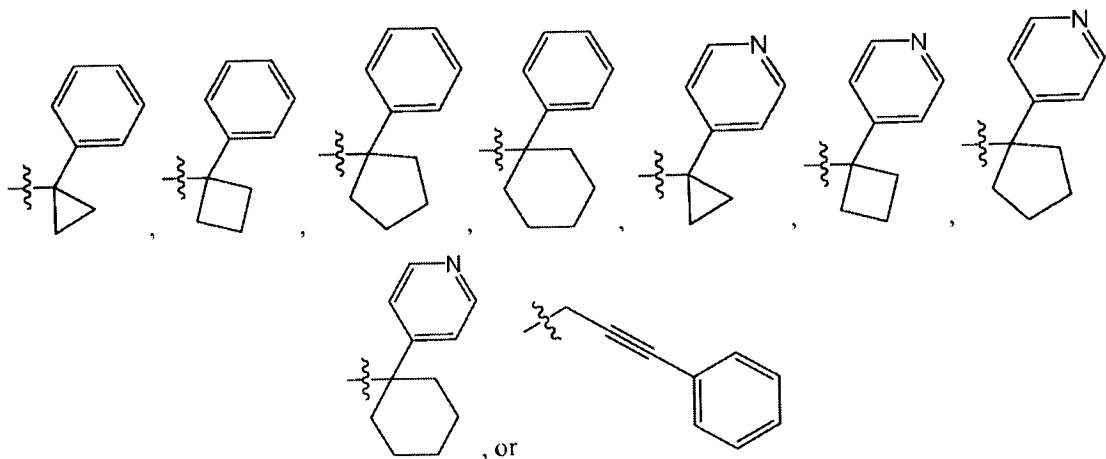
[0078] “Haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Haloalkyl groups include perhaloalkyl groups, wherein all hydrogens of an alkyl group have been replaced with halogens (e.g., -CF₃, -CF₂CF₃). Haloalkyl groups can optionally be substituted with one or more substituents in addition to halogen. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, dichloroethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

[0079] Non-limiting examples of alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl include at least the following: methyl, methyl amine (or protected analog thereof), methoxy, ethyl, ethyl amine (or protected analog thereof), ethoxy, n-propyl, propyl amine (or protected analog thereof), n-propoxy, isopropyl, isopropyl amine (or protected analog thereof), isopropoxy, n-butyl, n-butyl amine (or protected analog thereof), n-butoxy, sec-butyl, sec-butyl amine (or protected analog thereof),

thereof), *sec*-butoxy, *tert*-butyl, *tert*-butyl amine (or protected analog thereof), *tert*-butoxy, vinyl,







[0080] The term “alkoxy” refers to the group –O-alkyl, wherein the alkyl group is as defined above. Alkoxy groups optionally may be substituted. The term C₃-C₆ cyclic alkoxy refers to a ring containing 3 to 6 carbon atoms and at least one oxygen atom (e.g., tetrahydrofuran, tetrahydro-2H-pyran). C₃-C₆ cyclic alkoxy groups optionally may be substituted.

[0081] The term “amidine” refers to a structure of formula $-C(NR^{15})(R^{15})_2$, where R^{15} is defined below. Preferred amidine moieties of the present invention include those where R^{15} is, independently at each occurrence, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl (e.g., C_{3-6} cycloalkyl), aryl, heterocyclyl, or heteroaryl.

[0082] The term “aryl,” wherein used alone or as part of another group, is defined herein as an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 14 carbon members. Aryl rings can be, for example, phenyl or naphthyl ring each optionally substituted with one or more moieties capable of replacing one or more hydrogen atoms. Non-limiting examples of aryl groups include: phenyl, naphthylen-1-yl, naphthylen-2-yl, 4-fluorophenyl, 2-hydroxyphenyl, 3-methylphenyl, 2-amino-4-fluorophenyl, 2-(*N,N*-diethylamino)phenyl, 2-cyanophenyl, 2,6-di-*tert*-butylphenyl, 3-methoxyphenyl, 8-hydroxynaphthylen-2-yl, 4,5-dimethoxynaphthylen-1-yl, and 6-cyano-naphthylen-1-yl. Aryl groups also include, for example, phenyl or naphthyl rings fused with one or more saturated or partially saturated carbon rings (e.g., bicyclo[4.2.0]octa-1,3,5-trienyl, benzo[1,3]dioxolyl, indanyl), which can be substituted at one or more carbon atoms of the aromatic and/or saturated or partially saturated rings.

[0083] The term “arylalkyl” or “aralkyl” refers to the group –alkyl-aryl, where the alkyl and aryl groups are as defined herein. Aralkyl groups of the present invention are optionally substituted. Examples of arylalkyl groups include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl and the like.

[0084] The terms “heterocyclic” and/or “heterocycle” and/or “heterocylyl,” whether used alone or as part of another group, are defined herein as one or more ring having from 3 to 20 atoms wherein at least one atom in at least one ring is a heteroatom selected from nitrogen (N), oxygen (O), or sulfur (S), and wherein further the ring that includes the heteroatom is non-aromatic. In heterocycle groups that include 2 or more fused rings, the non-heteroatom bearing ring may be aryl (e.g., indoliny, tetrahydroquinoliny, chromanyl). Exemplary heterocycle groups have from 3 to 14 ring atoms of which from 1 to 5 are heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heterocycle group can be oxidized. Heterocycle groups can be optionally substituted.

[0085] Non-limiting examples of heterocyclic units having a single ring include: diaziriny, aziridiny, urazoly, azetidiny, thiazolidiny, oxathiazolidinonyl, oxazolidinonyl, hydantoinyl, tetrahydrofuranyl, pyrrolidiny, morpholiny, piperaziny, piperidiny, dihydropyranyl, tetrahydropyranyl, piperidin-2-onyl (valerolactam), 2,3,4,5-tetrahydro-1*H*-azepiny, 2,3-dihydro-1*H*-indole, and 1,2,3,4-tetrahydro-quinoline. Non-limiting examples of heterocyclic units having 2 or more rings include: hexahydro-1*H*-pyrroliziny, 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl, 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl, 1,2,3,4-tetrahydroquinoliny, chromanyl, isochromanyl, indoliny, isoindoliny, and decahydro-1*H*-cycloocta[b]pyrrolyl.

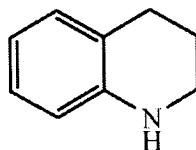
[0086] The term “heteroaryl,” whether used alone or as part of another group, is defined herein as one or more rings having from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), and wherein further at least one of the rings that includes a heteroatom is aromatic. In heteroaryl groups that include 2 or more fused rings, the non-heteroatom bearing ring may be a carbocycle (e.g., 6,7-Dihydro-5*H*-cyclopentapyrimidine) or aryl (e.g., benzofuranyl, benzothiophenyl, indolyl). Exemplary heteroaryl groups have from 5 to 14 ring atoms and contain from 1 to 5 ring heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heteroaryl group can be oxidized. Heteroaryl groups can be substituted. Non-limiting examples of heteroaryl rings containing a single ring include: 1,2,3,4-tetrazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, triazinyl,

thiazolyl, 1*H*-imidazolyl, oxazolyl, furanyl, thiophenyl, pyrimidinyl, 2-phenylpyrimidinyl, pyridinyl, 3-methylpyridinyl, and 4-dimethylaminopyridinyl. Non-limiting examples of heteroaryl rings containing 2 or more fused rings include: benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, cinnolyl, naphthyridinyl, phenanthridinyl, 7*H*-purinyl, 9*H*-purinyl, 6-amino-9*H*-purinyl, 5*H*-pyrrolo[3,2-*d*]pyrimidinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, 2-phenylbenzo[*d*]thiazolyl, 1*H*-indolyl, 4,5,6,7-tetrahydro-1-*H*-indolyl, quinoxalinyl, 5-methylquinoxalinyl, quinazolyl, quinolyl, 8-hydroxy-quinolyl, and isoquinolyl.

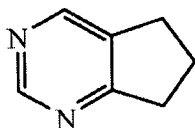
[0087] One non-limiting example of a heteroaryl group as described above is C₁-C₅ heteroaryl, which has 1 to 5 carbon ring atoms and at least one additional ring atom that is a heteroatom (preferably 1 to 4 additional ring atoms that are heteroatoms) independently selected from nitrogen (N), oxygen (O), or sulfur (S). Examples of C₁-C₅ heteroaryl include, but are not limited to, triazinyl, thiazol-2-yl, thiazol-4-yl, imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, isoxazolin-5-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

[0088] Unless otherwise noted, when two substituents are taken together to form a carbocyclic or heterocyclic ring having a specified number of ring atoms (e.g., R² and R³ taken together with the nitrogen (N) to which they are attached to form a ring having from 3 to 7 ring members), the ring can have carbon atoms and optionally one or more (e.g., 1 to 3) additional heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). The carbocyclic or heterocyclic ring can be saturated or partially saturated and can be optionally substituted.

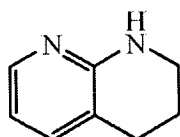
[0089] For the purposes of the present invention fused ring units, as well as spirocyclic rings, bicyclic rings and the like, which comprise a single heteroatom will be considered to belong to the cyclic family corresponding to the heteroatom containing ring. For example, 1,2,3,4-tetrahydroquinoline having the formula:



is, for the purposes of the present invention, considered a heterocyclic unit. 6,7-Dihydro-5*H*-cyclopentapyrimidine having the formula:

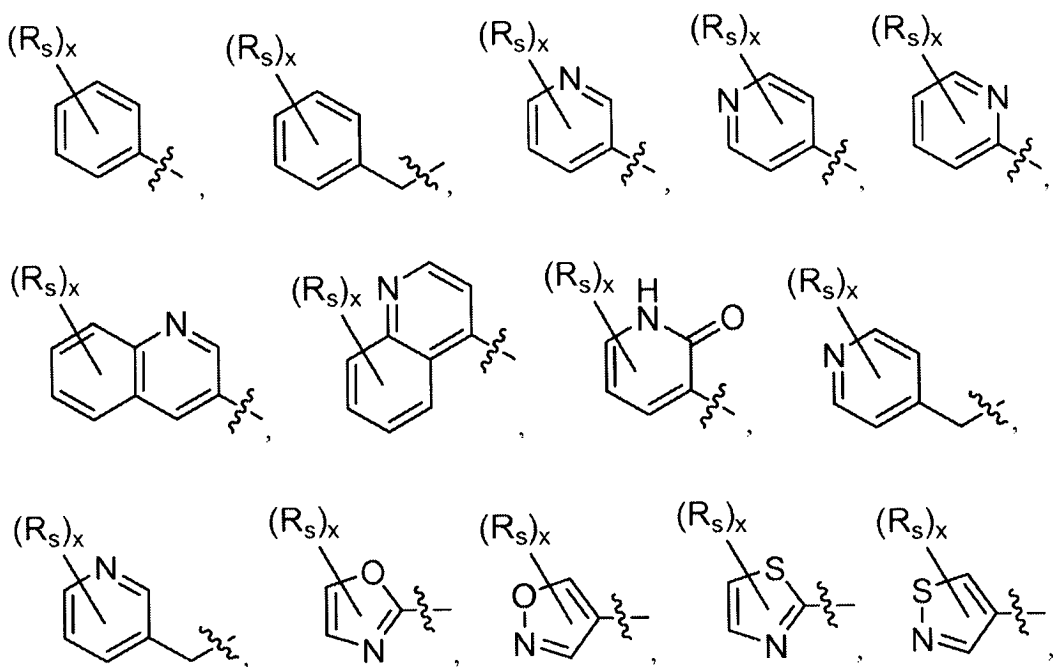


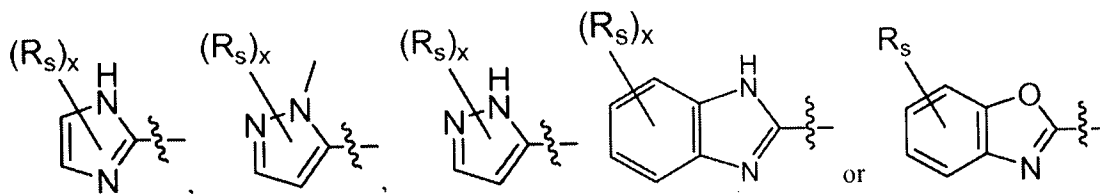
is, for the purposes of the present invention, considered a heteroaryl unit. When a fused ring unit contains heteroatoms in both a saturated and an aryl ring, the aryl ring will predominate and determine the type of category to which the ring is assigned. For example, 1,2,3,4-tetrahydro-[1,8]naphthyridine having the formula:



is, for the purposes of the present invention, considered a heteroaryl unit.

[0090] Non-limiting examples of aryls, heteraryls, alkaryls, and alkylheteroaryls (or heteroalkaryls) include at least the following structures:





wherein

R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl (e.g., $-CH_3$, $-CH_2F$, $-CF_2H$, $-CF_3$), $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and

x is 0, 1, 2, or 3.

[0091] It is appreciated that, where used, the designator $(R_S)_x$ indicates that the substituent(s) may be present on any available ring member, as valence allows (including alkyl substitution on nitrogen). For fused bicyclic systems, the same designator connote that the substituent(s) may be present on a ring member of either ring, as valence allows. Similarly, while the points of attachments shown above are to specific carbon atoms, it should be appreciated that the aryl or heteroaryl rings may be attached to any carbon or heteroatom that valence allows.

[0092] Whenever a term or either of their prefix roots appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, whenever the term “alkyl” or “aryl” or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl, alkylamino) the name is to be interpreted as including those limitations given above for “alkyl” and “aryl.”

[0093] The term “substituted” is used throughout the specification. The term “substituted” is defined herein as a moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several (e.g., 1 to 10) substituents as defined herein below. The substituents are capable of replacing one or two hydrogen atoms of a single moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety or unit. For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms

includes epoxy, and the like. The term “substituted” is used throughout the present specification to indicate that a moiety can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as “substituted” any number of the hydrogen atoms may be replaced. For example, difluoromethyl is a substituted C₁ alkyl; trifluoromethyl is a substituted C₁ alkyl; 4-hydroxyphenyl is a substituted aromatic ring; (N,N-dimethyl-5-amino)octanyl is a substituted C₈ alkyl; 3-guanidinopropyl is a substituted C₃ alkyl; and 2-carboxypyridinyl is a substituted heteroaryl.

[0094] The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted. Optionally substituted groups will be so indicated. The terms “optional” and “optionally,” in the context of substituents connotes that the indicated substituent may or may not be present and each of these conditions represents a separate embodiment of the invention.

[0095] The following are non-limiting examples of substituents which can substitute for hydrogen atoms on a moiety: halogen (chlorine (Cl), bromine (Br), fluorine (F) and iodine(I)), -CN, -NO₂, oxo (=O), -OR¹⁴, -SR¹⁴, -N(R¹⁴)₂, -NR¹⁴C(O)R¹⁴, -SO₂R¹⁴, -SO₂OR¹⁴, -SO₂N(R¹⁴)₂, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N(R¹⁴)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₁₄ cycloalkyl, aryl, heterocycle, or heteroaryl, wherein each of the alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heterocycle, and heteroaryl groups is optionally substituted with 1-10 (*e.g.*, 1-6 or 1-4) groups selected independently from halogen, -CN, -NO₂, oxo, and R¹⁴; wherein R¹⁴, at each occurrence, independently is hydrogen, -OR¹⁵, -SR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)N(R¹⁵)₂, -SO₂R¹⁵, -S(O)₂OR¹⁵, -N(R¹⁵)₂, -NR¹⁵C(O)R¹⁵, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, cycloalkyl (*e.g.*, C₃₋₆ cycloalkyl), aryl, heterocycle, or heteroaryl, or two R¹⁴ units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle has 3 to 7 ring atoms; wherein R¹⁵, at each occurrence, independently is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, cycloalkyl (*e.g.*, C₃₋₆ cycloalkyl), aryl, heterocycle, or heteroaryl, or two R¹⁵ units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle preferably has 3 to 7 ring atoms. Depending on the number of substitutable hydrogen atoms, there may be 0, 1, 2, 3, 4, 5, or 6 substituents independently substituted for hydrogen atoms on the moiety.

[0096] In some embodiments, the substituents are selected from

- i) $-OR^{16}$; for example, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$;
- ii) $-C(O)R^{16}$; for example, $-COCH_3$, $-COCH_2CH_3$, $-COCH_2CH_2CH_3$;
- iii) $-C(O)OR^{16}$; for example, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$;
- iv) $-C(O)N(R^{16})_2$; for example, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$;
- v) $-N(R^{16})_2$; for example, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$;
- vi) halogen: $-F$, $-Cl$, $-Br$, and $-I$;
- vii) $-CH_eX_g$; wherein X is halogen, m is from 0 to 2, e+g=3; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$;
- viii) $-SO_2R^{16}$; for example, $-SO_2H$; $-SO_2CH_3$; $-SO_2C_6H_5$;
- ix) C_1 - C_6 linear, branched, or cyclic alkyl;
- x) Cyano
- xi) Nitro;
- xii) $N(R^{16})C(O)R^{16}$;
- xiii) Oxo ($=O$);
- xiv) Heterocycle; and
- xv) Heteroaryl.

wherein each R^{16} is independently hydrogen, optionally substituted C_1 - C_6 linear or branched alkyl (e.g., optionally substituted C_1 - C_4 linear or branched alkyl), or optionally substituted C_3 - C_6 cycloalkyl (e.g. optionally substituted C_3 - C_4 cycloalkyl); or two R^{16} units can be taken together to form a ring comprising 3-7 ring atoms. In certain aspects, each R^{16} is independently hydrogen, C_1 - C_6 linear or branched alkyl optionally substituted with halogen or C_3 - C_6 cycloalkyl or C_{0-6} -[C_3 - C_6 cycloalkyl].

[0097] At various places in the present specification, substituents of compounds are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, the term " C_{1-6} alkyl" is specifically intended to individually disclose C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_1 - C_6 , C_1 - C_5 , C_1 - C_4 , C_1 - C_3 , C_1 - C_2 , C_2 - C_6 , C_2 - C_5 , C_2 - C_4 , C_2 - C_3 , C_3 - C_6 , C_3 - C_5 , C_3 - C_4 , C_4 - C_6 , C_4 - C_5 , and C_5 - C_6 , alkyl.

[0098] For the purposes of the present invention the terms "compound," "analog," and "composition of matter" stand equally well for nucleocapsid assembly inhibitors, especially but not exclusively, including the pregenomic RNA encapsidation inhibitors described herein, including all enantiomeric forms, diastereomeric forms, salts, and the like, and the terms

“compound,” “analog,” and “composition of matter” are used interchangeably throughout the present specification.

[0099] Compounds described herein can contain an asymmetric atom (also referred to as a chiral center), and some of the compounds can contain one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers. The present teachings and compounds disclosed herein include such enantiomers and diastereomers, as well as the racemic and resolved, enantiomerically pure R and S stereoisomers, as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, which include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. The present teachings also encompass cis and trans isomers of compounds containing alkenyl moieties (e.g., alkenes and imines). It is also understood that the present teachings encompass all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography. For those compounds that are described as, or may comprise, optical isomers, various embodiments embrace at least the individual isomer or an enriched or racemic mixture thereof.

[0100] Pharmaceutically acceptable salts of compounds of the present teachings, which can have an acidic moiety, can be formed using organic and inorganic bases. Both mono and polyanionic salts are contemplated, depending on the number of acidic hydrogens available for deprotonation. Suitable salts formed with bases include metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, or magnesium salts; ammonia salts and organic amine salts, such as those formed with morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine (e.g., ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine), or a mono-, di-, or trihydroxy lower alkylamine (e.g., mono-, di- or triethanolamine). Specific non-limiting examples of inorganic bases include NaHCO_3 , Na_2CO_3 , KHCO_3 , K_2CO_3 , Cs_2CO_3 , LiOH , NaOH , KOH , NaH_2PO_4 , Na_2HPO_4 , and Na_3PO_4 . Internal salts also can be formed. Similarly, when a compound disclosed herein contains a basic moiety, salts can be formed using organic and inorganic acids. For example, salts can be formed from the following acids: acetic, propionic, lactic, benzenesulfonic, benzoic, camphorsulfonic, citric, tartaric, succinic, dichloroacetic, ethenesulfonic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic,

malic, malonic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nitric, oxalic, pamoic, pantothenic, phosphoric, phthalic, propionic, succinic, sulfuric, tartaric, toluenesulfonic, and camphorsulfonic as well as other known pharmaceutically acceptable acids.

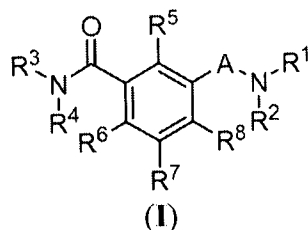
[0101] The terms “treat” and “treating” and “treatment” as used herein, refer to partially or completely alleviating, inhibiting, ameliorating and/or relieving a condition from which a patient is suspected to suffer.

[0102] As used herein, “therapeutically effective” and “effective dose” refer to a substance or an amount that elicits a desirable biological activity or effect. “Therapeutically effective amount” refers to the amount of a compound that, when administered to a subject for treating a disease or a condition, is sufficient to effect such treatment for the disease or condition. The “therapeutically effective amount” can vary depending on the compound, the disease or condition and its severity, and the age, weight, etc., of the subject to be treated.

[0103] Except when noted, the terms “subject” or “patient” are used interchangeably and refer to mammals such as human patients and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals. Accordingly, the term “subject” or “patient” as used herein means any mammalian patient or subject to which the compounds of the invention can be administered. In an exemplary embodiment of the present invention, to identify subject patients for treatment according to the methods of the invention, accepted screening methods are employed to determine risk factors associated with a targeted or suspected disease or condition or to determine the status of an existing disease or condition in a subject. These screening methods include, for example, conventional work-ups to determine risk factors that may be associated with the targeted or suspected disease or condition. These and other routine methods allow the clinician to select patients in need of therapy using the methods and compounds of the present invention.

Compounds and Compositions

[0104] The compounds and compositions of the present invention useful for the treatment of viruses including Hepatitis B virus (HBV) infection and related conditions include all enantiomeric and diastereomeric forms and pharmaceutically accepted salts thereof having the formula (I):



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R¹ may also alternatively or additionally optionally include optionally substituted C₁₋₆ haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R² is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl; R² may also alternatively or additionally optionally include optionally substituted C₃₋₇ cycloalkyl or optionally substituted heterocyclic; or

R¹ and R² are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms; and

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl; R³ may also optionally comprise an optionally substituted C₁₋₆ linear alkyl;

R⁴ is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; in

some embodiments, R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

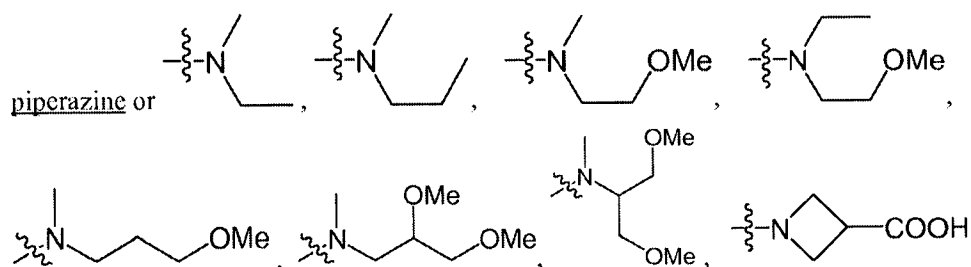
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms; and

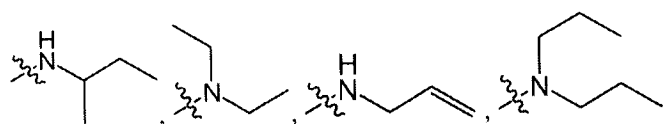
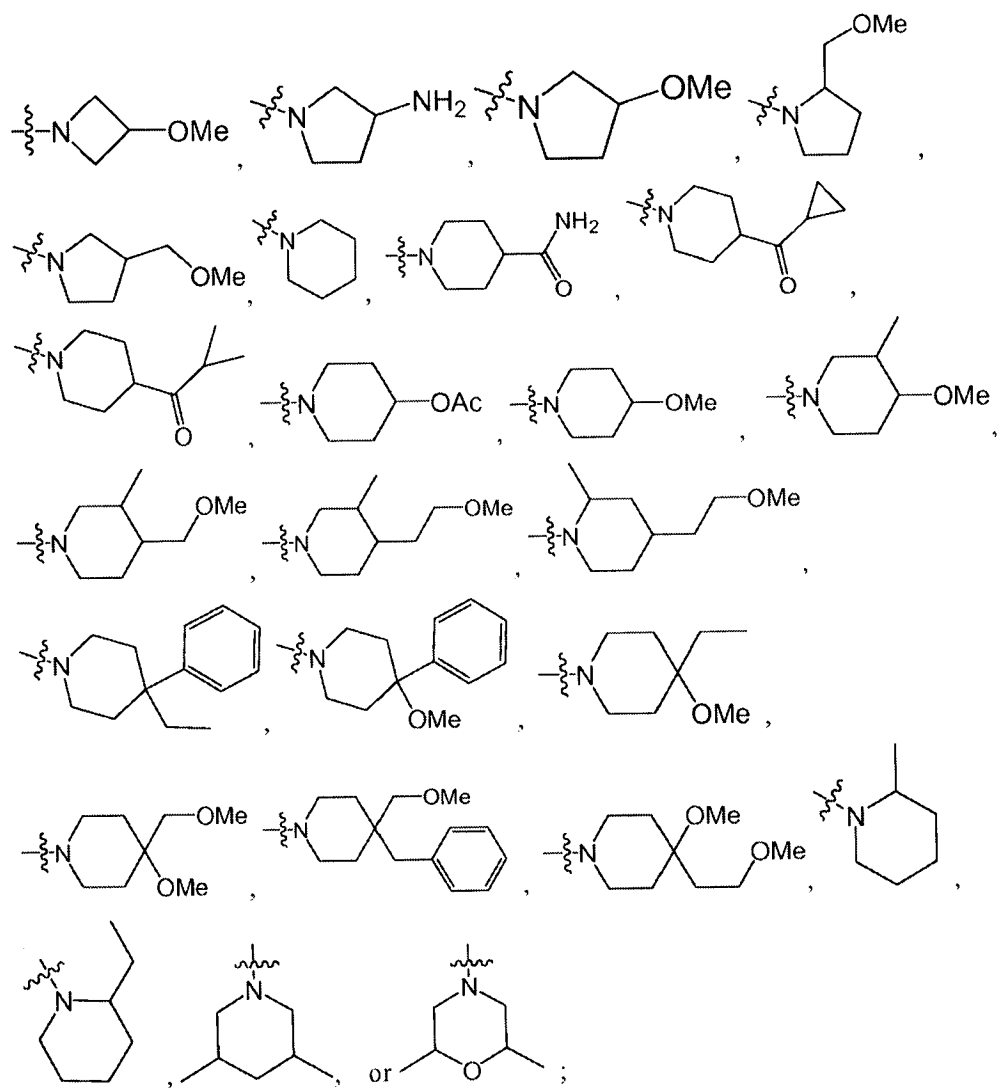
R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; R^9 may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

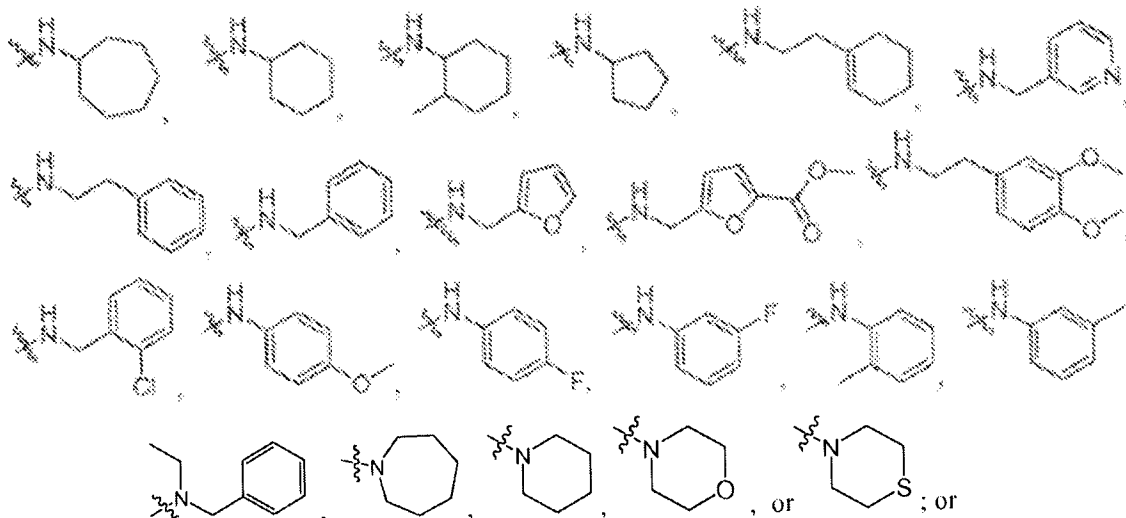
[0105] provided that when A is SO_2 ; R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring, then none of the following (a) through (d) apply:

(a) R^3 is an optionally substituted phenyl and R^1 or R^2 , either individually or when taken together, contain a hydroxyl group, or

(b) R^3 is an optionally substituted alkyl or phenyl, and $N(R^1)(R^2)$ is an optionally substituted

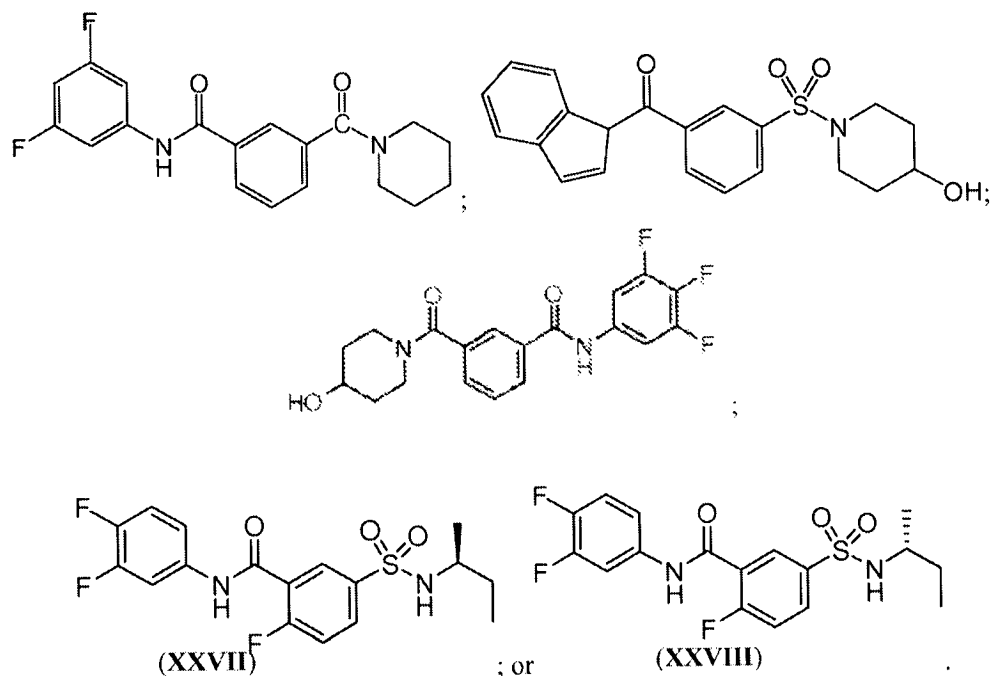






- (d) either R^3 or R^4 is an unsubstituted or monosubstituted aryl, or an unsubstituted or monosubstituted aralkyl, or unsubstituted or monosubstituted heteroaryl and R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocyclic ring structure with 6 to 12 atoms; or

[0106] provided that the compound is not 3-(((dicyclopropylmethyl)amino)sulfonyl)-N-(4-isopropoxyphenyl)benzamide; or 3-([2-(1H-benzimidazol-2-yl)propyl]amino)sulfonyl)-N-(4-isopropoxyphenyl)benzamide; or 3-[(cyclohexylamino)sulfonyl]-N-(4-isopropylphenyl)benzamide; or 3-(anilinosulfonyl)-N-(4-isopropylphenyl)benzamide; or 5-[(3-[(4-methoxyphenyl)amino]carbonyl)phenyl)sulfonyl]amino]pentanoic acid; or 3-[(*tert*-butylamino)sulfonyl]-N-(4-methoxyphenyl)benzamide; or (3S)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl)phenyl)sulfonyl]piperidine-3-carboxamide; or (3R)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl)phenyl)sulfonyl]piperidine-3-carboxamide; or 3-(piperidin-1-ylsulfonyl)-N-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide; or N-(5-bromo-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenylpyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenoxy-pyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-[3-methoxy-5-(phenylthio)pyridin-2-yl]-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(5-ethyl-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-vinylpyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or



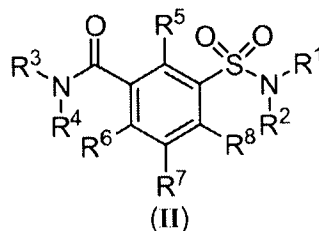
[0107] Some embodiments of the compounds of formula (I) also exclude those compounds when A is SO₂; R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R² and R⁸ taken together with the atoms to which they are bound do not to form an optionally substituted ring, R³ is optionally substituted alkyl, aryl, or alkaryl and N(R¹)(R²) is an optionally substituted piperidine.

[0108] The embodiments of the present invention include compounds of formula (I) where A is SO₂;

R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring; and

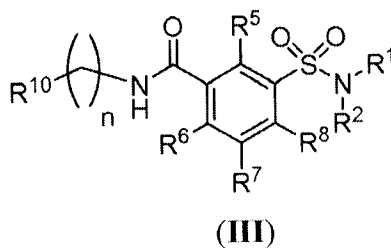
R² and R⁸ taken together with the atoms to which they are bound do not to form an optionally substituted carbocyclic or heterocyclic ring;

thereby providing compounds having formula (II),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof and considering the exclusions described above. In some embodiments, R^1 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^8 are as defined below.

[0109] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , thereby providing compounds having formula (III),



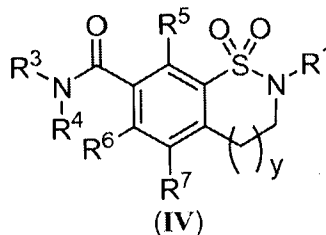
including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and

n is 0 or 1.

[0110] In some embodiments, R^1 , R^2 , and R^5 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 , R^2 , and R^5 through R^8 are as defined below.

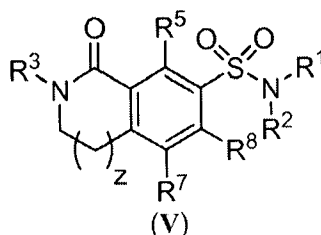
[0111] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , thereby providing compounds having formula (IV),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: y is 0 or 1. In some embodiments, y is 2.

[0112] In some embodiments, R^1 and R^3 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 and R^3 through R^8 are as defined below.

[0113] The embodiments of the present invention include compounds of formula (I) where A is SO_2 , thereby providing compounds having formula (V),

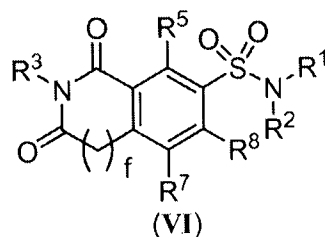


including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

z is 0 or 1.

[0114] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below.

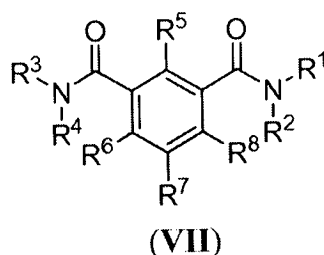
[0115] The embodiments of the present invention include compounds having formula (VI),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: f is 0 or 1.

[0116] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below.

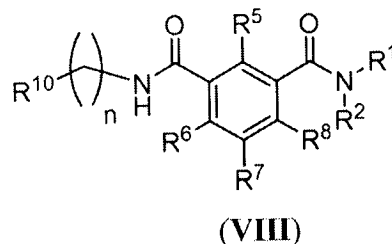
[0117] The embodiments of the present invention include compounds of formula (I) where A is CO, thereby providing compounds having formula (VII),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0118] In some embodiments, R^1 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^8 are as defined below.

[0119] The embodiments of the present invention include compounds of formula (I) where A is CO, thereby providing compounds having formula (VIII),

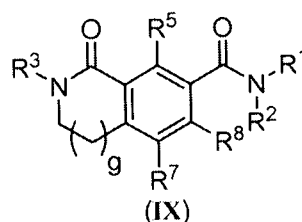


including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and n is 0 or 1.

[0120] In some embodiments, R^1 through R^2 and R^5 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^2 and R^5 through R^8 are as defined below.

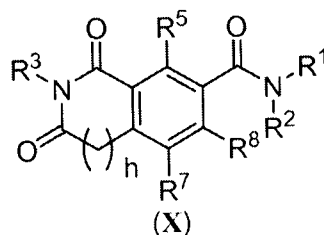
[0121] The embodiments of the present invention include compounds having formula (IX),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: *g* is 0 or 1.

[0122] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below.

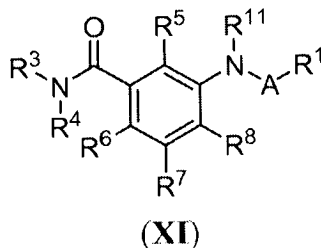
[0123] The embodiments of the present invention include compounds of formula (I) where *A* is CO, thereby providing compounds having formula (X),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein: *h* is 0 or 1.

[0124] In some embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined for the compound of formula (I). In other independent embodiments, R^1 through R^3 , R^5 , and R^7 through R^8 are as defined below.

[0125] The embodiments of the present invention include compounds having formula (XI), useful as nucleocapsid assembly inhibitors, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



including all enantiomeric forms, diastereomeric forms, hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof,

wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl; in some embodiments, R³ may also comprise an optionally substituted C₁₋₆ linear alkyl;

R⁴ is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁶ may also alternatively or additionally optionally include cyano or N(R⁹)₂; or

R⁴ and R⁶ are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

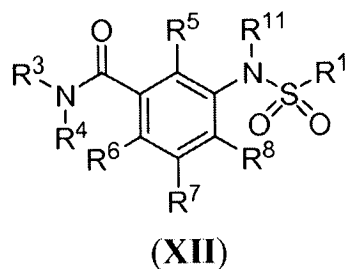
R⁷ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁷ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{1-6} haloalkyl; R^9 may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

R^{11} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl.

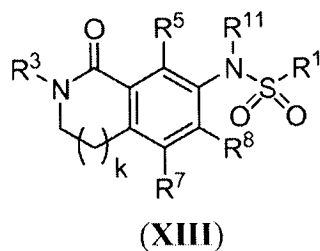
[0126] The embodiments of the present invention include compounds having formula (XII),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0127] In some embodiments, R^1 , R^3 through R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 through R^8 and R^{11} are as defined below.

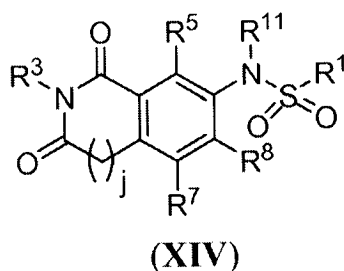
[0128] The embodiments of the present invention include compounds having formula (XIII),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: k is 0 or 1.

[0129] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other independent embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

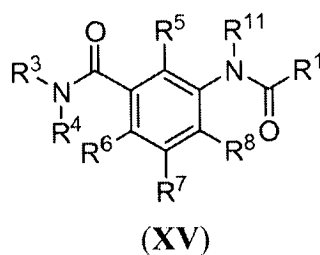
[0130] The embodiments of the present invention include compounds having formula (XIV),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: j is 0 or 1.

[0131] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

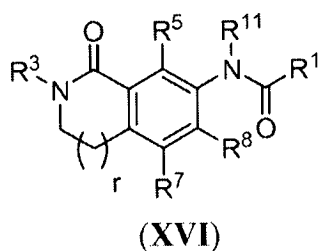
[0132] The embodiments of the present invention include compounds having formula (XV),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0133] In some embodiments, R^1 , R^3 through R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 through R^8 and R^{11} are as defined below.

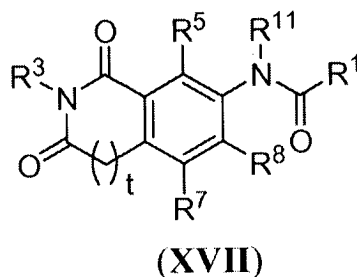
[0134] The embodiments of the present invention include compounds having formula (XVI),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: r is 0 or 1.

[0135] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

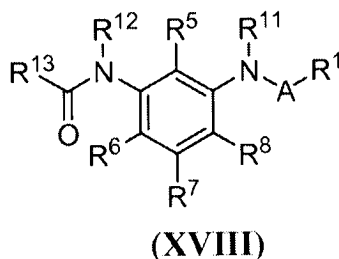
[0136] The embodiments of the present invention include compounds having formula (XVII),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein: t is 0 or 1.

[0137] In some embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined for the compound of formula (XI). In other embodiments, R^1 , R^3 , R^5 , R^7 , R^8 and R^{11} are as defined below.

[0138] The embodiments of the present invention include compounds having formula (XVIII), useful as nucleocapsid assembly inhibitors, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



including all enantiomeric forms, diastereomeric forms, hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof wherein:

A is selected from a group consisting of SO_2 and CO ;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁶ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁷ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁷ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁸ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁸ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

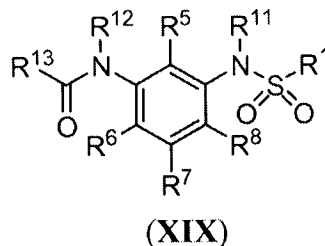
R⁹ is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl; R⁹ may also alternatively or additionally optionally include independently at each occurrence optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R¹¹ is selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl;

R¹² is selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl; and

R¹³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

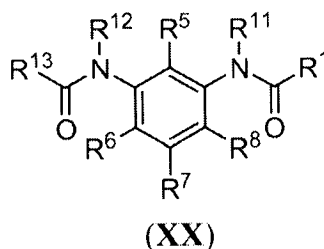
[0139] The embodiments of the present invention include compounds having formula (XIX),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0140] In some embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined for the compound of formula (XVIII). In other embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined below.

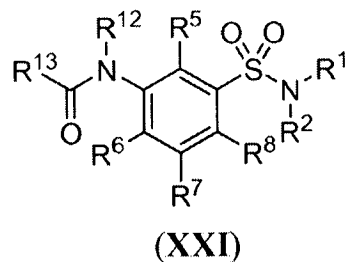
[0141] The embodiments of the present invention include compounds having formula (XX),



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof.

[0142] In some embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined for the compound of formula (XVIII). In other embodiments, R^1 , R^5 through R^8 and R^{11} through R^{13} are as defined below.

[0143] The embodiments of the present invention include compounds having formula (XXI), useful as nucleocapsid assembly inhibitors, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions



including all enantiomeric forms, diastereomeric forms, hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted C_{1-6} haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy- C_{1-6} -alkoxide, $-SO_2$ - C_{1-6} alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R^2 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl; R^2 may also alternatively or additionally optionally include optionally substituted C_{3-7} cycloalkyl or optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including cyclic and heterocyclic structures) with 3 to 10 atoms;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

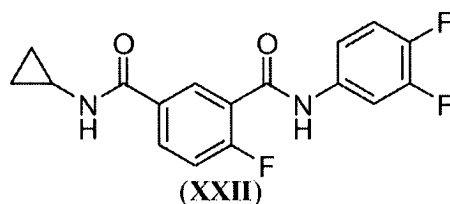
R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{1-6} haloalkyl; R^9 may also alternatively or

additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

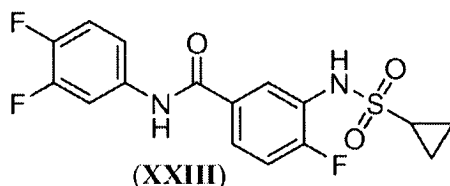
R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

[0144] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula (XXII):



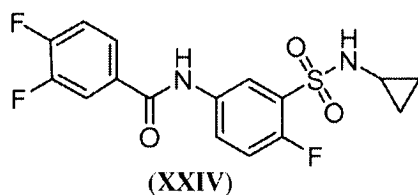
has the chemical name N¹-cyclopropyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide.

[0145] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula (XXIII):



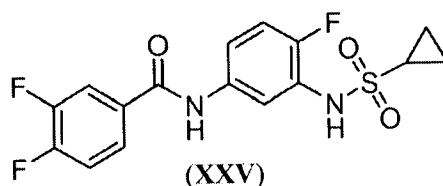
has the chemical name 3-(cyclopropanesulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide.

[0146] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula (XXIV):



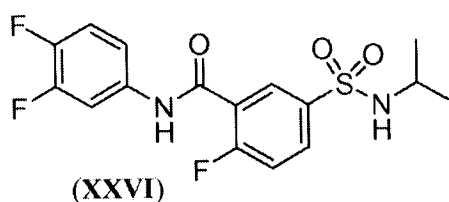
has the chemical name N-(3-(N-cyclopropylsulfamoyl)-4-fluorophenyl)-3,4-difluorobenzamide.

[0147] For the purposes of demonstrating the manner in which the compounds of the present invention are named and referred to herein, the compound having the formula (XXV):

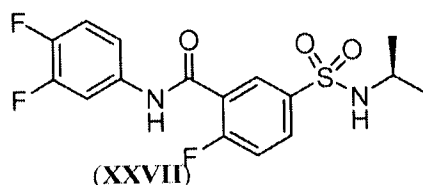


has the chemical name N-(3-(cyclopropanesulfonamido)-4-fluorophenyl)-3,4-difluorobenzamide.

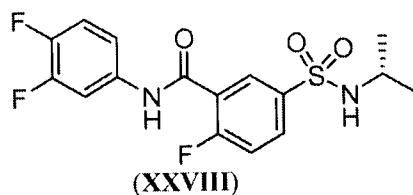
[0148] For the purposes of the present invention, a compound depicted by the racemic formula (XXVI), for example:



will stand equally well for either of the two enantiomers having the formula (XXVII):



or the formula (XXVIII):



or mixtures thereof, or in the case where a second chiral center is present, all diastereomers.

[0149] In some embodiments of the preceding compounds, A is SO₂.

[0150] In some embodiments of the preceding compounds, A is CO.

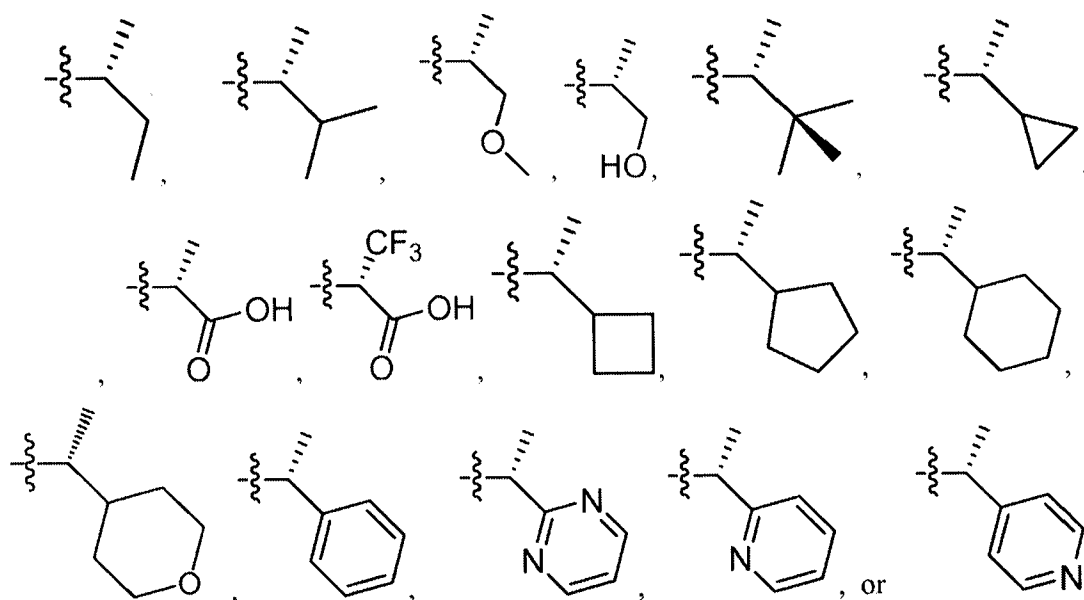
[0151] In some embodiments of the preceding compounds, R¹ is optionally substituted C₁₋₆ linear alkyl.

[0152] In some embodiments of the preceding compounds, R¹ is optionally substituted C₁₋₆ branched alkyl.

[0153] In some embodiments of the preceding compounds, R¹ is optionally substituted C₃₋₇ cycloalkyl.

[0154] In some embodiments of the preceding compounds, R¹ is optionally substituted aryl.

[0155] In some embodiments of the preceding compounds, R¹ is optionally substituted benzyl. The alkyl or benzyl substituents may be chiral or achiral, and if chiral may be S- or R-configured. Particularly attractive embodiments appear to comprise those where R¹ has predominantly an R-configured branched alkyl group, such as



As used herein, the term “predominantly R-configured” includes those compounds where the carbon is pure or enriched in R-isomer at the respective position. In other embodiments, useful enbodiments include those where R¹ has predominantly an S-configured branched alkyl group.

[0156] In some embodiments of the preceding compounds, R² is hydrogen.

[0157] In some embodiments of the preceding compounds, R^2 is optionally substituted C_{1-6} linear alkyl.

[0158] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted ring with 3 atoms.

[0159] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted ring with 4 atoms.

[0160] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted ring with 5 atoms.

[0161] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted ring with 6 atoms.

[0162] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted ring with 7 atoms.

[0163] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 6 atoms.

[0164] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 7 atoms.

[0165] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 8 atoms.

[0166] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 9 atoms.

[0167] In some embodiments of the preceding compounds, R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 10 atoms.

[0168] In some embodiments of the preceding compounds, R^3 is optionally substituted aryl.

[0169] In some embodiments of the preceding compounds, R^3 is optionally substituted benzyl

[0170] In some embodiments of the preceding compounds, R^3 is optionally substituted alkylaryl

[0171] In some embodiments of the preceding compounds, R^3 is optionally substituted heteroaryl

[0172] In some embodiments of the preceding compounds, R^3 is optionally substituted alkylheteroaryl

[0173] In some embodiments of the preceding compounds, R^4 is hydrogen.

[0174] In some embodiments of the preceding compounds, R^4 is optionally substituted C_{1-6} linear alkyl.

[0175] In some embodiments of the preceding compounds, R^5 is hydrogen.

[0176] In some embodiments of the preceding compounds, R^5 is halogen.

[0177] In some embodiments of the preceding compounds, R^5 is optionally substituted C_{1-6} linear alkyl.

[0178] In some embodiments of the preceding compounds, R^5 is optionally substituted C_{1-6} branched alkyl.

[0179] In some embodiments of the preceding compounds, R^5 is optionally substituted C_{1-6} haloalkyl.

[0180] In some embodiments of the preceding compounds, R^5 is OR^9 .

[0181] In some embodiments of the preceding compounds, R^6 is hydrogen.

[0182] In some embodiments of the preceding compounds, R^6 is halogen.

[0183] In some embodiments of the preceding compounds, R^6 is optionally substituted C_{1-6} linear alkyl.

[0184] In some embodiments of the preceding compounds, R^6 is optionally substituted C_{1-6} branched alkyl.

[0185] In some embodiments of the preceding compounds, R^6 is optionally substituted C_{1-6} haloalkyl.

[0186] In some embodiments of the preceding compounds, R^6 is OR^9 .

[0187] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 atoms.

[0188] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 6 atoms.

[0189] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 atoms containing a carbonyl.

[0190] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 6 atoms containing a carbonyl.

[0191] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 atoms containing two carbonyls.

[0192] In some embodiments of the preceding compounds, R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 6 atoms containing two carbonyls.

[0193] In some embodiments of the preceding compounds, R^7 is hydrogen.

[0194] In some embodiments of the preceding compounds, R^7 is halogen.

[0195] In some embodiments of the preceding compounds, R^7 is optionally substituted C_{1-6} linear alkyl.

[0196] In some embodiments of the preceding compounds, R^7 is optionally substituted C_{1-6} branched alkyl.

[0197] In some embodiments of the preceding compounds, R^7 is optionally substituted C_{1-6} haloalkyl.

[0198] In some embodiments of the preceding compounds, R^7 is OR^9 .

[0199] In some embodiments of the preceding compounds, R^8 is hydrogen.

[0200] In some embodiments of the preceding compounds, R^8 is halogen.

[0201] In some embodiments of the preceding compounds, R^8 is optionally substituted C_{1-6} linear alkyl.

[0202] In some embodiments of the preceding compounds, R^8 is optionally substituted C_{1-6} branched alkyl.

[0203] In some embodiments of the preceding compounds, R^8 is optionally substituted C_{1-6} haloalkyl.

[0204] In some embodiments of the preceding compounds, R^8 is OR^9 .

[0205] In some embodiments of the preceding compounds, R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 atoms.

[0206] In some embodiments of the preceding compounds, R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 6 atoms.

[0207] In some embodiments of the preceding compounds, R^9 is hydrogen.

[0208] In some embodiments of the preceding compounds, R^9 is optionally substituted C_{1-6} linear alkyl.

[0209] In some embodiments of the preceding compounds, R^9 is optionally substituted C_{1-6} branched alkyl.

[0210] In some embodiments of the preceding compounds, R^9 is optionally substituted C_{3-7} cycloalkyl.

[0211] In some embodiments of the preceding compounds, R^9 is optionally substituted C_{1-6} haloalkyl.

[0212] In some embodiments of the preceding compounds, R^9 is optionally substituted aryl.

[0213] In some embodiments of the preceding compounds, R^9 is optionally substituted heteroaryl.

[0214] In some embodiments of the preceding compounds, R^9 is optionally substituted benzyl.

[0215] In some embodiments of the preceding compounds, R^9 is optionally substituted heterocyclyl.

[0216] In some embodiments of the preceding compounds, R^{10} is optionally substituted aryl.

[0217] In some embodiments of the preceding compounds, R^{10} is optionally substituted heteroaryl.

[0218] In some embodiments of the preceding compounds, n is 0.

[0219] In some embodiments of the preceding compounds, n is 1.

[0220] In some embodiments of the preceding compounds, y is 0.

[0221] In some embodiments of the preceding compounds, y is 1.

[0222] In some embodiments of the preceding compounds, y is 2.

[0223] In some embodiments of the preceding compounds, z is 0.

[0224] In some embodiments of the preceding compounds, z is 1.

[0225] In some embodiments of the preceding compounds, f is 0.

[0226] In some embodiments, f is 1.

[0227] In some embodiments of the preceding compounds, g is 0.

[0228] In some embodiments of the preceding compounds, g is 1.

[0229] In some embodiments of the preceding compounds, h is 0.

[0230] In some embodiments of the preceding compounds, h is 1.

[0231] In some embodiments of the preceding compounds, R¹¹ is hydrogen.

[0232] In some embodiments of the preceding compounds, R¹¹ is optionally substituted C₁₋₆ linear alkyl.

[0233] In some embodiments of the preceding compounds, R¹¹ is optionally substituted C₁₋₆ branched alkyl.

[0234] In some embodiments of the preceding compounds, R¹¹ is optionally substituted C₃₋₇ cycloalkyl.

[0235] In some embodiments of the preceding compounds, k is 0.

[0236] In some embodiments of the preceding compounds, k is 1.

[0237] In some embodiments of the preceding compounds, j is 0.

[0238] In some embodiments of the preceding compounds, j is 1.

[0239] In some embodiments of the preceding compounds, r is 0.

[0240] In some embodiments of the preceding compounds, r is 1.

[0241] In some embodiments of the preceding compounds, t is 0.

[0242] In some embodiments of the preceding compounds, t is 1.

[0243] In some embodiments, R¹² is hydrogen.

[0244] In some embodiments of the preceding compounds, R¹² is optionally substituted C₁₋₆ linear alkyl.

[0245] In some embodiments of the preceding compounds, R¹² is optionally substituted C₁₋₆ branched alkyl.

[0246] In some embodiments of the preceding compounds, R¹² is optionally substituted C₃₋₇ cycloalkyl.

[0247] In some embodiments of the preceding compounds, R¹³ is optionally substituted aryl.

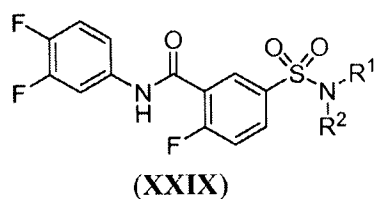
[0248] In some embodiments of the preceding compounds, R¹³ is optionally substituted benzyl.

[0249] In some embodiments of the preceding compounds, R¹³ is optionally substituted alkylaryl.

[0250] In some embodiments of the preceding compounds, R¹³ is optionally substituted heteroaryl.

[0251] In some embodiments of the preceding compounds, R¹³ is optionally substituted alkylheteroaryl.

[0252] Exemplary embodiments include compounds having the formula (XXIX) or a pharmaceutically acceptable salt form thereof:

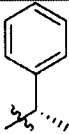


wherein non-limiting examples of R¹ and R² are defined herein below in **Table 1**.

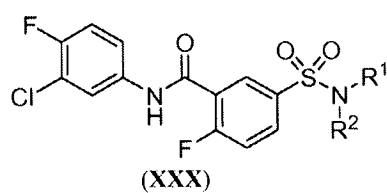
[0253] **Table 1:** Exemplary embodiments of compounds of the formula (XXIX):

R ¹	R ²		R ¹	R ²
	H			H
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₃ CH ₂ -	

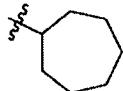
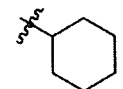
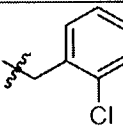
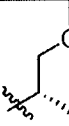
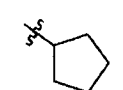
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

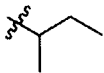
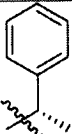
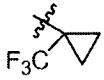
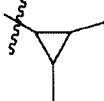
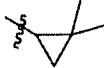
[0254] Exemplary embodiments include compounds having the formula (XXX) or a pharmaceutically acceptable salt form thereof:



wherein non-limiting examples of R^1 and R^2 are defined herein below in Table 2.

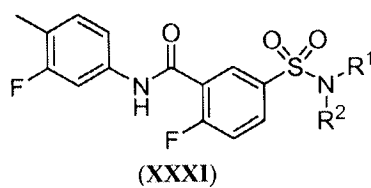
[0255] Table 2: Exemplary embodiments of compounds of the formula (XXX):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

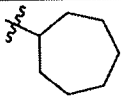
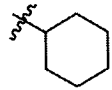
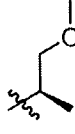
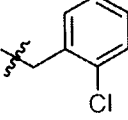
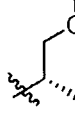
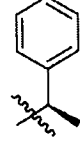
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

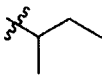
[0256] Exemplary embodiments include compounds having the formula (XXXI) or a pharmaceutically acceptable salt form thereof:

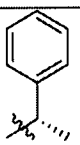
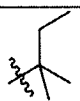


wherein non-limiting examples of R^1 and R^2 are defined herein below in Table 3.

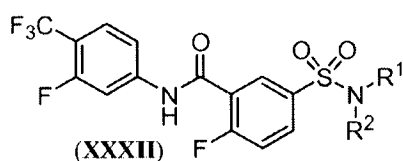
[0257] Table 3: Exemplary embodiments of compounds of the formula (XXXI):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

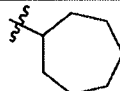
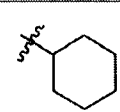
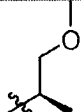
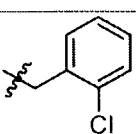
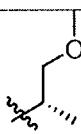
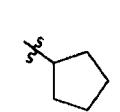
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

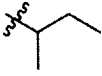
[0258] Exemplary embodiments include compounds having the formula (XXXII) or a pharmaceutically acceptable salt form thereof:

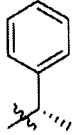


wherein non-limiting examples of R^1 and R^2 are defined herein below in **Table 4**.

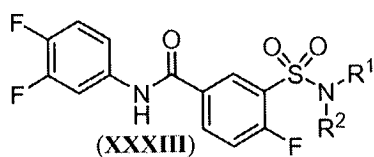
[0259] **Table 4:** Exemplary embodiments of compounds of the formula (XXXII):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

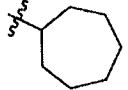
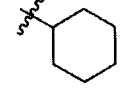
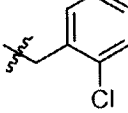
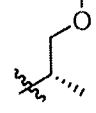
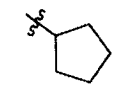
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

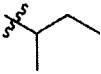
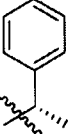
[0260] Exemplary embodiments include compounds having the formula (XXXIII) or a pharmaceutically acceptable salt form thereof:

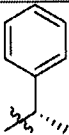


wherein non-limiting examples of R^1 and R^2 are defined herein below in **Table 5**.

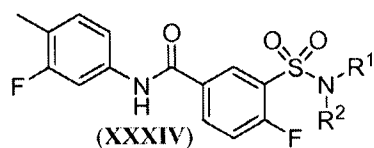
[0261] **Table 5:** Exemplary embodiments of compounds of the formula (XXXIII):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

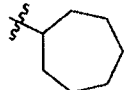
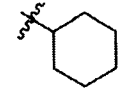
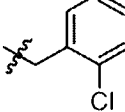
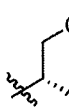
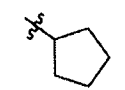
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

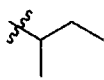
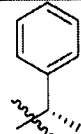
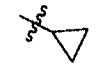
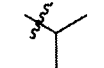
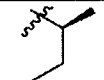
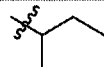
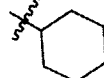
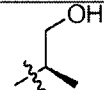
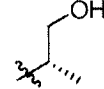
[0262] Exemplary embodiments include compounds having the formula (XXXIV) or a pharmaceutically acceptable salt form thereof:

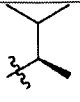
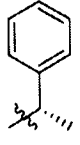
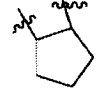


wherein non-limiting examples of R^1 and R^2 are defined herein below in Table 6.

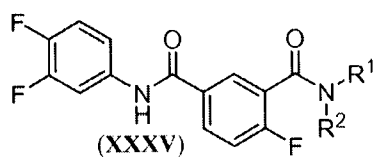
[0263] Table 6: Exemplary embodiments of compounds of the formula (XXXIV):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

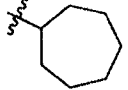
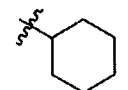
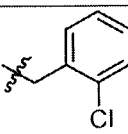
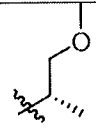
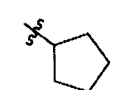
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

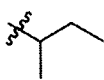
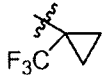
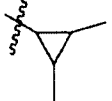
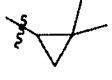
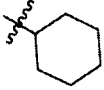
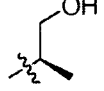
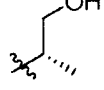
[0264] Exemplary embodiments include compounds having the formula (XXXV) or a pharmaceutically acceptable salt form thereof:

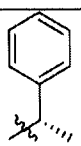
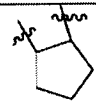


wherein non-limiting examples of R^1 and R^2 are defined herein below in Table 7.

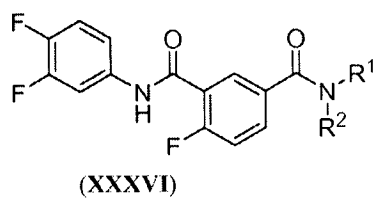
[0265] Table 7: Exemplary embodiments of compounds of the formula (XXXV):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

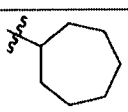
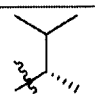
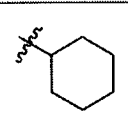
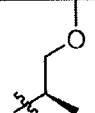
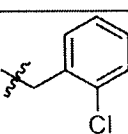
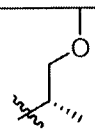
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

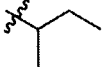
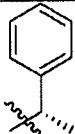
[0266] Exemplary embodiments include compounds having the formula (XXXVI) or a pharmaceutically acceptable salt form thereof:

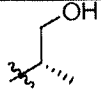
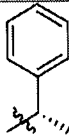


wherein non-limiting examples of R^1 and R^2 are defined herein below in **Table 8**.

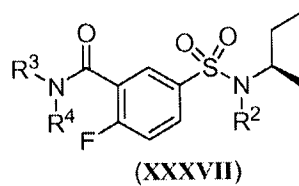
[0267] **Table 8:** Exemplary embodiments of compounds of the formula (XXXVI):

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H

	H			H
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	

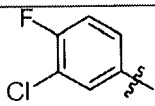
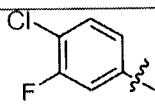
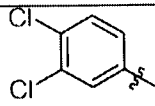
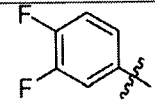
	H		$-\text{CH}_2(\text{CH}_2)_2\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

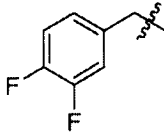
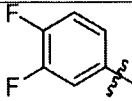
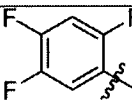
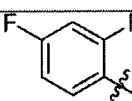
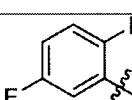
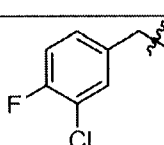
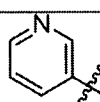
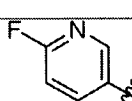
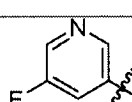
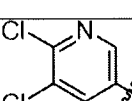
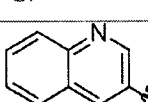
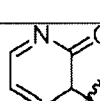
[0268] Exemplary embodiments include compounds having the formula (XXXVII) or a pharmaceutically acceptable salt form thereof:

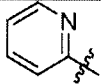
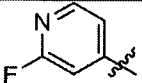
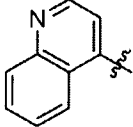
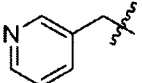
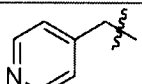
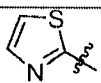
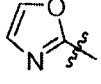
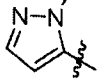
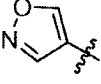
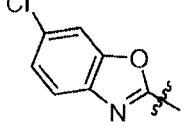


wherein non-limiting examples of R^2 , R^3 , and R^4 are defined herein below in Table 9.

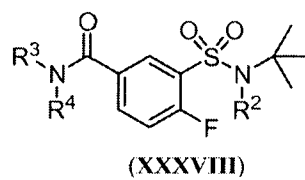
[0269] Table 9: Exemplary embodiments of compounds of the formula (XXXVII):

R^2	R^3	R^4
H		H
H		H
H		H
H		CH_3

H		H
Me		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

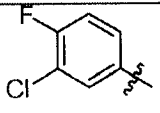
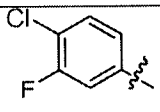
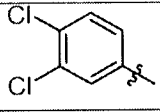
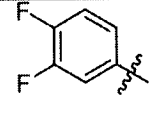
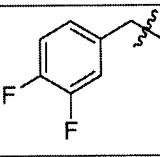
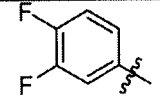
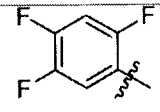
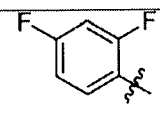
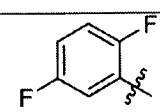
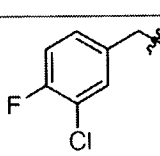
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

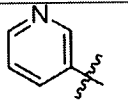
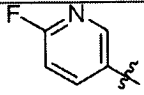
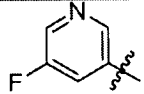
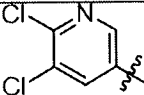
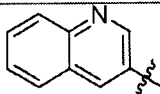
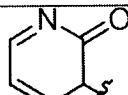
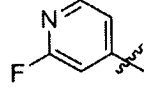
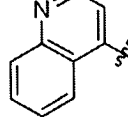
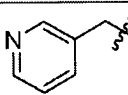
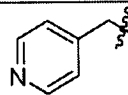
[0270] Exemplary embodiments include compounds having the formula (XXXVIII) or a pharmaceutically acceptable salt form thereof:

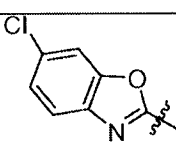


wherein non-limiting examples of R^2 , R^3 , and R^4 are defined herein below in **Table 10**.

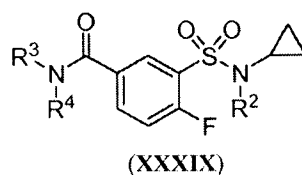
[0271] **Table 10:** Exemplary embodiments of compounds of the formula (XXXVIII):

R^2	R^3	R^4
H		H
H		H
H		H
H		CH ₃
H		H
Me		H
H		H
H		H
H		H
H		H

H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

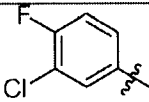
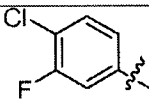
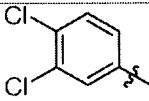
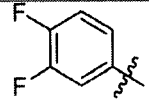
H		H
H		H
H		H
H		H

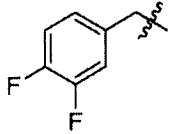
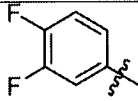
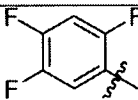
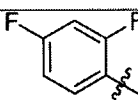
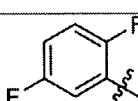
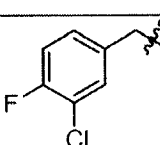
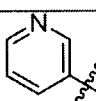
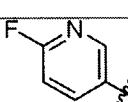
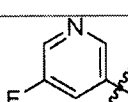
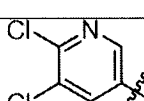
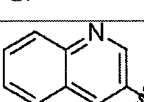
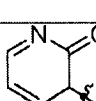
[0272] Exemplary embodiments include compounds having the formula (XXXIX) or a pharmaceutically acceptable salt form thereof:

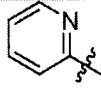
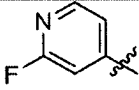
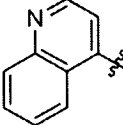
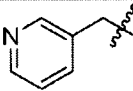
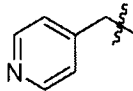
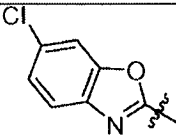


wherein non-limiting examples of R^2 , R^3 , and R^4 are defined herein below in **Table 11**.

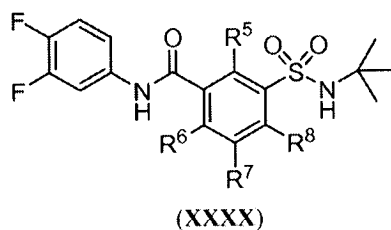
[0273] **Table 11:** Exemplary embodiments of compounds of the formula (XXXIX):

R^2	R^3	R^4
H		H
H		H
H		H
H		CH ₃

H		H
Me		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0274] Exemplary embodiments include compounds having the formula (XXXX) or a pharmaceutically acceptable salt form thereof:

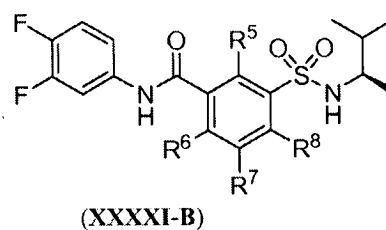
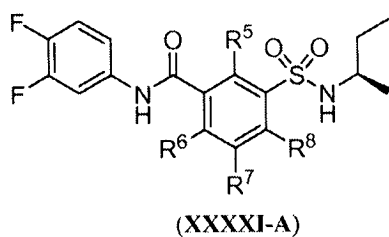


wherein non-limiting examples of R^5 , R^6 , R^7 , and R^8 are defined herein below in **Table 12**.

[0275] **Table 12:** Exemplary embodiments of compounds of the formula (XXXX):

R^5	R^6	R^7	R^8
H	H	H	Me
H	H	H	OMe
H	H	H	Cl
H	F	H	F
H	H	F	F

[0276] Exemplary embodiments include compounds having the formula (XXXXI-A or XXXXI-B) or a pharmaceutically acceptable salt form thereof:



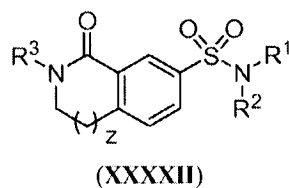
wherein non-limiting examples of R^5 , R^6 , R^7 , and R^8 are defined herein below in **Table 13**.

[0277] **Table 13:** Exemplary embodiments of compounds of the formula (XXXXI-A or XXXXI-B):

R^5	R^6	R^7	R^8

H	Me	H	H
H	OMe	H	H
H	Cl	H	H
F	F	H	H
H	F	F	H
H	F	H	F

[0278] Exemplary embodiments include compounds having the formula (XXXXII) or a pharmaceutically acceptable salt form thereof:

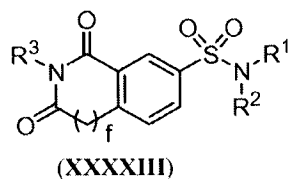


wherein non-limiting examples of R^1 , R^2 , R^3 , and z are defined herein below in Table 14.

[0279] Table 14: Exemplary embodiments of compounds of the formula (XXXXII):

z	R^1	R^2	R^3
0		H	
1		H	
0		H	
1		H	

[0280] Exemplary embodiments include compounds having the formula (XXXXIII) or a pharmaceutically acceptable salt form thereof:

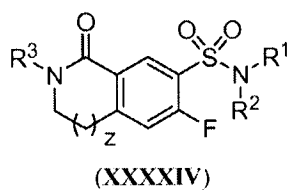


wherein non-limiting examples of R^1 , R^2 , R^3 , and f are defined herein below in **Table 15**.

[0281] Table 15: Exemplary embodiments of compounds of the formula (XXXXIII):

f	R^1	R^2	R^3
0		H	
1		H	
0		H	
1		H	

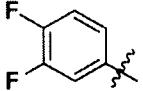
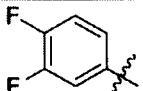
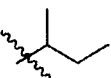
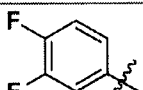
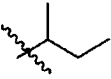
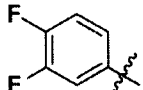
[0282] Exemplary embodiments include compounds having the formula (XXXXIV) or a pharmaceutically acceptable salt form thereof:



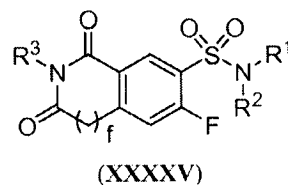
wherein non-limiting examples of R^1 , R^2 , R^3 , and z are defined herein below in **Table 16**.

[0283] Table 16: Exemplary embodiments of compounds of the formula (XXXXIV):

z	R^1	R^2	R^3
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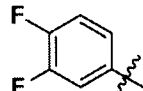
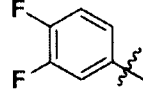
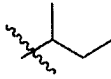
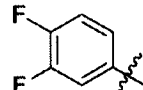
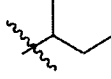
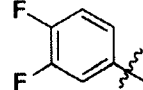
0		H	
1		H	
0		H	
1		H	

[0284] Exemplary embodiments include compounds having the formula (XXXXV) or a pharmaceutically acceptable salt form thereof:

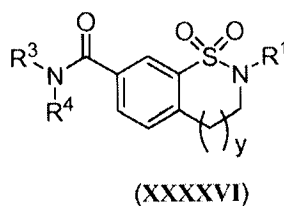


wherein non-limiting examples of R^1 , R^2 , R^3 , and f are defined herein below in **Table 17**.

[0285] **Table 17:** Exemplary embodiments of compounds of the formula (XXXXV):

f	R^1	R^2	R^3
0		H	
1		H	
0		H	
1		H	

[0286] Exemplary embodiments include compounds having the formula (XXXXVI) or a pharmaceutically acceptable salt form thereof:

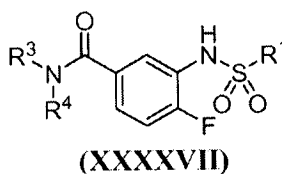


wherein non-limiting examples of R^1 , R^3 , R^4 , and y are defined herein below in **Table 18**.

[0287] **Table 18:** Exemplary embodiments of compounds of the formula (XXXXVI):

y	R^1	R^3	R^4
0			H
1			H
2			H

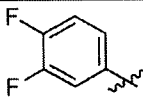
[0288] Exemplary embodiments include compounds having the formula (XXXXVII) or a pharmaceutically acceptable salt form thereof:



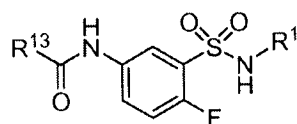
wherein non-limiting examples of R^1 , R^3 and R^4 are defined herein below in **Table 19**.

[0289] **Table 19:** Exemplary embodiments of compounds of the formula (XXXXVII):

R^1	R^3	R^4
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		H
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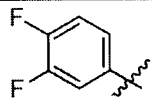
[0290] Exemplary embodiments include compounds having the formula (XXXXVIII) or a pharmaceutically acceptable salt form thereof:



(XXXXVIII)

wherein non-limiting examples of R¹ and R¹³ defined herein below in Table 19.

[0291] Table 20: Exemplary embodiments of compounds of the formula (XXXXVIII):

R ¹	R ¹³
	

[0292] In all of the embodiments provided herein, examples of suitable optional substituents are not intended to limit the scope of the claimed invention. The compounds of the invention may contain any of the substituents, or combinations of substituents, provided herein.

[0293] Each compound enumerated herein by name, structure, or both name and structure is considered an individual embodiment as a composition of matter. Additional embodiments include each compound enumerated herein by name, structure, or both name and structure is considered an individual embodiment as part of a pharmaceutical composition when combined with a pharmaceutically acceptable excipient. Additional embodiments include the use of each compound enumerated herein by name, structure, or both name and structure, either by itself or as part of a pharmaceutical composition or an enumerated treatment regimen for the treatment of at least one of the conditions described herein. Additional embodiments include methods of treating a patient for at least one of the conditions described herein by the administration to a patient in need thereof of a pharmaceutically effective amount of at least one of the compounds enumerated herein by name,

structure, or both name and structure, either by itself or as part of a pharmaceutical composition or an enumerated treatment regimen.

[0294] Compounds of the present teachings can be prepared in accordance with the procedures outlined herein, from commercially available starting materials, compounds known in the literature, or readily prepared intermediates, by employing standard synthetic methods and procedures known to those skilled in the art. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be readily obtained from the relevant scientific literature or from standard textbooks in the field. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions can vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures. Those skilled in the art of organic synthesis will recognize that the nature and order of the synthetic steps presented can be varied for the purpose of optimizing the formation of the compounds described herein.

[0295] The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatography such as high-pressure liquid chromatography (HPLC), gas chromatography (GC), gel-permeation chromatography (GPC), or thin layer chromatography (TLC).

[0296] Preparation of the compounds can involve protection and deprotection of various chemical groups. The need for protection and deprotection and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene et al., *Protective Groups in Organic Synthesis*, 2d. Ed. (Wiley & Sons, 1991), the entire disclosure of which is incorporated by reference herein for all purposes.

[0297] The reactions or the processes described herein can be carried out in suitable solvents which can be readily selected by one skilled in the art of organic synthesis. Suitable solvents typically are substantially nonreactive with the reactants, intermediates, and/or products at the temperatures at which the reactions are carried out, i.e., temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried

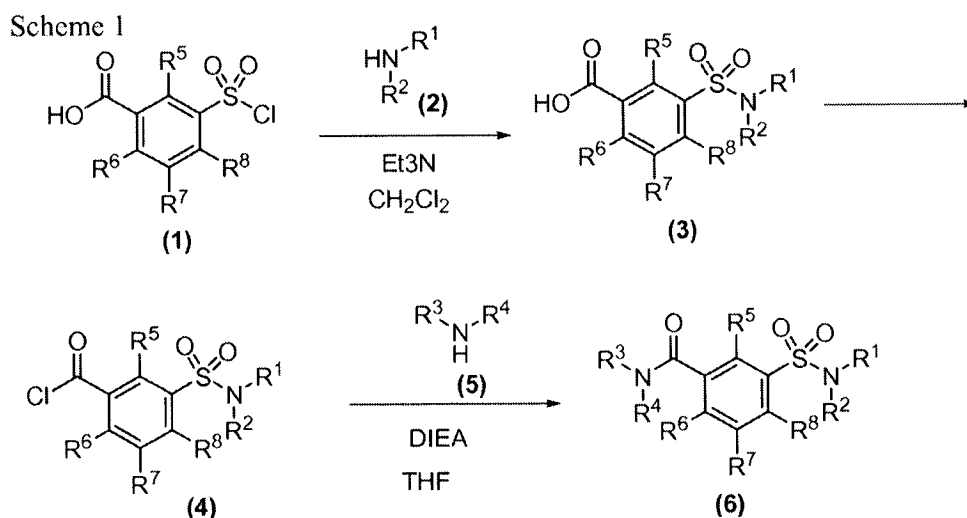
out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

[0298] The compounds of these teachings can be prepared by methods known in the art of organic chemistry. The reagents used in the preparation of the compounds of these teachings can be either commercially obtained or can be prepared by standard procedures described in the literature. For example, compounds of the present invention can be prepared according to the method illustrated in the General Synthetic Schemes:

GENERAL SYNTHETIC SCHEMES FOR PREPARATION OF COMPOUNDS.

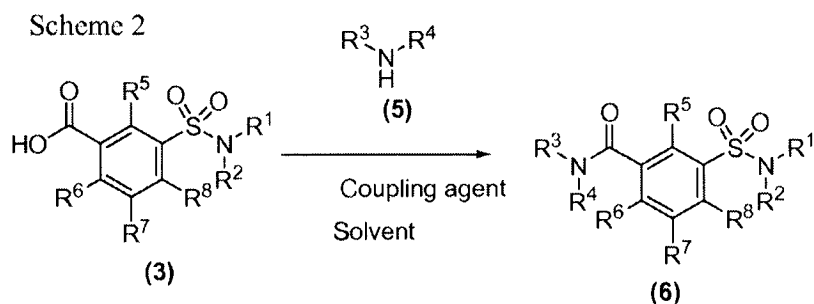
[0299] The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. In accordance with this invention, compounds in the genus may be produced by one of the following reaction schemes.

[0300] Compounds of the formula (6) may be prepared according to the process outlined in Schemes 1-2.



[0301] Accordingly, a compound of the formula (1), a known compound or compound prepared by known methods, is reacted with a compound of the formula (2), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine,

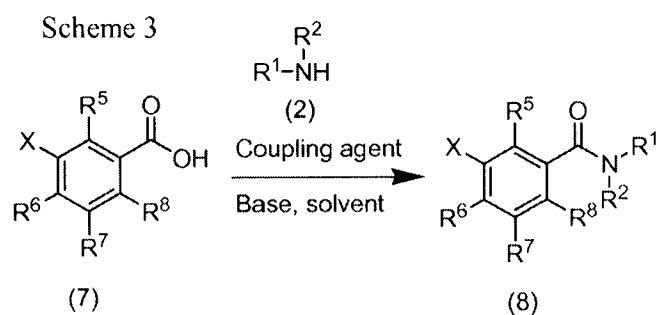
diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (3). A compound of the formula (3) is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (4). Alternatively, A compound of the formula (3) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (4). A compound of the formula (4) is then reacted with a compound of the formula (5), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (6).



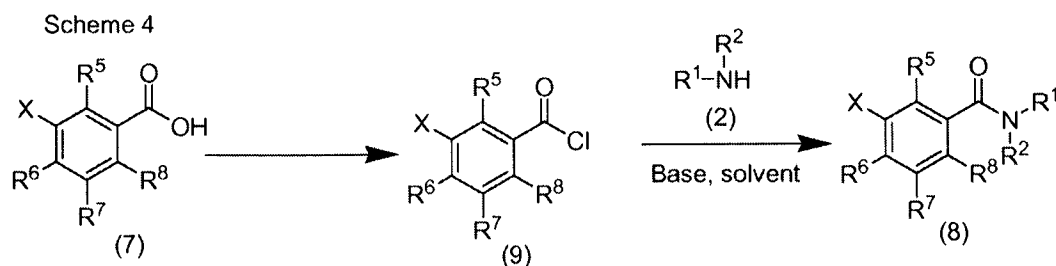
[0302] Alternatively, a compound of the formula (3) is reacted with a compound of the formula (5), a known compound or compound prepared by known methods, in the presence of a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N,N'-Dicyclohexylcarbodiimide, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethylformamide, methylene chloride, dichloroethane, methanol,

ethanol, and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, to provide a compound of the formula (6).

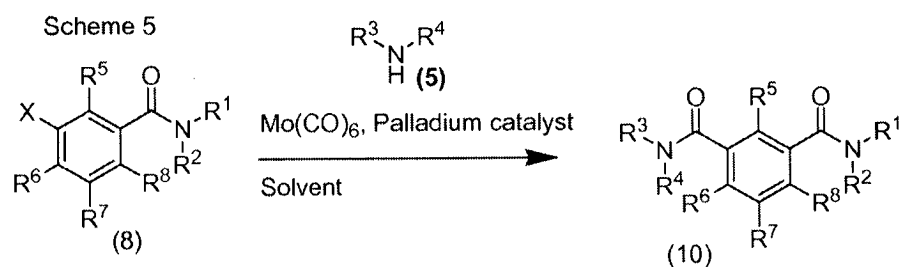
[0303] Compounds of formula (10) may be prepared according to the process outlined in Schemes 3-5.



[0304] A suitably substituted compound of the formula (7), a known compound or compound prepared by known methods, where X is a halogen, is reacted with a compound of the formula (2), a known compound or compound prepared by known methods, in the presence of a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N,N'-Dicyclohexylcarbodiimide, O-Benzotriazole-N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethylformamide, methylene chloride, dichloroethane, methanol, ethanol, and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, to provide a compound of the formula (8).

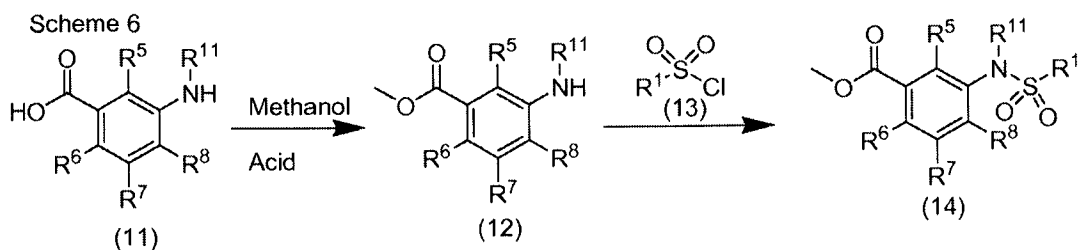


[0305] Alternatively, a suitably substituted compound of the formula (7), a known compound or compound prepared by known methods where X is a halogen, is reacted with thionyl chloride, optionally in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (9). Alternatively, a compound of the formula (7) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (9). A compound of the formula (9) is then reacted with a compound of the formula (2), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (8).

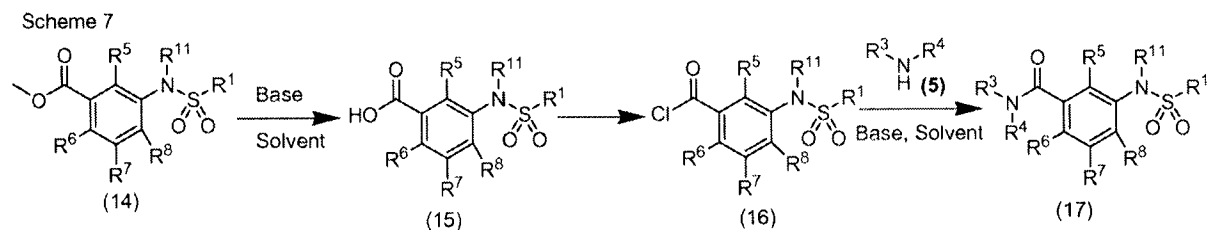


[0306] A compound of the formula (8) is reacted with a compound of the formula (5) in the presence of Molybdenum hexacarbonyl, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, in the presence of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), in a solvent such as water, dimethyl formamide, dimethyl acetamide, methanol, ethanol, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation, optionally in an inert atmosphere such as nitrogen or argon, to provide a compound of the formula (10).

[0307] Compounds of formula (17) may be prepared according to the process outlined in Schemes 6-7.



[0308] A compound of the formula (11), a known compound or compound prepared by known methods, is reacted with an methanol in the presence of an acid such as hydrochloric acid, sulfuric acid, optionally with heating to provide a compound of the formula (12). A compound of the formula (12) is reacted with a compound of the formula (13), a known compound or compound prepared by known methods, in the presence of a base such as pyridine, 2,6-lutidine, and the like, optionally in the presence of dimethylaminopyridine (DMAP), optionally in the presence of a solvent such as dimethyl formamide, dimethyl acetamide, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, to provide a compound of the formula (14)

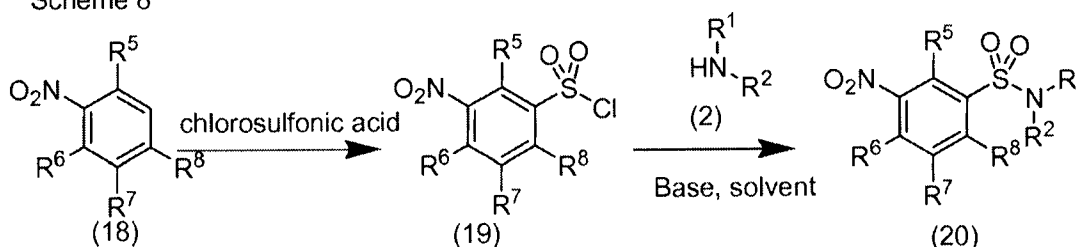


[0309] A compound of the formula (14) is reacted with a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, and the like, in an solvent such as ethanol, methanol, water, dimethyl formamide, dimethyl acetamide, tetrahydrofuran, 1,4-dioxane, and the like, to provide a compound of the formula (15). A compound of the formula (15) is then reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (16). Alternatively, A compound of the formula (15) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an

organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (16). A compound of the formula (16) is then reacted with a compound of the formula (5), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (17).

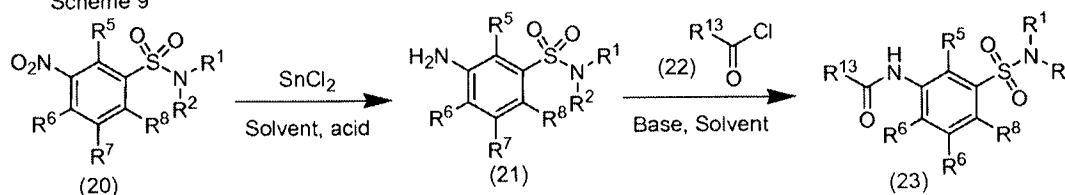
[0310] Compounds of formula (23) may be prepared according to the process outlined in Schemes 8-9.

Scheme 8



[0311] A compound of the formula (18), a known compound or compound prepared by known methods, is reacted with chlorosulfonic acid, optionally in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (19). A compound of the formula (19) is reacted with a compound of the formula (2) a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (20).

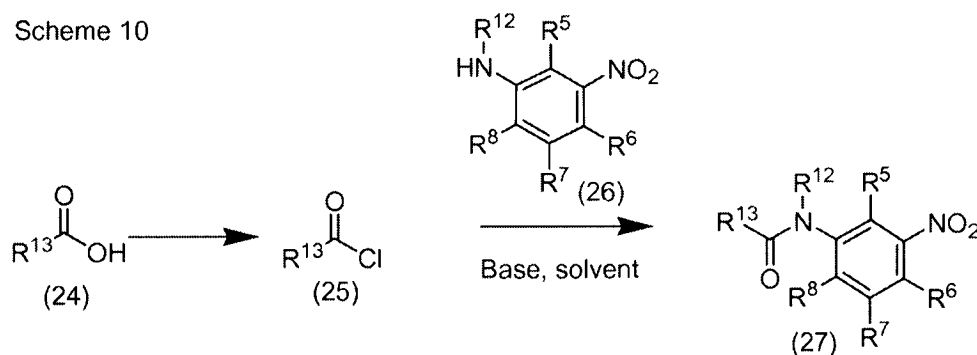
Scheme 9



[0312] A compound of the formula (20) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (21). A compound of the formula (21) is then reacted with a compound of the formula (22), a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula to provide a compound of the formula (23).

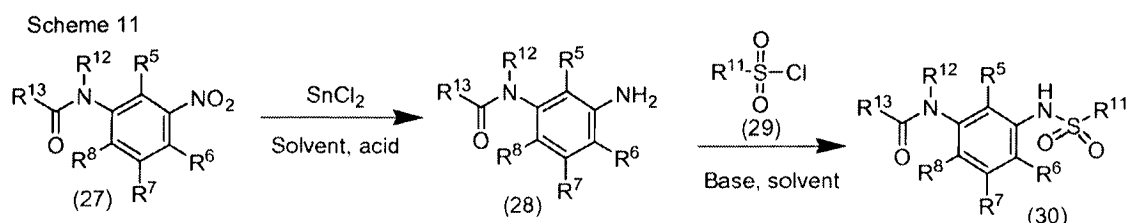
[0313] Compounds of formula (30) may be prepared according to the process outlined in Schemes 10-11.

Scheme 10



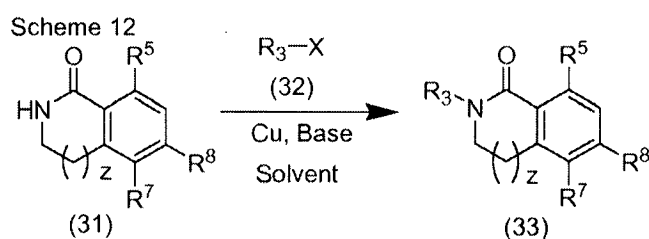
[0314] A compound of the formula (24), a known compound or compound prepared by known methods, is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (25). Alternatively, a compound of the formula (24) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (25). A compound of the formula (25) is then reacted with a compound of the formula (26), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an

organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (27).



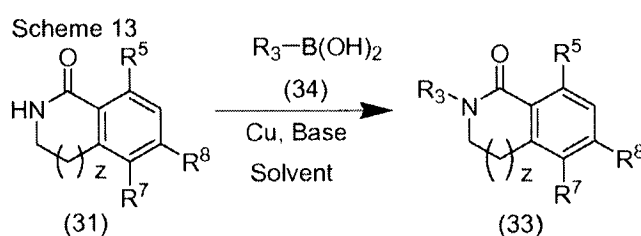
[0315] A compound of the formula (27) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (28). A compound of the formula (28) is then reacted with a compound of the formula (29), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (30).

[0316] Compounds of formula (36) may be prepared according to the process outlined in Schemes 12-14.

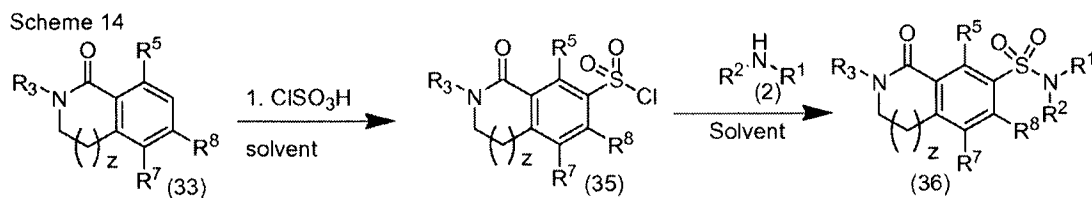


[0317] A compound of the formula (31), a known compound or compound prepared by known methods, is reacted with a compound of the formula (32), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0),

dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (33).



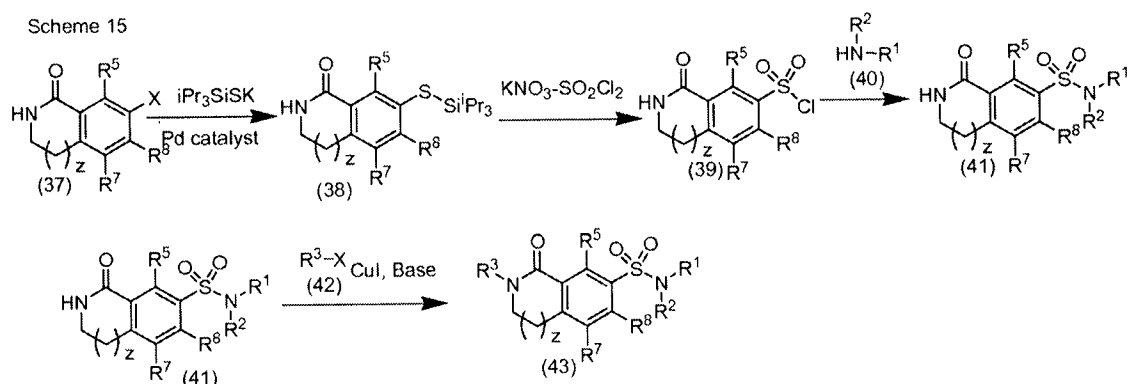
[0318] Alternatively, a compound of the formula (31), a known compound or compound prepared by known methods, is reacted with a compound of the formula (34), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (33).



[0319] A compound of the formula (33) is reacted with chlorosulfonic acid, optionally in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula to provide a

compound of the formula (35). A compound of the formula (35) is reacted with a compound of the formula (2) a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (36).

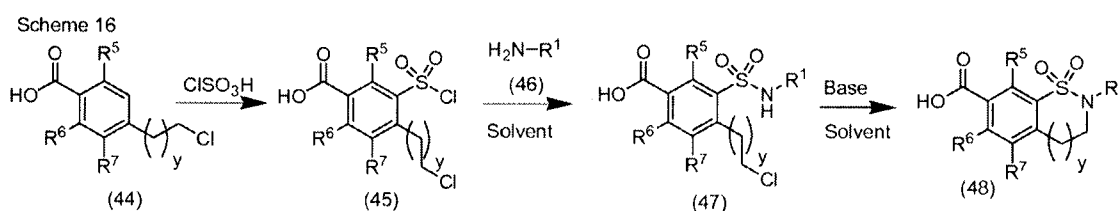
[0320] Compounds of formula (43) may be prepared according to the process outlined in Scheme 15.



[0321] A compound of the formula (37), a known compound or compound prepared by known methods wherein X is a halogen, is reacted with triisopropyl-silanethiol potassium salt in the presence of a palladium catalyst such as palladium(II)acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, in an solvent such as dimethyl formamide, dimethyl acetamide, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation, optionally in an inert atmosphere such as nitrogen or argon, to provide a compound of the formula (38). A compound of the formula (38) is then reacted with KNO₃-SO₂Cl₂ in a solvent such as dimethyl formamide, dimethyl acetamide, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, methanol, ethanol, and the like, to provide a compound of the formula (39). A compound of the formula (39) is reacted with a compound of the formula (40) a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-

lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (41). A compound of the formula (41) is then reacted with a compound of the formula (42), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (43).

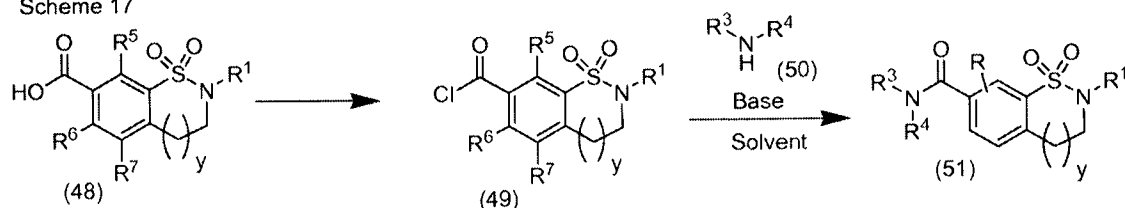
[0322] Compounds of formula (51) may be prepared according to the process outlined in Schemes 16-18.



[0323] A compound of the formula (44), a known compound or compound prepared by known methods, is reacted with chlorosulfonic acid, optionally in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (45). A compound of the formula (45) is then reacted with a compound of the formula (46), a known compound or compound prepared by known methods, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (47). A compound of the formula (47) is then reacted with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl

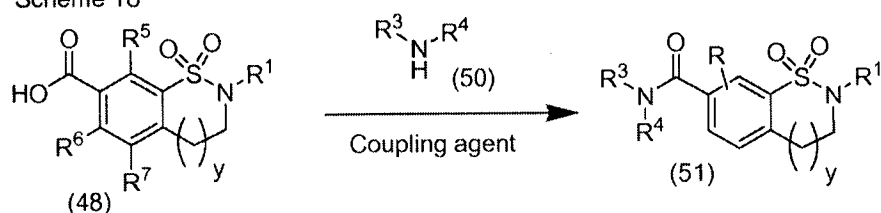
formamide, methanol, ethanol, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (48).

Scheme 17



[0324] A compound of the formula (48) is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (49). Alternatively, a compound of the formula (48) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (49). A compound of the formula (49) is then reacted with a compound of the formula (50), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (51).

Scheme 18

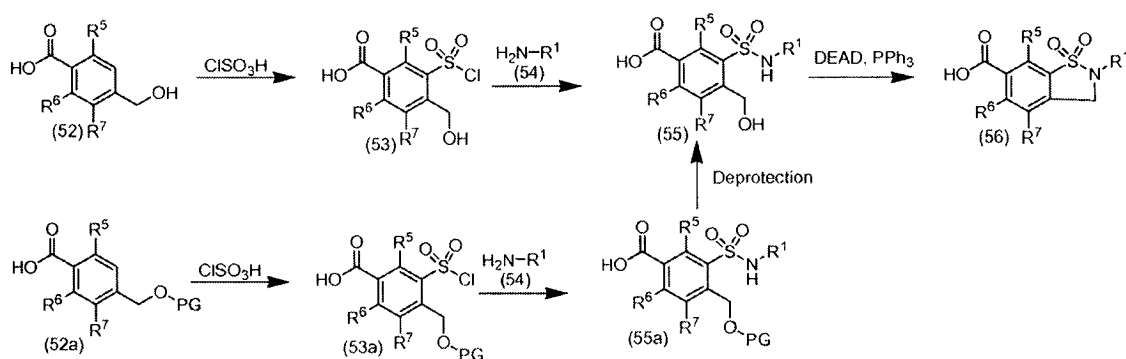


[0325] Alternatively, a compound of the formula (48) is reacted with a compound of the formula (50), a known compound or compound prepared by known methods, in the presence of a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N,N'-Dicyclohexylcarbodiimide, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate,

O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethylformamide, methylene chloride, dichloroethane, methanol, ethanol, and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, to provide a compound of the formula (51).

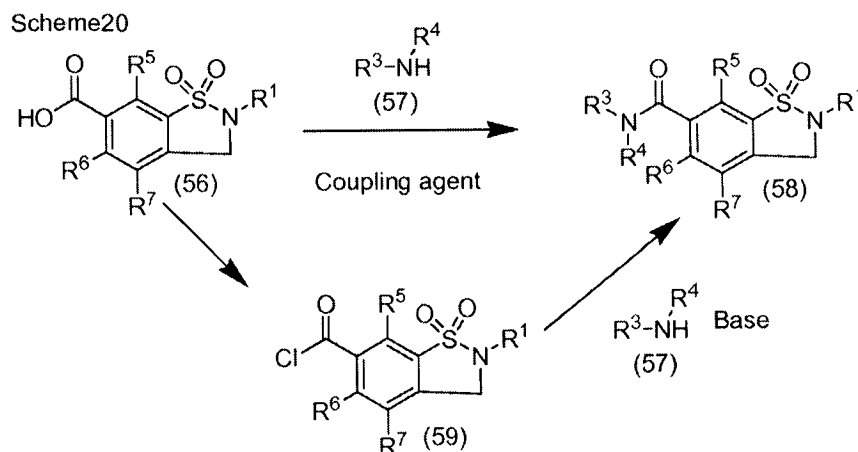
[0326] Compounds of formula (58) may be prepared according to the process outlined in Schemes 19-20.

Scheme 19



[0327] A compound of the formula (52), a known compound or compound prepared by known methods, is reacted with chlorosulfonic acid, optionally in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (53). A compound of the formula (53) is then reacted with a compound of the formula (54), a known compound or compound prepared by known methods, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (55). A compound of the formula (55) is then reacted with diethyl azodicarboxylate (DEAD) in the presence of triphenylphosphine, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (56).

[0328] Alternatively, a compound of the formula (52a), a known compound or compound prepared by known methods wherein PG is a protecting group such as tert-butyldimethylsilyl ether, methyl ether, tert-butyl ether, benzyl ether, β -methoxyethoxymethyl ether, acetyl, benzoyl, carbobenzyloxy, tert-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and the like, is reacted with chlorosulfonic acid, optionally in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (53a). A compound of the formula (53a) is then reacted with a compound of the formula (54), a known compound or compound prepared by known methods, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (55a). A compound of the formula (55a) is then deprotected by reaction with an acid such as trifluoroacetic acid, hydrochloric acid, and the like in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, methanol, ethanol, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (55). Alternatively, a compound of the formula (55a) is then deprotected by reaction with hydrogen in the presence of a catalyst such as palladium on carbon, platinum oxide and the like in a suitable solvent such as methanol, ethanol, tetrahydrofuran and the like to provide a compound of formula (55). Alternatively, a compound of the formula (55a) is then deprotected by reaction with a base such as sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (55). Alternatively, a compound of the formula (55a) is then deprotected by reaction with a base such as piperidine in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (55). A compound of the formula (55) is then reacted with diethyl azodicarboxylate (DEAD) in the presence of triphenylphosphine, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (56).

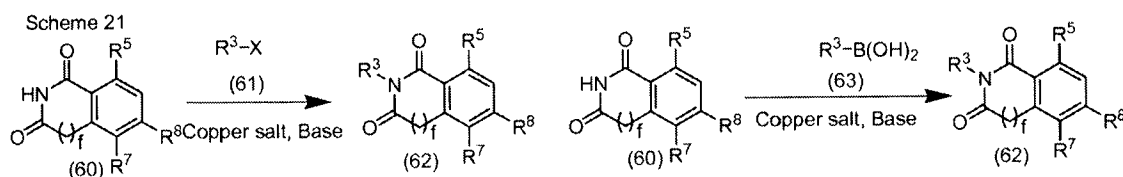


[0329] A compound of the formula (56) is reacted with a compound of the formula (57), a known compound or compound prepared by known methods, in the presence of a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N,N'-Dicyclohexylcarbodiimide, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethylformamide, methylene chloride, dichloroethane, methanol, ethanol, and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, to provide a compound of the formula (58).

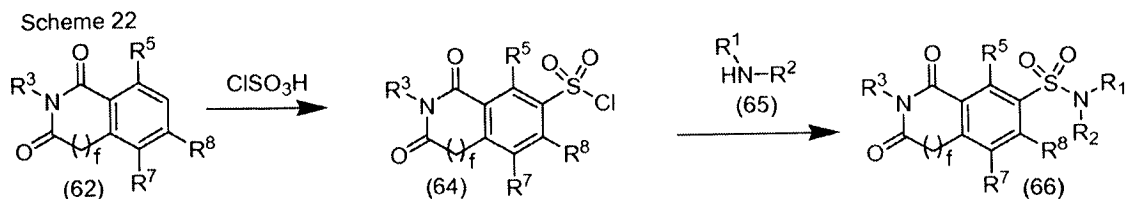
[0330] Alternatively, a compound of the formula (56) is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (59). Alternatively, a compound of the formula (56) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (59). A compound of the formula (59) is then reacted with a compound of the formula (57), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like,

optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (58).

[0331] Compounds of formula (66) may be prepared according to the process outlined in Schemes 21-22.

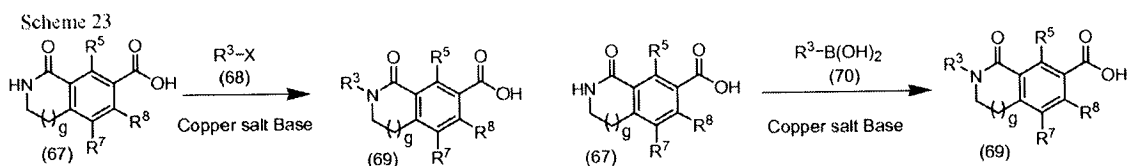


[0332] A compound of the formula (60), a known compound or compound prepared by known methods, is reacted with a compound of the formula (61), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (62). Alternatively, a compound of the formula (30), a known compound or compound prepared by known methods, is reacted with a compound of the formula (63), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (62).



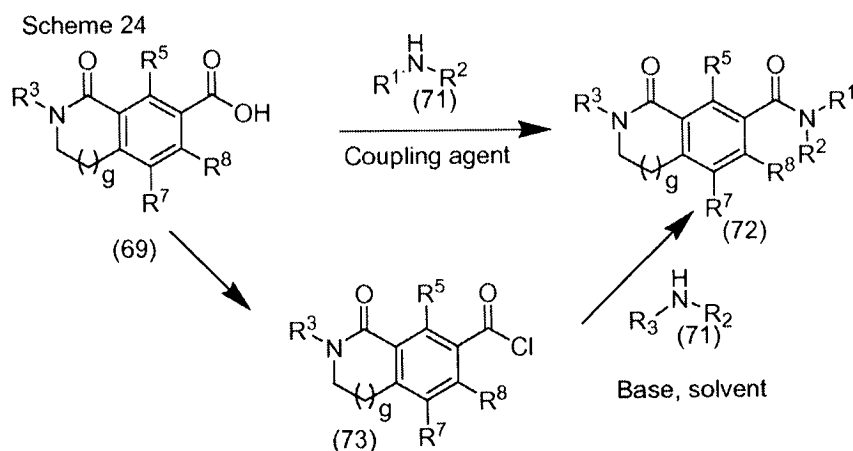
[0333] A compound of the formula (62), a known compound or compound prepared by known methods, is reacted with chlorosulfonic acid, optionally in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula to provide a compound of the formula (64). A compound of the formula (64) is reacted with a compound of the formula (65) a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in the presence of an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (66).

[0334] Compounds of formula (71) may be prepared according to the process outlined in Schemes 23-24.



[0335] A compound of the formula (67), a known compound or compound prepared by known methods, is reacted with a compound of the formula (68), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like,

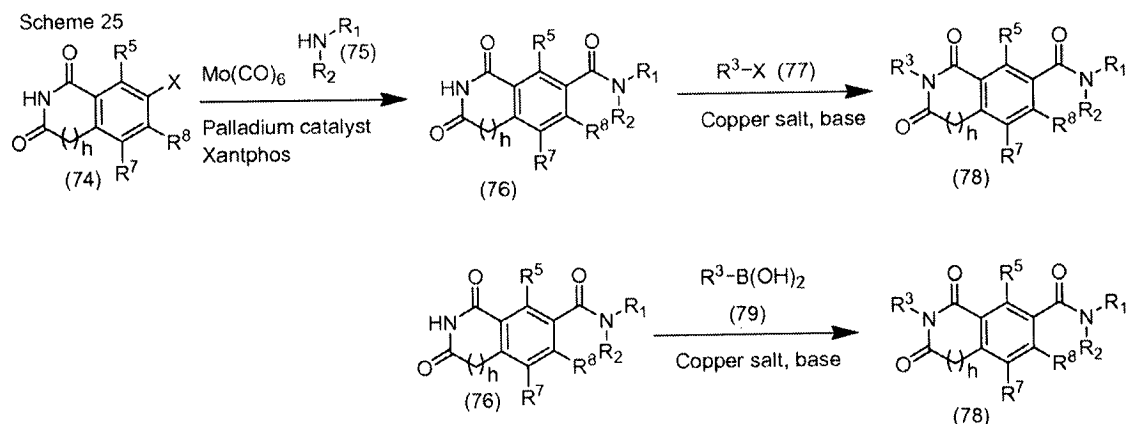
optionally with heating, optionally with microwave irradiation to provide a compound of the formula (69). Alternatively, a compound of the formula (67), a known compound or compound prepared by known methods, is reacted with a compound of the formula (70), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (69).



[0336] A compound of the formula (69) is reacted with a compound of the formula (71), a known compound or compound prepared by known methods, in the presence of a coupling agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N,N'-Dicyclohexylcarbodiimide, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethylformamide, methylene chloride, dichloroethane, methanol, ethanol, and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the

like, optionally in the presence of 4-N,N-dimethylaminopyridine, to provide a compound of the formula (72). Alternatively, a compound of the formula (69) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (73). Alternatively, a compound of the formula (69) is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (73). A compound of the formula (73) is then reacted with a compound of the formula (71), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (72).

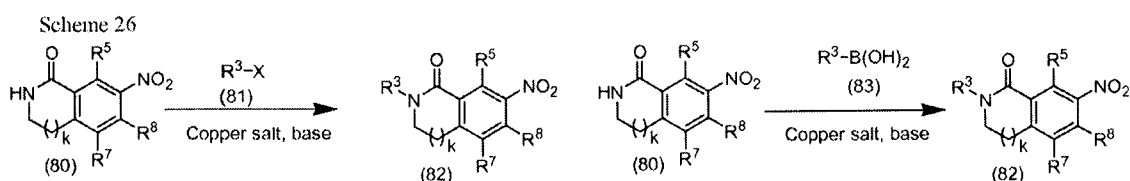
[0337] Compounds of formula (78) may be prepared according to the process outlined in Scheme 25.



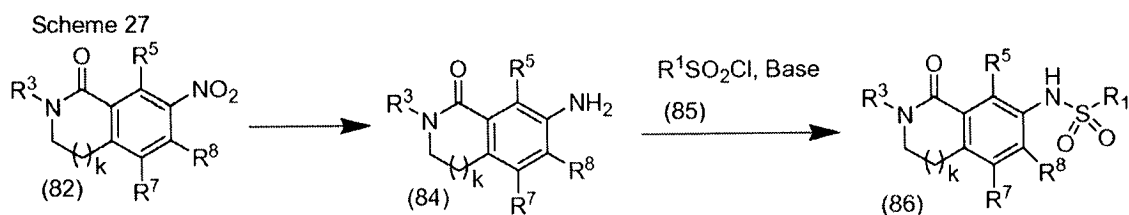
[0338] A compound of the formula (74) is reacted with a compound of the formula (75) in the presence of Molybdenum hexacarbonyl, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, in the presence of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), in an solvent such as water, dimethyl

formamide, dimethyl acetamide, methanol, ethanol, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation, optionally in an inert atmosphere such as nitrogen or argon, to provide a compound of the formula (76). A compound of the formula (76) is reacted with a compound of the formula (77), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (78). Alternatively, a compound of the formula (76) is reacted with a compound of the formula (79), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (78).

[0339] Compounds of formula (86) may be prepared according to the process outlined in Schemes 26-27.



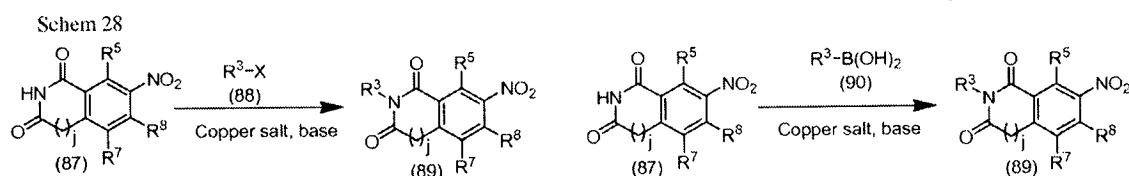
[0340] A compound of the formula (80) is reacted with a compound of the formula (81), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (82). Alternatively, a compound of the formula (80) is reacted with a compound of the formula (83), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate, and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (82).



[0341] A compound of the formula (82) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (84). Alternatively, a compound of the formula (82) is reacted with hydrogen in the presence of a palladium catalyst such as palladium on carbon, palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II),

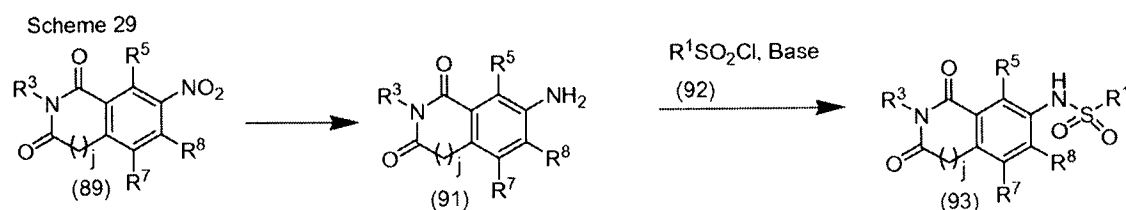
palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of acetic acid, optionally in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, and the like to provide a compound of the formula (84). A compound of the formula (84) is then reacted with a compound of the formula (85), a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (86).

[0342] Compounds of formula (93) may be prepared according to the process outlined in Schemes 28-29.



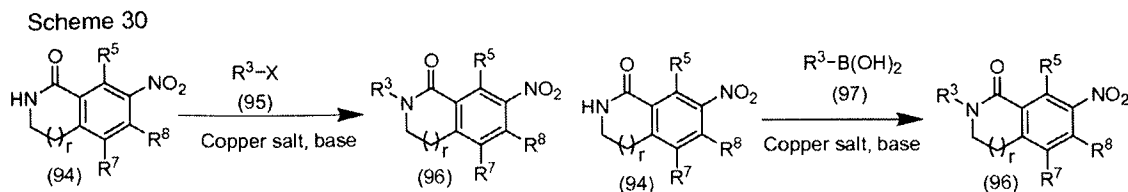
[0343] A compound of the formula (87) is reacted with a compound of the formula (88), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (89). Alternatively, a compound of the formula (87) is reacted with a compound of the formula (90), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as

triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (89).



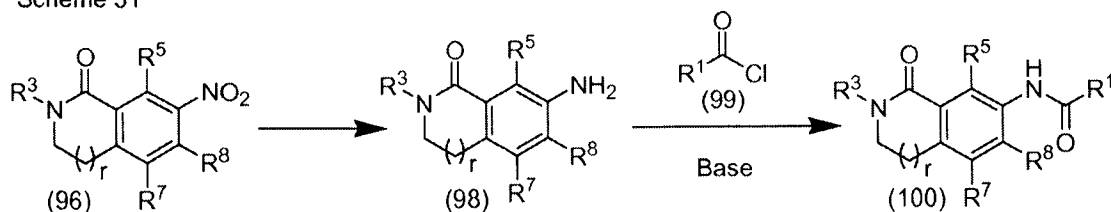
[0344] A compound of the formula (89) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (91). Alternatively, a compound of the formula (89) is reacted with hydrogen in the presence of a palladium catalyst such as palladium on carbon, palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of acetic acid, optionally in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, and the like to provide a compound of the formula (91). A compound of the formula (91) is then reacted with a compound of the formula (92), a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (93).

[0345] Compounds of formula (100) may be prepared according to the process outlined in Schemes 30-31.



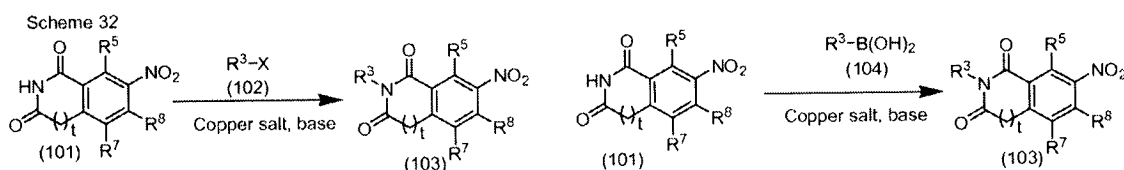
[0346] A compound of the formula (94) is reacted with a compound of the formula (95), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (96). Alternatively, a compound of the formula (94) is reacted with a compound of the formula (97), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (96).

Scheme 31



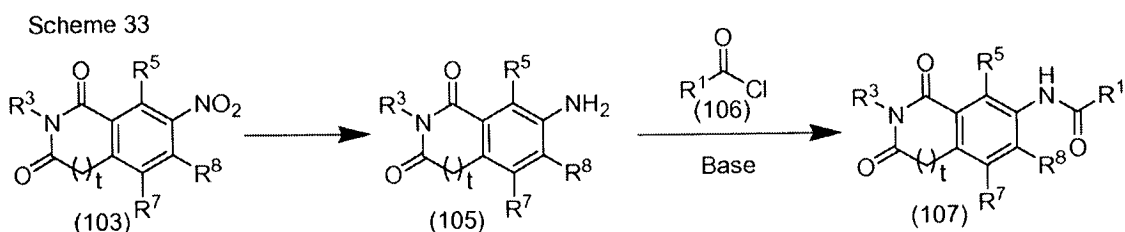
[0347] A compound of the formula (96) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (98). Alternatively, a compound of the formula (96) is reacted with hydrogen in the presence of a palladium catalyst such as palladium on carbon, palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of acetic acid, optionally in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, and the like to provide a compound of the formula (98). A compound of the formula (98) is then reacted with a compound of the formula (99), a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (100).

[0348] Compounds of formula (107) may be prepared according to the process outlined in Schemes 32-33.



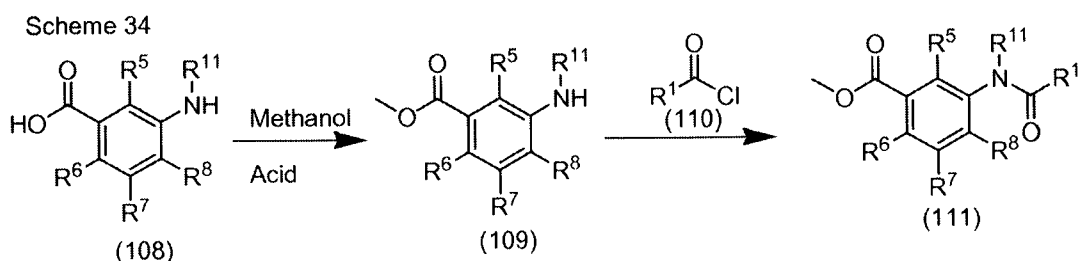
[0349] A compound of the formula (101) is reacted with a compound of the formula (102), a known compound or compound prepared by known methods wherein X is a halogen, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (103). Alternatively, a compound of the formula (101) is reacted with a compound of the formula

(104), a known compound or compound prepared by known methods, in the presence of a copper salt such as copper sulfate, copper iodide, copper chloride, copper acetate and the like, optionally in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in a solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (103).

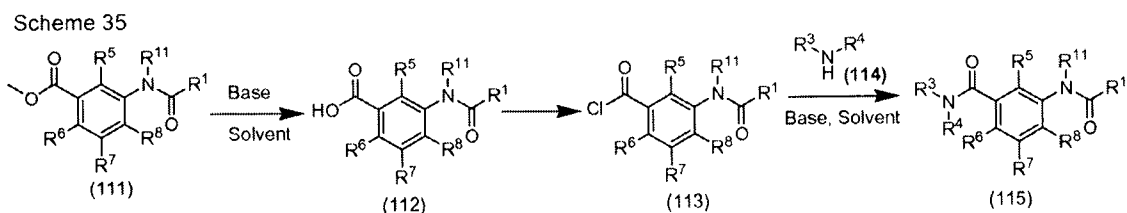


[0350] A compound of the formula (103) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (105). Alternatively, a compound of the formula (103) is reacted with hydrogen in the presence of a palladium catalyst such as palladium on carbon, palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloropalladium(II), and the like, optionally in the presence of acetic acid, optionally in a solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane, and the like to provide a compound of the formula (105). A compound of the formula (105) is then reacted with a compound of the formula (106), a known compound or compound prepared by known methods, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (107).

[0351] Compounds of formula (115) may be prepared according to the process outlined in Schemes 34-35.



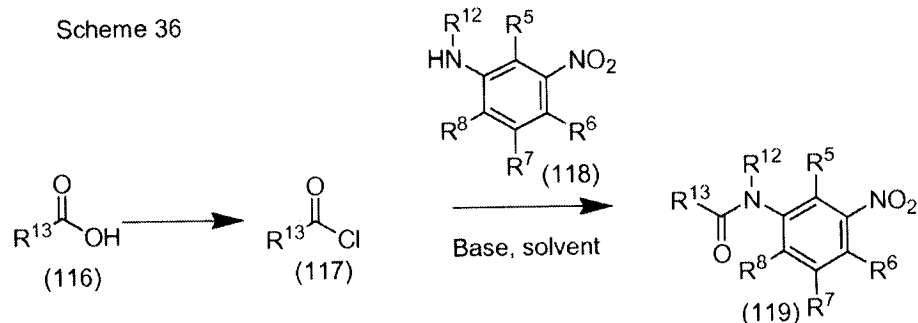
A compound of the formula (108), a known compound or compound prepared by known methods, is reacted with methanol in the presence of an acid such as hydrochloric acid, sulfuric acid, optionally with heating to provide a compound of the formula (109). A compound of the formula (109) is reacted with a compound of the formula (110), a known compound or compound prepared by known methods, in the presence of a base such as pyridine, 2,6-lutidine, and the like, optionally in the presence of dimethylaminopyridine (DMAP), optionally in the presence of a solvent such as dimethyl formamide, dimethyl acetamide, methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, to provide a compound of the formula (111).



[0352] A compound of the formula (111) is reacted with a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, and the like, in an solvent such as ethanol, methanol, water, dimethyl formamide, dimethyl acetamide, tetrahydrofuran, 1,4-dioxane, and the like, to provide a compound of the formula (112). A compound of the formula (112) is then reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (113). Alternatively, a compound of

the formula (112) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (113). A compound of the formula (113) is then reacted with a compound of the formula (114), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (115).

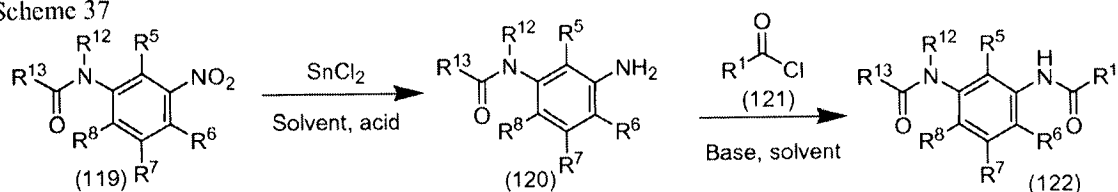
[0353] Compounds of formula (122) may be prepared according to the process outlined in Schemes 36-37.



[0354] A compound of the formula (116), a known compound or compound prepared by known methods, is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (117). Alternatively, a compound of the formula (116) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (117). A compound of the formula (117) is then reacted with a compound of the formula (118), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane,

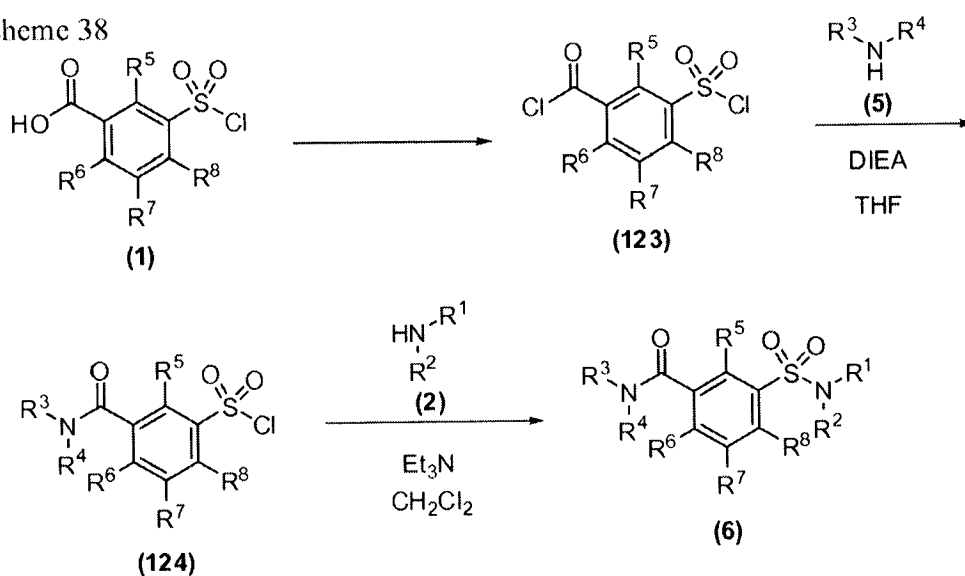
tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (119).

Scheme 37



[0355] A compound of the formula (119) is then reacted with tin chloride in the presence of an acid such as hydrochloric acid, sulfuric acid, and the like, in an organic solvent such as tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (120). A compound of the formula (120) is then reacted with a compound of the formula (121), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (122).

Scheme 38



[0356] Alternatively, a compound of the formula (1), a known compound or compound prepared by known methods, is reacted with thionyl chloride, optionally in the presence an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (123). Alternatively, a compound of the formula (1) is reacted with oxalyl chloride, optionally in the presence of dimethyl formamide, optionally in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (123). A compound of the formula (123) is then reacted with a compound of the formula (5), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (124). A compound of formula (124) is then reacted with a compound of the formula (2), a known compound or compound prepared by known methods, optionally in the presence of a base such as triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, and the like, optionally in the presence of 4-N,N-dimethylaminopyridine, in an organic solvent such as methylene chloride, dichloroethane, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, and the like to provide a compound of the formula (6).

FORMULATIONS AND METHODS OF TREATMENT

[0357] The present invention also relates to compositions or formulations which comprise the compounds of the present invention. In general, the compositions of the present invention comprise an effective amount of one or more of the compounds of the disclosure and salts thereof according to the present invention which are effective for useful for the treatment of viral infection, especially Hepatitis B virus (HBV) infection and related conditions; and one or more pharmaceutically acceptable excipient.

[0358] For the purposes of the present invention the term “excipient” and “carrier” are used interchangeably throughout the description of the present invention and said terms are defined herein as, “ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition.”

[0359] The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle

for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

[0360] The present teachings also provide pharmaceutical compositions that include at least one compound described herein and one or more pharmaceutically acceptable carriers, excipients, or diluents. Examples of such carriers are well known to those skilled in the art and can be prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in *Remington's Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985), the entire disclosure of which is incorporated by reference herein for all purposes. As used herein, "pharmaceutically acceptable" refers to a substance that is acceptable for use in pharmaceutical applications from a toxicological perspective and does not adversely interact with the active ingredient. Accordingly, pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and are biologically acceptable. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0361] Compounds of the present teachings can be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents, or encapsulating materials. The compounds can be formulated in conventional manner, for example, in a manner similar to that used for known antiviral agents. Oral formulations containing a compound disclosed herein can comprise any conventionally used oral form, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. In powders, the carrier can be a finely divided solid, which is an admixture with a finely divided compound. In tablets, a compound disclosed herein can be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets can contain up to 99 % of the compound.

[0362] Capsules can contain mixtures of one or more compound(s) disclosed herein with inert filler(s) and/or diluent(s) such as pharmaceutically acceptable starches (e.g., corn, potato or tapioca

starch), sugars, artificial sweetening agents, powdered celluloses (e.g., crystalline and microcrystalline celluloses), flours, gelatins, gums, and the like.

[0363] Useful tablet formulations can be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins. Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein can utilize standard delay or time-release formulations to alter the absorption of the compound(s). The oral formulation can also consist of administering a compound disclosed herein in water or fruit juice, containing appropriate solubilizers or emulsifiers as needed.

[0364] Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups, elixirs, and for inhaled delivery. A compound of the present teachings can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a mixture of both, or a pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, and osmo-regulators. Examples of liquid carriers for oral and parenteral administration include, but are not limited to, water (particularly containing additives as described herein, e.g., cellulose derivatives such as a sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration, the carrier can be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral

administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellants.

[0365] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

[0366] Preferably the pharmaceutical composition is in unit dosage form, for example, as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the pharmaceutical composition can be sub-divided in unit dose(s) containing appropriate quantities of the compound. The unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. Alternatively, the unit dosage form can be a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form can contain from about 1 mg/kg of compound to about 500 mg/kg of compound, and can be given in a single dose or in two or more doses. Such doses can be administered in any manner useful in directing the compound(s) to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally.

[0367] When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that an effective dosage can vary depending upon the particular compound utilized, the mode of administration, and severity of the condition being treated, as well as the various physical factors related to the individual being treated. In therapeutic applications, a compound of the present teachings can be provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. The dosage to be used in the treatment of a specific individual typically must be subjectively determined by the attending physician. The variables involved include the specific condition and its state as well as the size, age and response pattern of the patient.

[0368] In some cases it may be desirable to administer a compound directly to the airways of the patient, using devices such as, but not limited to, metered dose inhalers, breath-operated inhalers, multidose dry-powder inhalers, pumps, squeeze-actuated nebulized spray dispensers, aerosol dispensers, and aerosol nebulizers. For administration by intranasal or intrabronchial inhalation, the compounds of the present teachings can be formulated into a liquid composition, a solid composition,

or an aerosol composition. The liquid composition can include, by way of illustration, one or more compounds of the present teachings dissolved, partially dissolved, or suspended in one or more pharmaceutically acceptable solvents and can be administered by, for example, a pump or a squeeze-actuated nebulized spray dispenser. The solvents can be, for example, isotonic saline or bacteriostatic water. The solid composition can be, by way of illustration, a powder preparation including one or more compounds of the present teachings intermixed with lactose or other inert powders that are acceptable for intrabronchial use, and can be administered by, for example, an aerosol dispenser or a device that breaks or punctures a capsule encasing the solid composition and delivers the solid composition for inhalation. The aerosol composition can include, by way of illustration, one or more compounds of the present teachings, propellants, surfactants, and co-solvents, and can be administered by, for example, a metered device. The propellants can be a chlorofluorocarbon (CFC), a hydrofluoroalkane (HFA), or other propellants that are physiologically and environmentally acceptable.

[0369] Compounds described herein can be administered parenterally or intraperitoneally. Solutions or suspensions of these compounds or a pharmaceutically acceptable salts, hydrates, or esters thereof can be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations typically contain a preservative to inhibit the growth of microorganisms.

[0370] The pharmaceutical forms suitable for injection can include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In some embodiments, the form can be sterile and its viscosity permits it to flow through a syringe. The form preferably is stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0371] Compounds described herein can be administered transdermally, i.e., administered across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administration can be carried out using the compounds of the present teachings including pharmaceutically acceptable salts, hydrates, or esters thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[0372] Transdermal administration can be accomplished through the use of a transdermal patch containing a compound, such as a compound disclosed herein, and a carrier that can be inert to the compound, can be non-toxic to the skin, and can allow delivery of the compound for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the compound can also be suitable. A variety of occlusive devices can be used to release the compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing the compound with or without a carrier, or a matrix containing the compound. Other occlusive devices are known in the literature.

[0373] Compounds described herein can be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations can be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, can also be used.

[0374] Lipid formulations or nanocapsules can be used to introduce compounds of the present teachings into host cells either *in vitro* or *in vivo*. Lipid formulations and nanocapsules can be prepared by methods known in the art.

[0375] To increase the effectiveness of compounds of the present teachings, it can be desirable to combine a compound with other agents effective in the treatment of the target disease. For example, other active compounds (i.e., other active ingredients or agents) effective in treating the target disease can be administered with compounds of the present teachings. The other agents can be administered at the same time or at different times than the compounds disclosed herein.

[0376] Compounds of the present teachings can be useful for the treatment or inhibition of a pathological condition or disorder in a mammal, for example, a human subject. The present teachings accordingly provide methods of treating or inhibiting a pathological condition or disorder by providing to a mammal (including a human patient) a compound of the present teachings including its pharmaceutically acceptable salt) or a pharmaceutical composition that includes one or more compounds of the present teachings in combination or association with pharmaceutically acceptable carriers. Compounds of the present teachings can be administered alone or in combination with other

therapeutically effective compounds or therapies for the treatment or inhibition of the pathological condition or disorder.

[0377] Non-limiting examples of compositions according to the present invention include from about 0.001 mg to about 1000 mg of one or more of the compounds of the present invention and one or more excipient; from about 0.01 mg to about 100 mg of one or more of the compounds according to the present invention and one or more excipients; and from about 0.1 mg to about 10 mg of one or more of the compounds according to the present invention; and one or more excipients.

[0378] In any above methods, the compound, or pharmaceutically acceptable salt of the present invention, can be administered either in monotherapy or in combination with one or more additional therapeutic agents. In certain embodiments the additional therapeutic agent may include an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, literature-described capsid assembly modulator, 5 reverse transcriptase inhibitor, a TLR-agonist, or an agents of distinct or unknown mechanism, or a combination thereof.

[0379] The additional therapeutic agent selected from immune modulator or immune stimulator therapies, which includes biological agents belonging to the interferon class, such as interferon alpha 2a or 2b or modified interferons such as pegylated interferon, alpha 2a, alpha 2b, lamda; or TLR modulators such as TLR-7 agonists or TLR-9 agonists, or antiviral agents that block viral entry or maturation or target the HBV polymerase such as nucleoside or nucleotide or non-nucleos(t)ide polymerase inhibitors, and agents of distinct or unknown mechanism including agents that disrupt the function of other essential viral protein(s) or host proteins required for HB V replication or persistence.

[0380] The reverse transcriptase inhibitor may include at least one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

[0381] The combination therapy, the TLR-7 agonist may be SM360320 (9-benzyl-8-hydroxy-2-(2-methoxyethoxy) adenine) or AZD 8848 (methyl [3-({ [3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl] [3 -(4-morpholinyl)propyl]amino} methyl)phenyl]acetate).

[0382] In some embodiments of these combination therapies, the compound, or pharmaceutically acceptable salt of the present invention, and the additional therapeutic agent are co-formulated. In other embodiments, the compound and the additional therapeutic agent are co-

administered. In other embodiments the compound, or pharmaceutically acceptable salt, of the present invention, and the additional therapeutic agent are separately formulated or administered.

[0383] In still other embodiments of the combination therapy, administering the compound, or pharmaceutically acceptable salt of the present invention allows for administering of the additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

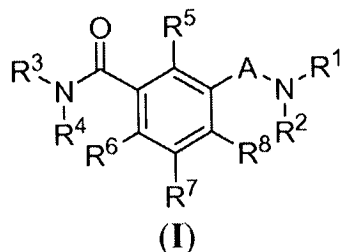
[0384] In other embodiments of the combination therapy, before administering the therapeutically effective amount of the compound, or pharmaceutically acceptable salt of the present invention, the individual is known to be refractory to a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, an antiviral compound of distinct or unknown mechanism, or a combination thereof.

[0385] In still other embodiments of the methods, administering a compound, or pharmaceutically acceptable salt of the present invention reduces viral load in the individual to a greater extent compared to the administering of a a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, an antiviral compound of distinct or unknown mechanism, or a combination thereof.

[0386] In further embodiments, administering a compound, or pharmaceutically acceptable salt of the present invention causes a lower incidence of viral mutation and/or viral resistance than the administering of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, an antiviral compound of distinct or unknown mechanism, or a combination thereof.

[0387] The following listing of Embodiments is intended to complement, rather than displace or supersede, the previous descriptions.

[0388] Embodiment 1. A compound comprising a structure of Formula (I), or an enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate thereof:



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R¹ may also alternatively or additionally optionally include optionally substituted C₁₋₆ haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R² is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl; R² may also alternatively or additionally optionally include optionally substituted C₃₋₇ cycloalkyl or optionally substituted heterocyclic; or

R¹ and R² are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms; and

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl; in some embodiments, R³ may also comprise an optionally substituted C₁₋₆ linear alkyl;

R⁴ is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

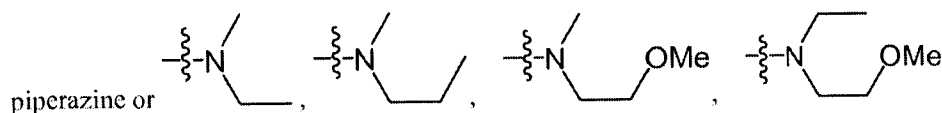
R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

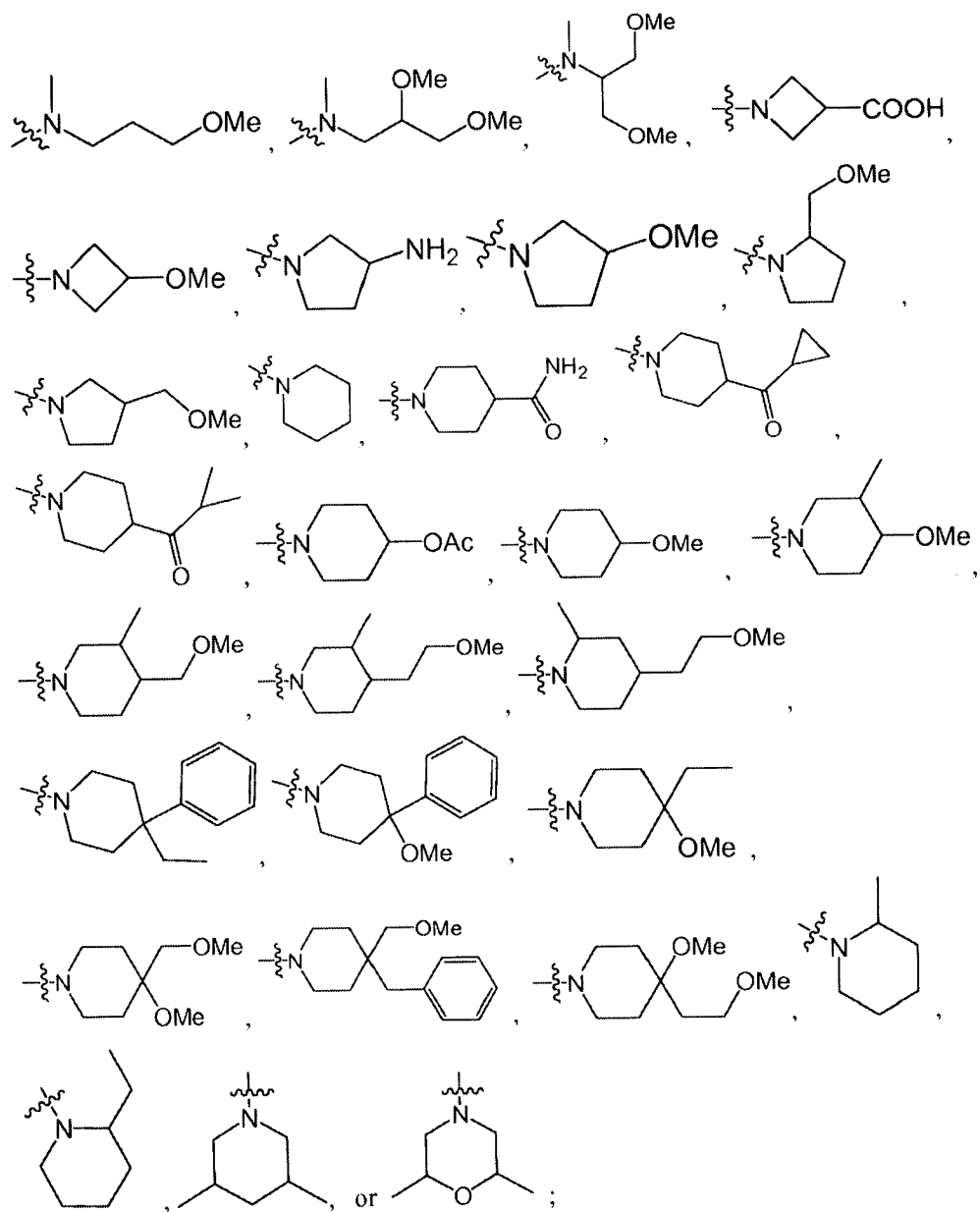
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms; and

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; R^9 may also alternatively or additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

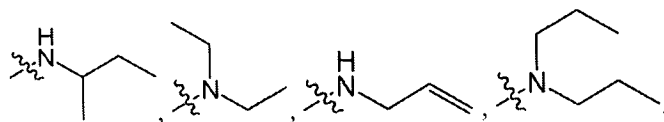
[0389] provided that when A is SO_2 ; R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring, then none of the following (a) through (d) apply:

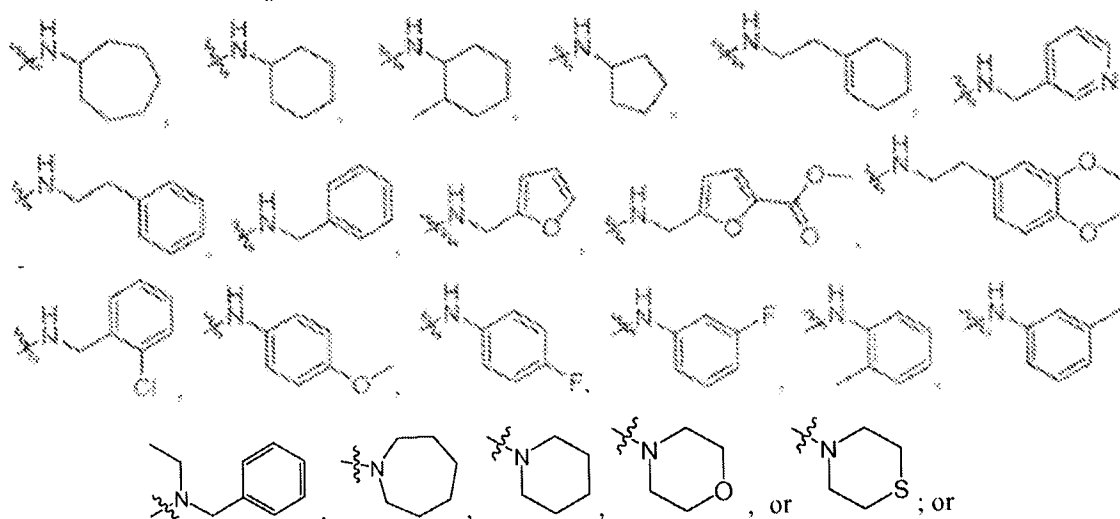
- (a) R^3 is an optionally substituted phenyl and R^1 or R^2 , either individually or when taken together, contain a hydroxyl group, or
- (b) R^3 is an optionally substituted alkyl or phenyl, and $N(R^1)(R^2)$ is an optionally substituted





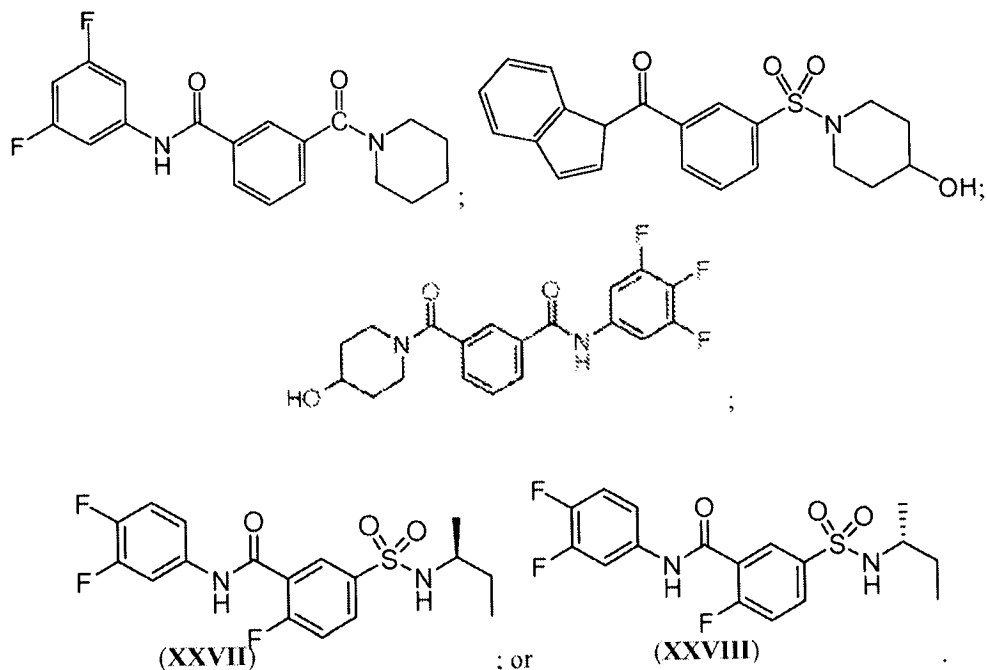
(c) R^3 is optionally substituted alkyl, aryl, or alkaryl and $N(R^1)(R^2)$ is





- (d) either R^3 or R^4 is an unsubstituted or monosubstituted aryl, or an unsubstituted or monosubstituted aralkyl, or unsubstituted or monosubstituted heteroaryl and R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocyclic ring structure with 6 to 12 atoms; or

[0390] provided that the compound is not 3-[(dicyclopropylmethylamino)sulfonyl]-N-(4-isopropoxyphenyl)benzamide; or 3-([2-(1H-benzimidazol-2-yl)propyl]amino)sulfonyl)-N-(4-isopropoxyphenyl)benzamide; or 3-[(cyclohexylamino)sulfonyl]-N-(4-isopropylphenyl)benzamide; or 3-(anilinosulfonyl)-N-(4-isopropylphenyl)benzamide; or 5-[(3-[(4-methoxyphenyl)amino]carbonyl]phenyl)sulfonyl]amino}pentanoic acid; or 3-[(*tert*-butylamino)sulfonyl]-N-(4-methoxyphenyl)benzamide; or (3S)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or (3R)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or 3-(piperidin-1-ylsulfonyl)-N-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide; or N-(5-bromo-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenylpyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenoxypyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-[3-methoxy-5-(phenylthio)pyridin-2-yl]-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(5-ethyl-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-vinylpyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or



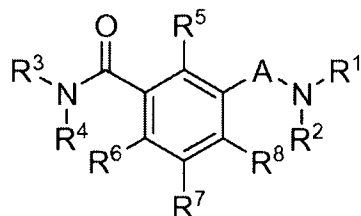
[0391] Some embodiments of the compounds of formula (I) also exclude those compounds when A is SO₂; R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R² and R⁸ taken together with the atoms to which they are bound do not to form an optionally substituted ring, R³ is optionally substituted alkyl, aryl, or alkaryl and N(R¹)(R³) is an optionally substituted piperidine.

[0392] Embodiment 2. The compound of formula (I) wherein:

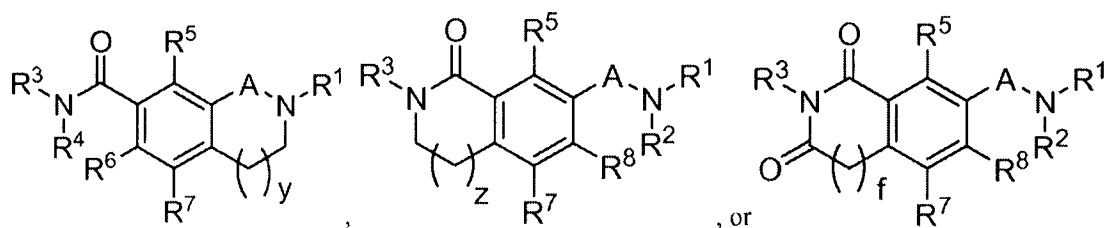
R⁴ and R⁶ taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

R² and R⁸ taken together with the atoms to which they are bound do not to form an optionally substituted ring;

thereby providing a compound having a formula:



[0393] Embodiment 3. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 1, the compound comprising one of the following structures:



wherein, as appropriate:

R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

wherein z and f are independently is 0 or 1, and y is independently 0, 1, or 2.

[0394] Embodiment 4. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 3, wherein A is SO_2 .

[0395] Embodiment 5. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 3, wherein A is CO.

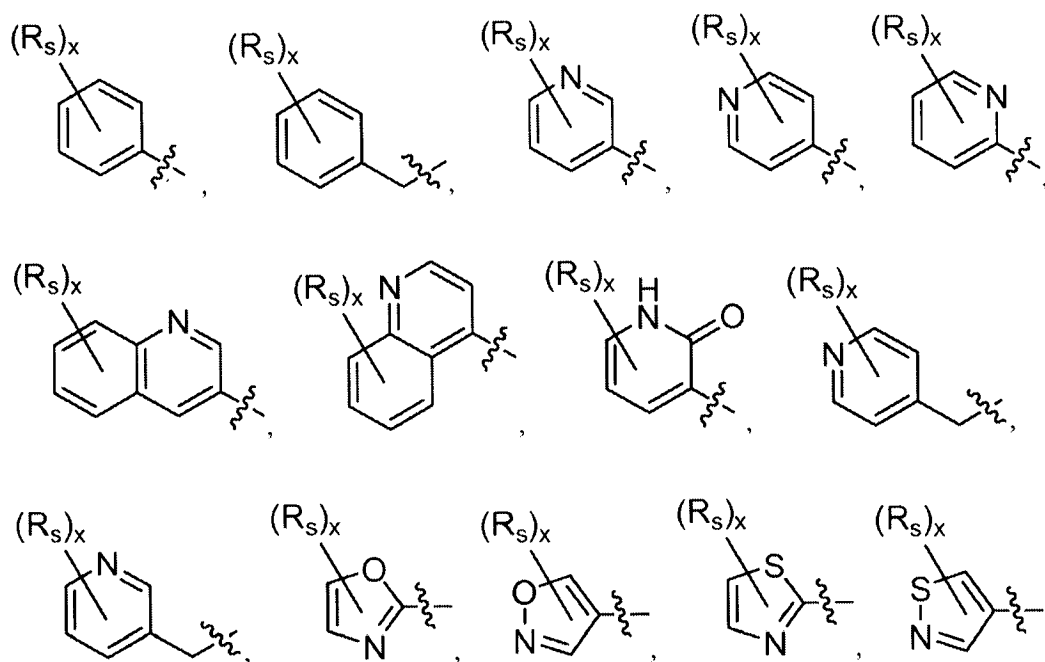
[0396] Embodiment 6. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 5, wherein

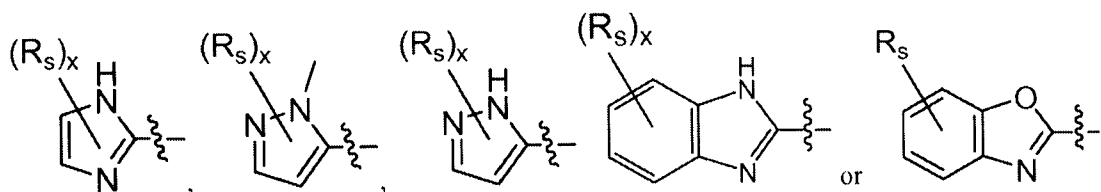
R^3 is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, optionally substituted alkylheteroaryl, and optionally substituted C_{1-6} linear alkyl; and
where present, R^4 is hydrogen.

[0397] Embodiment 7. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 6, wherein

R^3 is selected from a group consisting of optionally substituted phenyl, optionally substituted benzyl, optionally substituted benzoisoxazolyl, optionally substituted benzooxazolyl, optionally substituted furyl, optionally substituted imidazolyl, optionally substituted indoyl, optionally substituted isoxazolyl, optionally substituted isothiazolyl, optionally substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted pyridin-2-on-yl, optionally substituted pyridyl, optionally substituted pyrrolyl, optionally substituted quinolinyl, optionally substituted thiazolyl optionally substituted thienyl, and optionally substituted methylpyridyl.

[0398] Embodiment 8. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 7, wherein R^3 is





wherein

R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C₁₋₆alkyl (e.g., -CH₃, -CH₂F, -CF₂H, -CF₃), -O-(C₁₋₆alkyl), or when two are taken form a fused cyclic or heterocyclic moiety; and

x is 0, 1, 2, or 3; and

where present, R^4 is hydrogen.

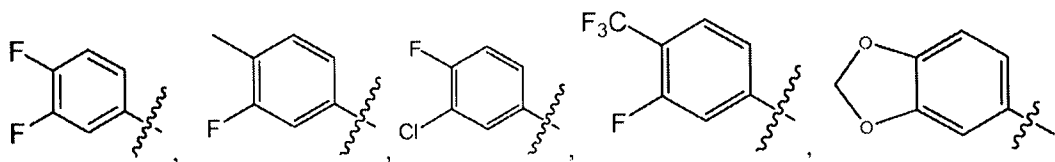
It is appreciated that the designator

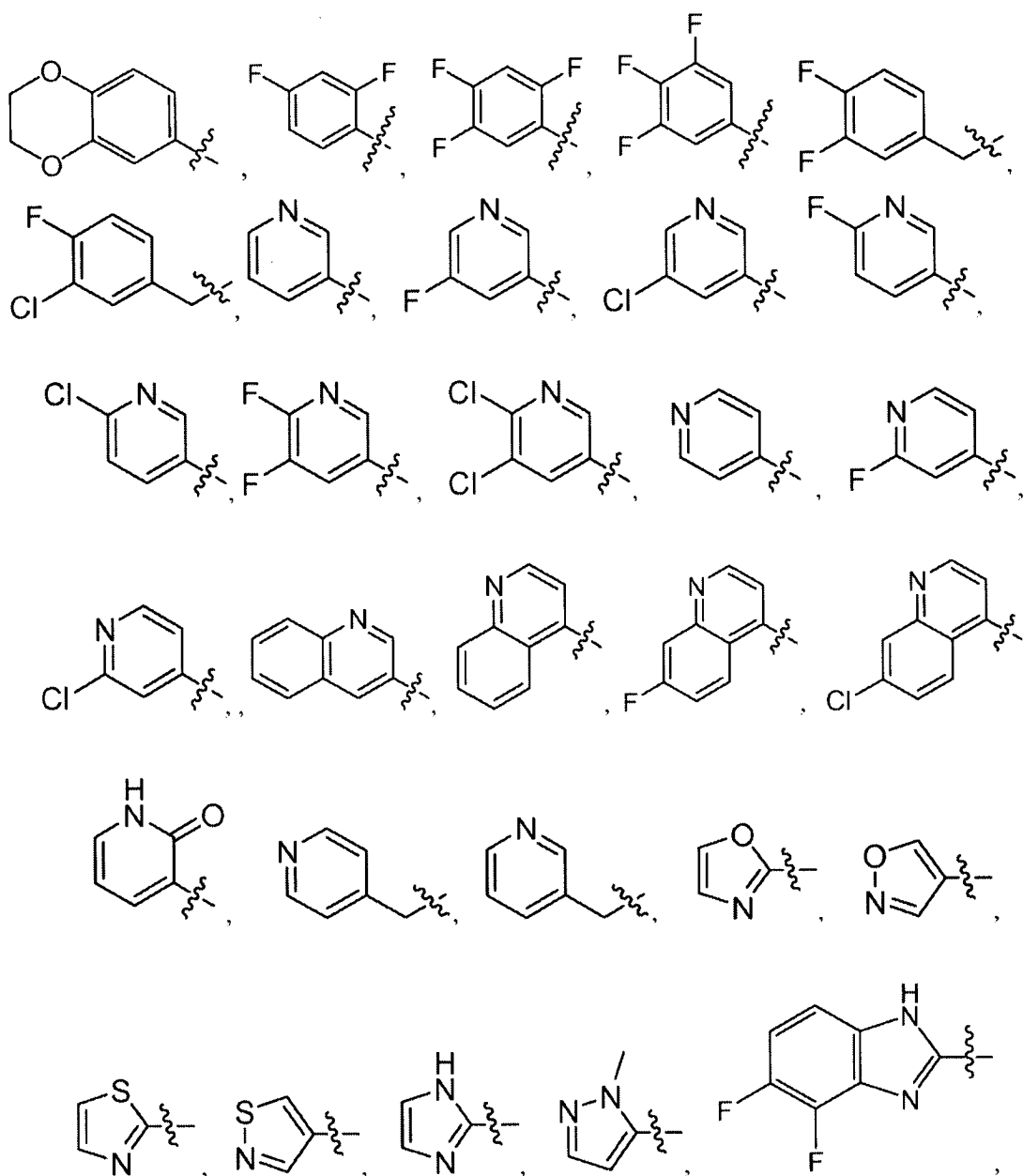
It is appreciated that the designator indicates that the substituent(s) may be present on any available ring member, as valence allows (including alkyl substitution on nitrogen). For fused bicyclic systems, the same designator connote that the substituent(s) may be present on a ring member of either ring, as valence allows.

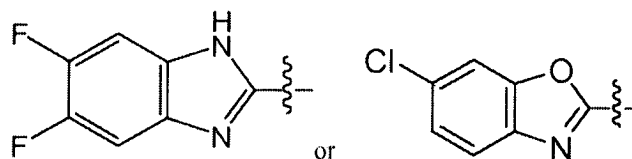
[0399] Embodiment 9. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 7, wherein the optional substitution of R³ comprises at least one halo or C₁₋₆ alkyl.

[0400] Embodiment 10. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 8, wherein the optional substitution of R³ comprises at least one halo.

[0401] Embodiment 11. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of any one of Embodiments 1 to 9, wherein R³ is





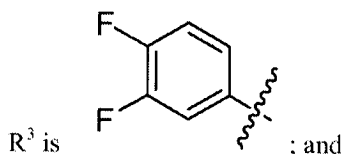


[0402] Embodiment 12. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any of the Embodiments 1 to 10, wherein

R^5 and R^7 are each independently at each occurrence H or F; and

R^6 and R^8 are each independently at each occurrence hydrogen, chloro, fluoro, or C_{1-3} alkyl, or C_{1-3} alkoxy.

[0403] Embodiment 13. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of any one of Embodiments 1 to 11, wherein



where present, R^4 is hydrogen.

[0404] Embodiment 14. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 12, wherein

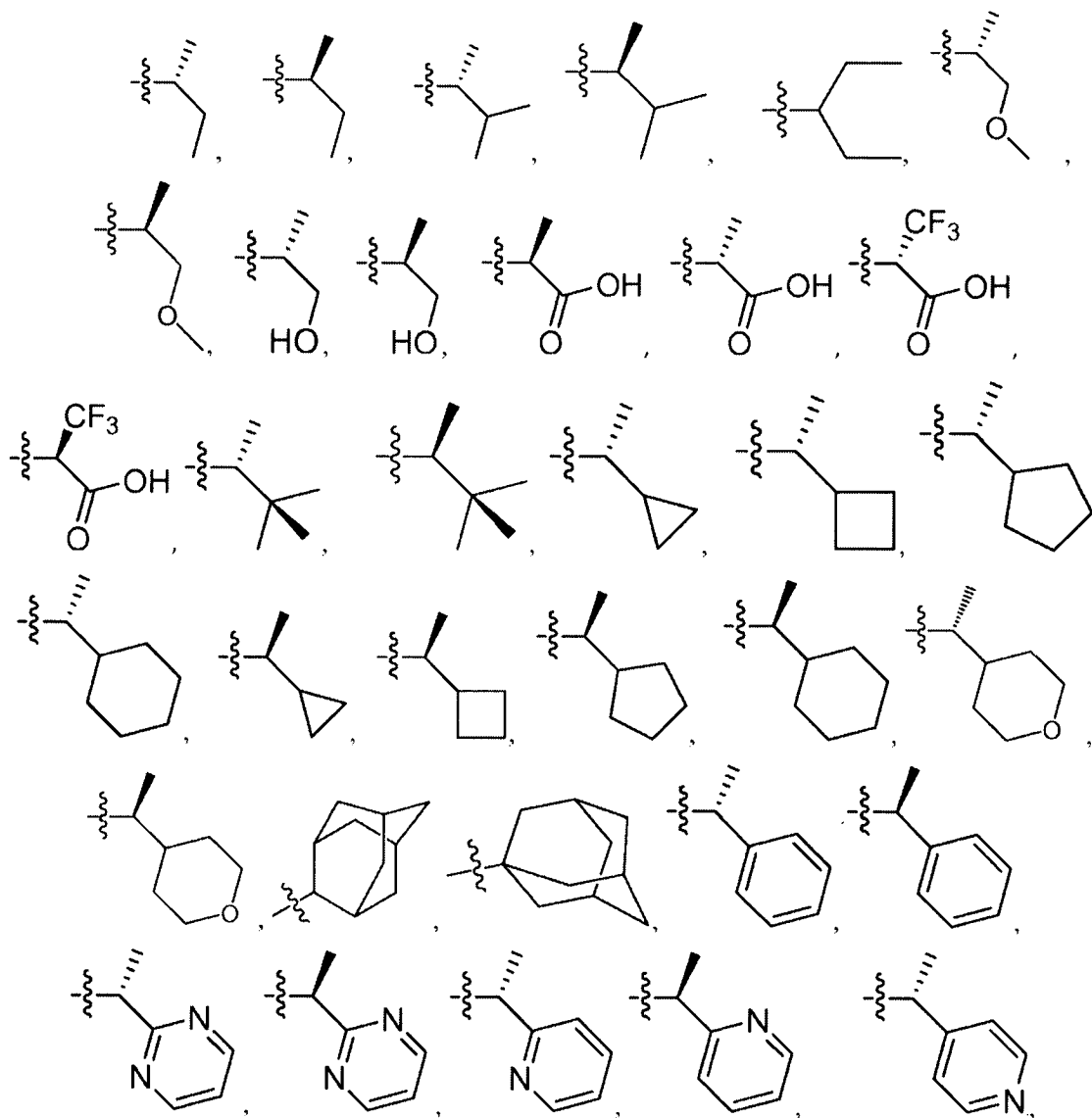
R^5 , R^7 , and R^8 are each H; and

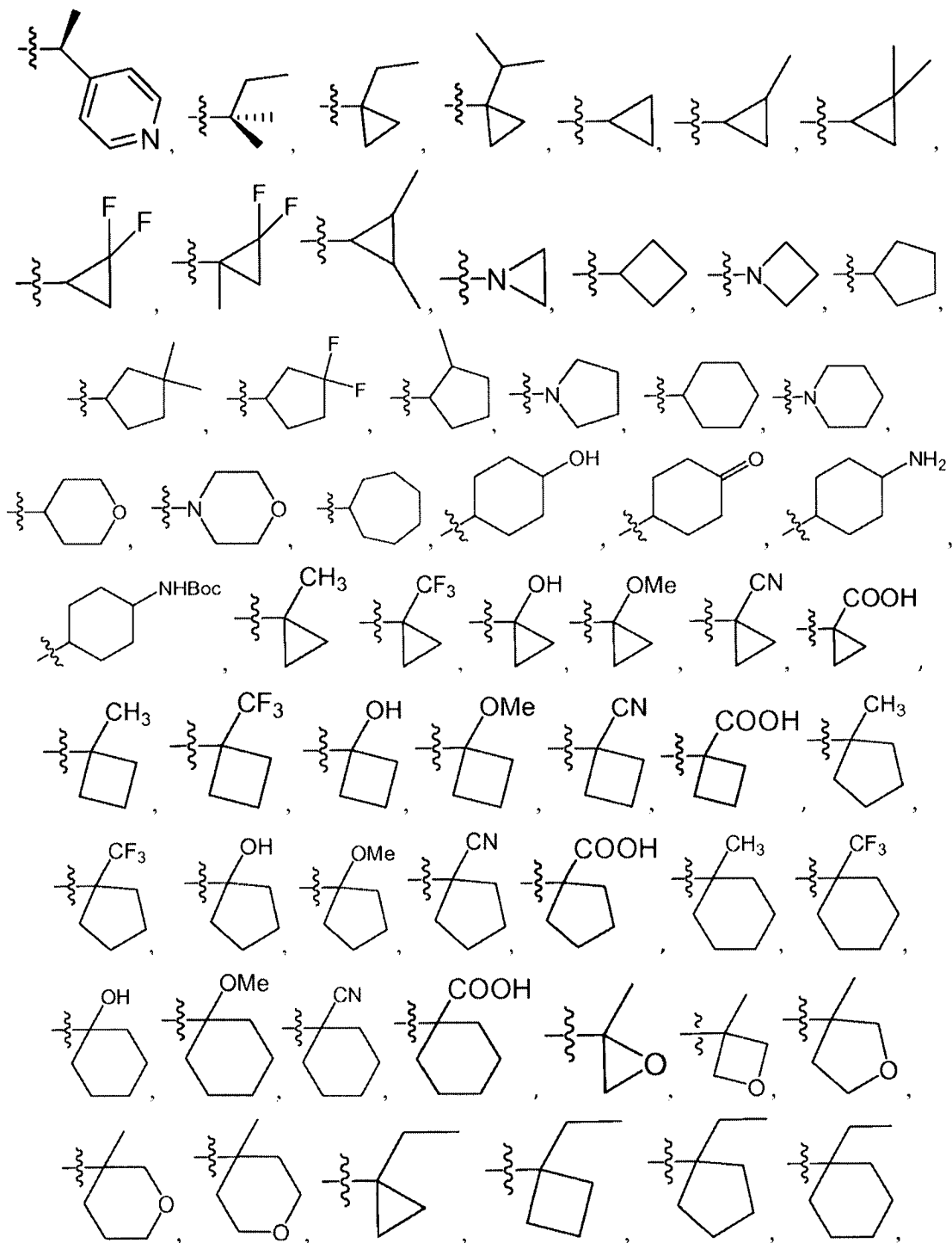
R^6 is hydrogen, chloro, fluoro, or methoxy.

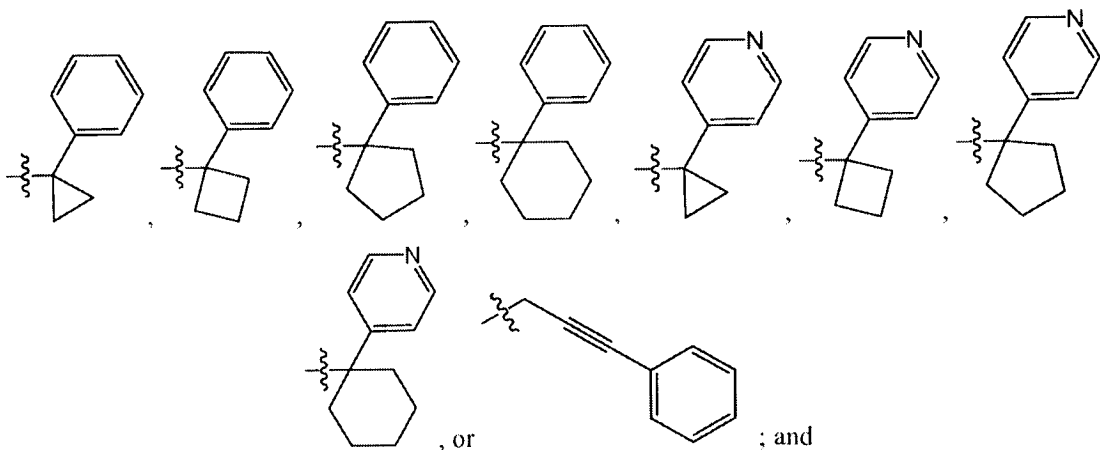
[0405] Embodiment 15. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 13, wherein,

R^1 is methyl, methyl amine (or protected analog thereof), methoxy, ethyl, ethyl amine (or protected analog thereof), ethoxy, n-propyl, propyl amine (or protected analog thereof), n-propoxy, isopropyl, isopropyl amine (or protected analog thereof), isopropoxy, n-butyl, n-butyl amine (or protected analog thereof), n-butoxy, sec-butyl, sec-butyl amine (or protected analog thereof), *sec*-butoxy, *tert*-butyl, *tert*-butyl amine (or protected analog thereof), *tert*-butoxy, vinyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted benzoisoxazolyl, optionally substituted benzoxazolyl, optionally substituted furyl, optionally substituted imidazolyl, optionally substituted indoyl, optionally substituted isoxazolyl, optionally substituted isothiazolyl, optionally

substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted pyridin-2-on-yl, optionally substituted pyridyl, optionally substituted pyrrolyl, optionally substituted quinolinyl, optionally substituted thiazolyl optionally substituted thienyl, and optionally substituted methylpyridyl,

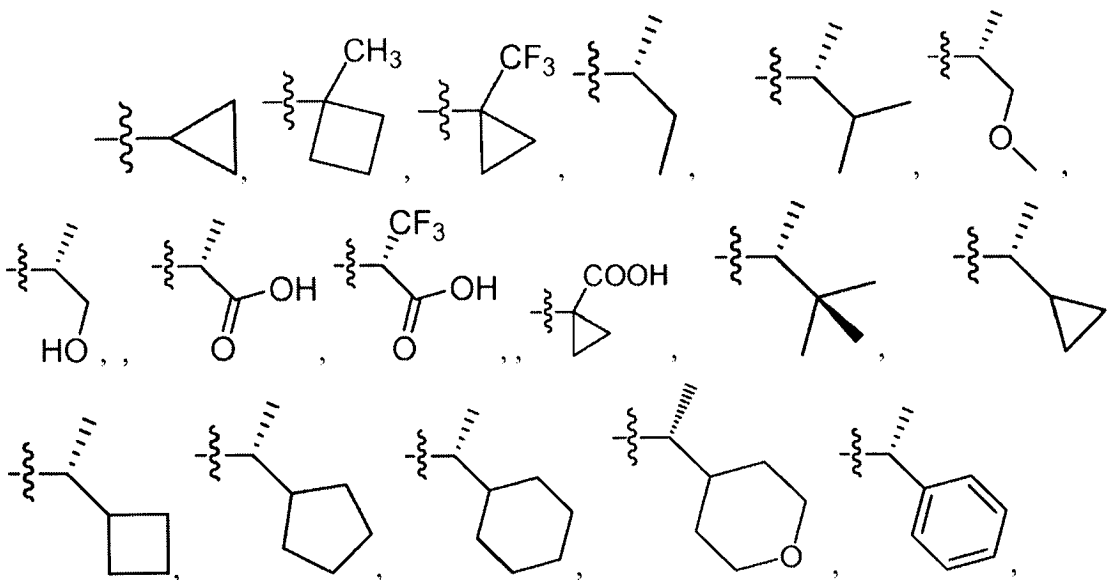


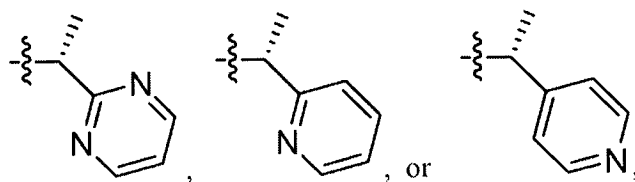




where present, R^2 is H.

[0406] Embodiment 16. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, salt, or hydrate of any one of the Embodiments 1 to 14, wherein R¹ is isopropyl, t-butyl,



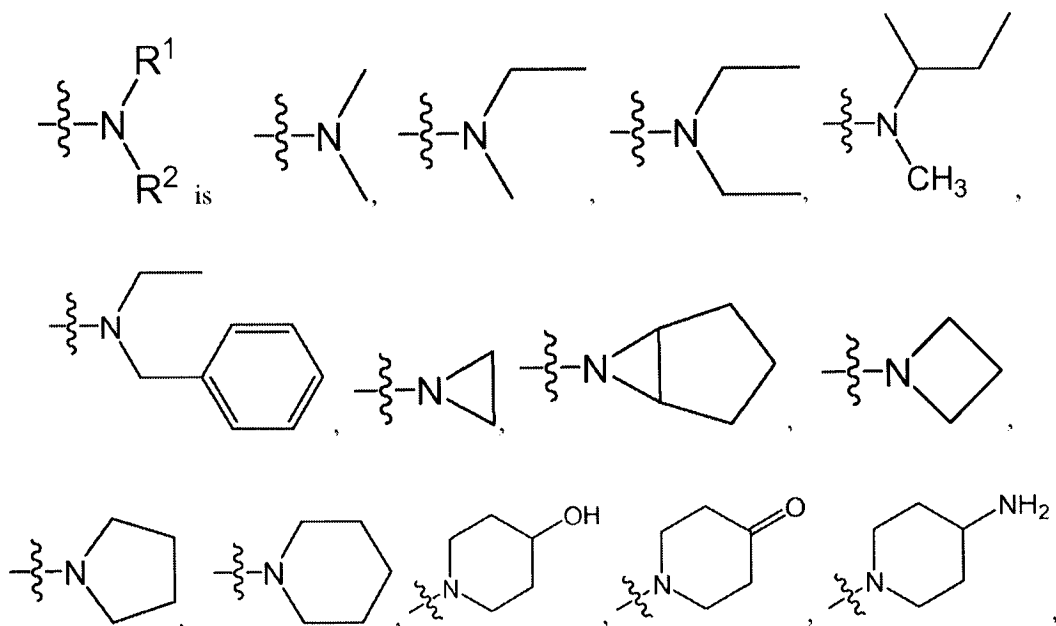


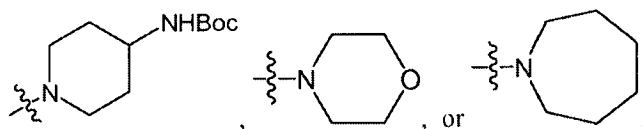
and where present, R^2 is H.

[0407] Embodiment 17. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 15, with the proviso that the -N(R^1)(R^2) moiety does not contain hydroxyl.

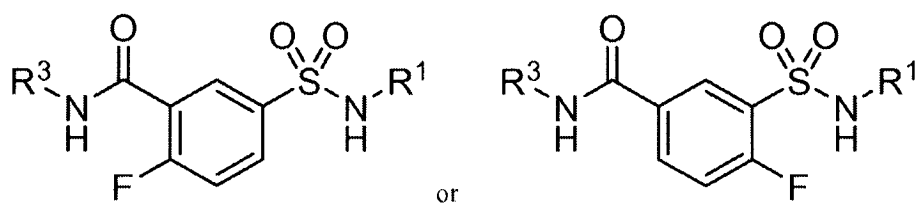
[0408] Embodiment 18. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of Embodiments 1 to 15, with the proviso that R^1 is not cyclopentane

[0409] Embodiment 19. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of any one of the Embodiments 1 to 15, wherein

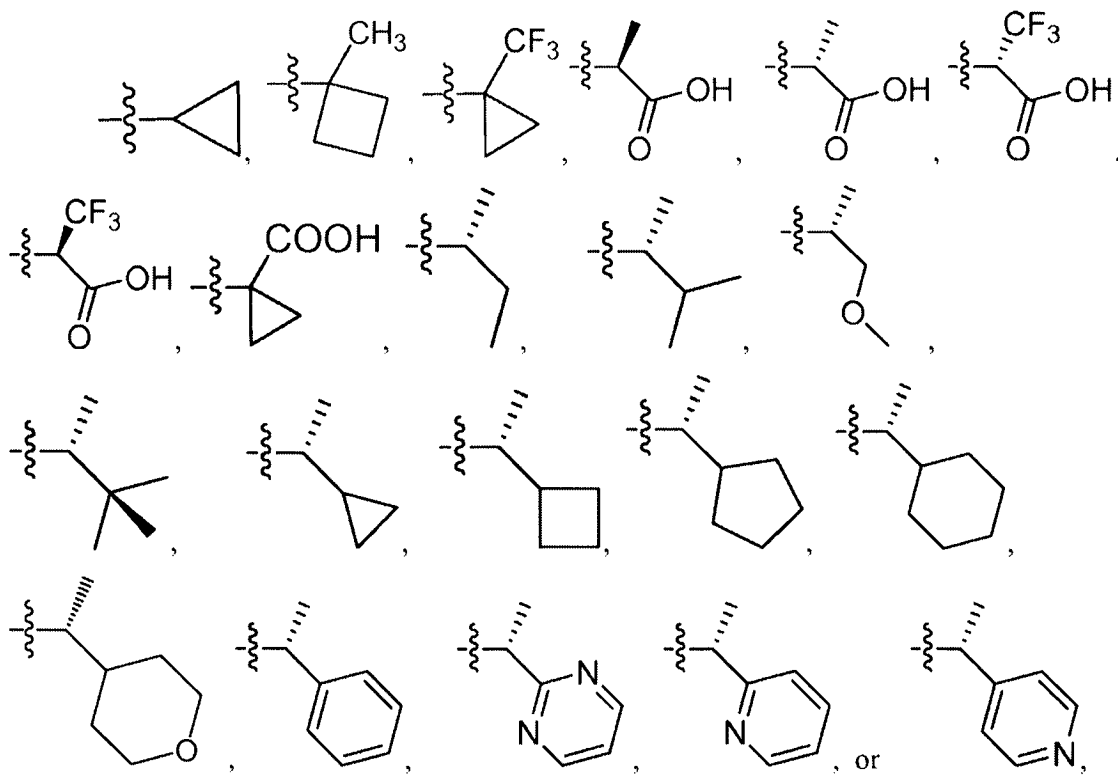




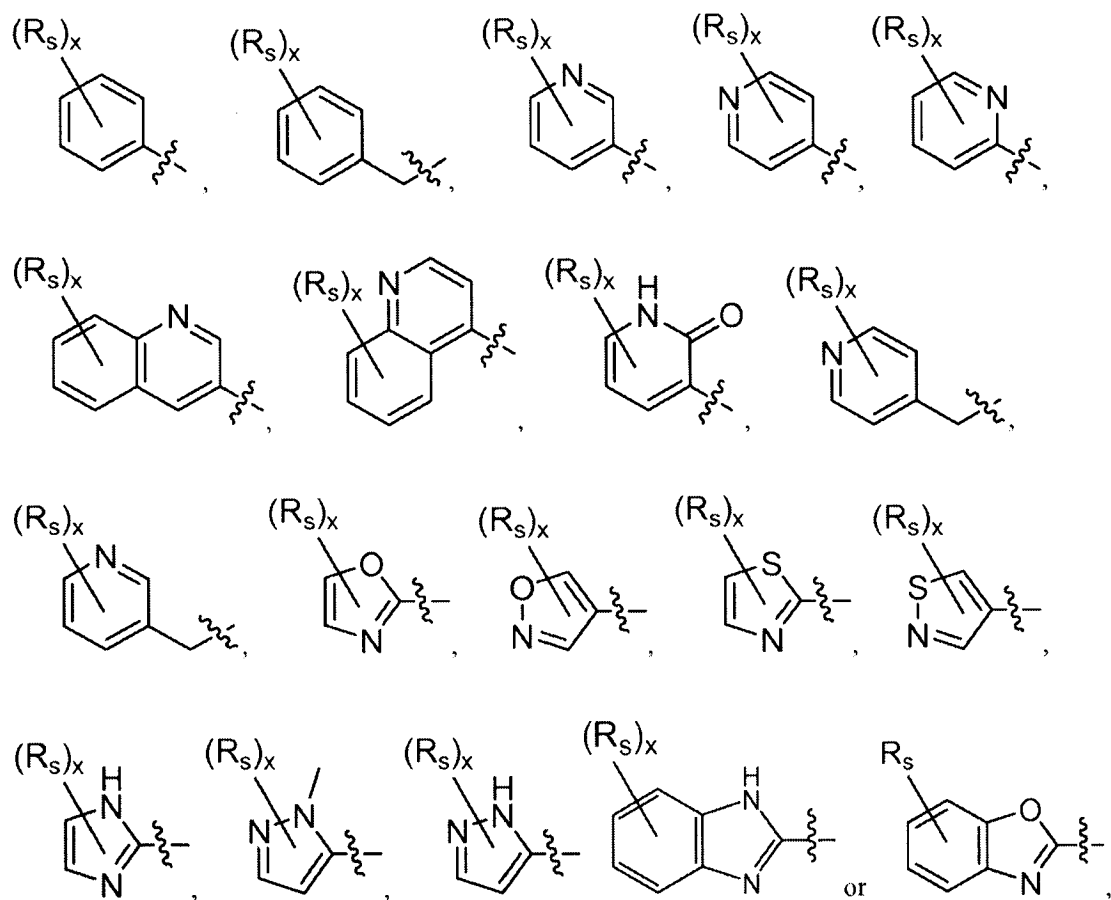
[0410] Embodiment 20. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 1, comprising a structure



wherein R¹ is

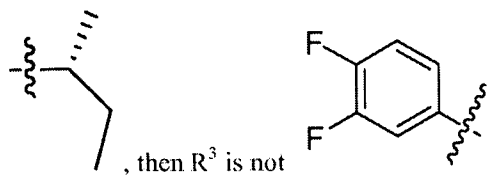


and R^3 is

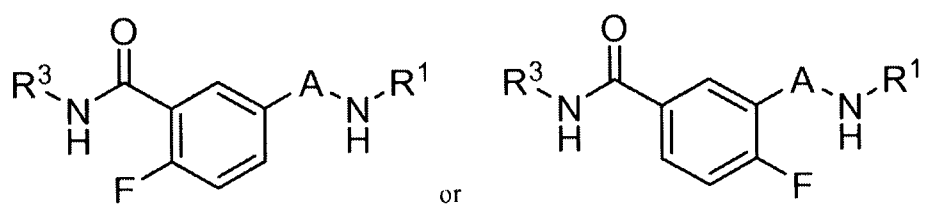


wherein

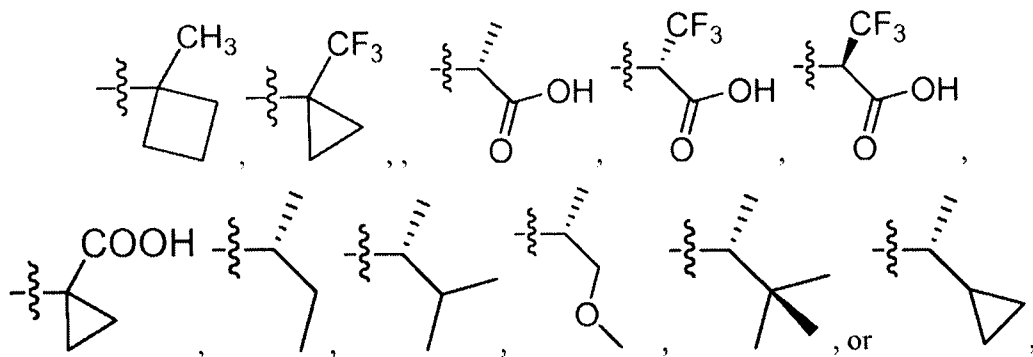
R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl (e.g., $-CH_3$, $-CH_2F$, $-CF_2H$, $-CF_3$), $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3 with the proviso that when R^1 is



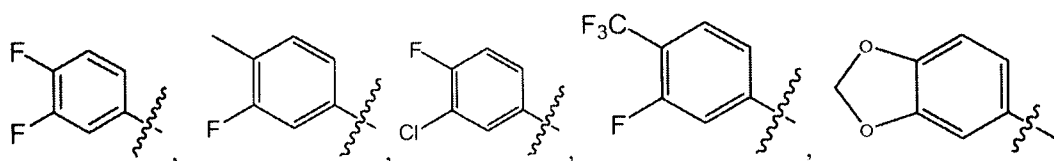
[0411] Embodiment 21. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 20, comprising a structure

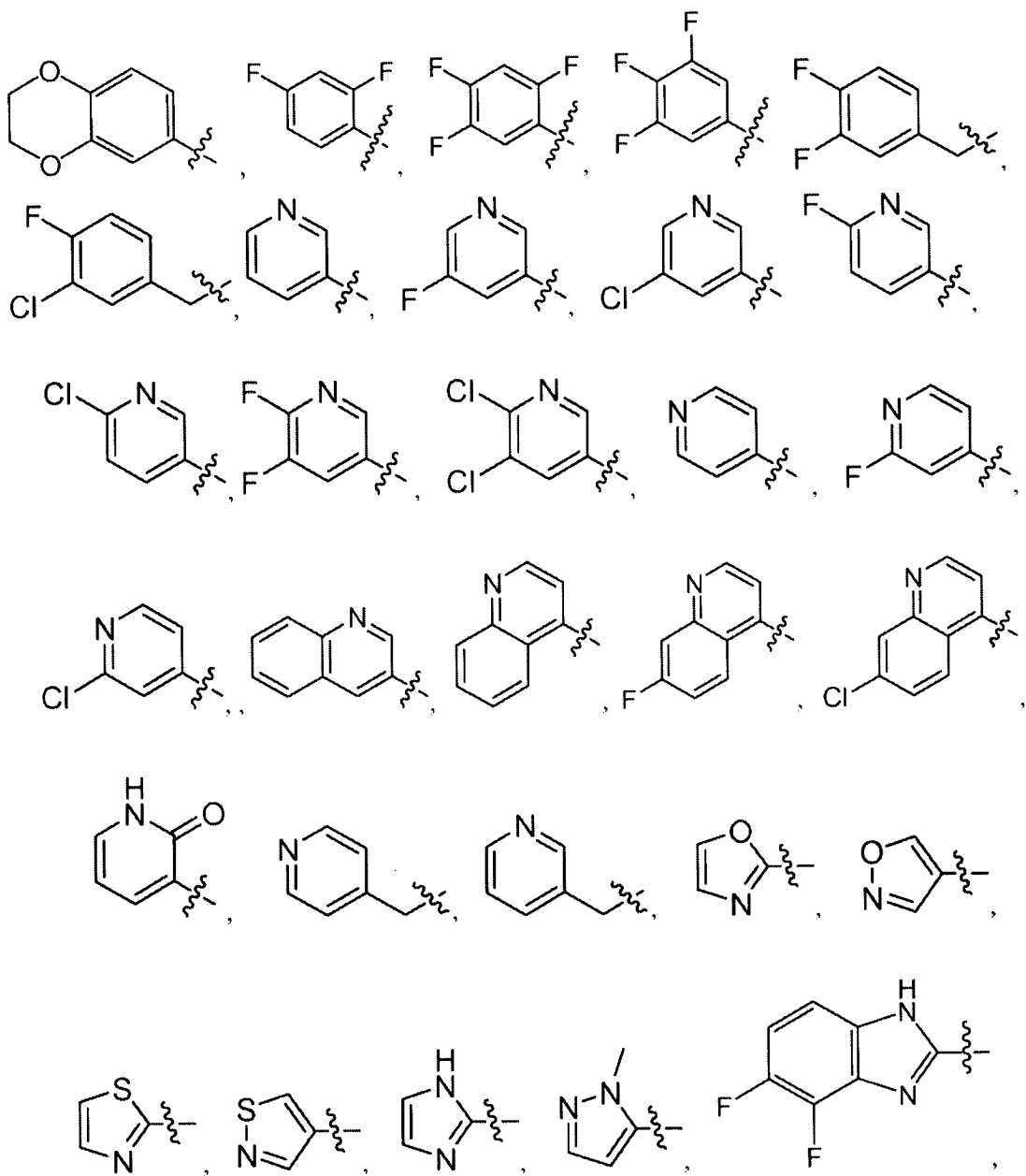


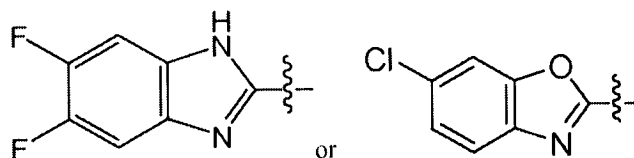
wherein R^1 is isopropyl, *tert*-butyl,



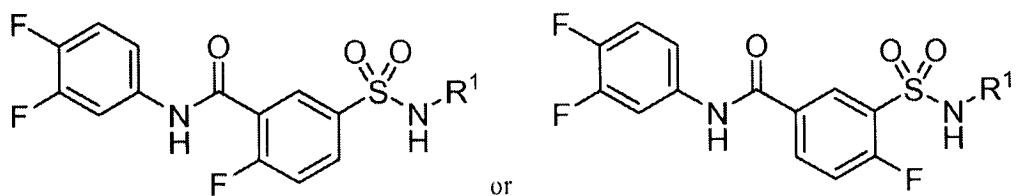
and R^3 is



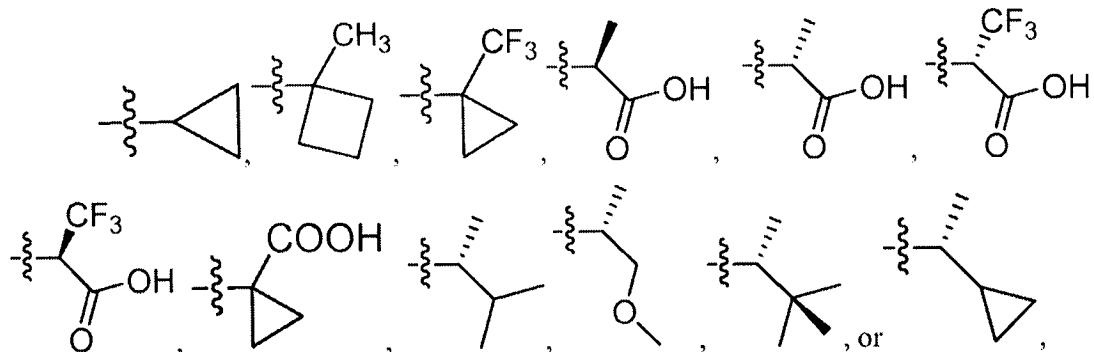




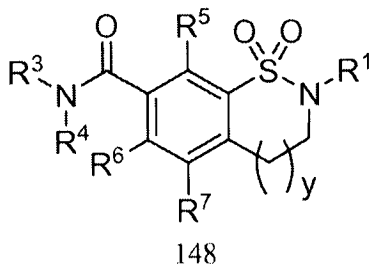
[0412] Embodiment 22. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 1, comprising a structure



wherein R^1 is isopropyl, t-butyl,



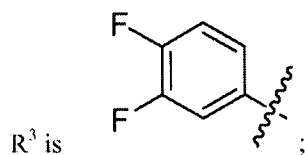
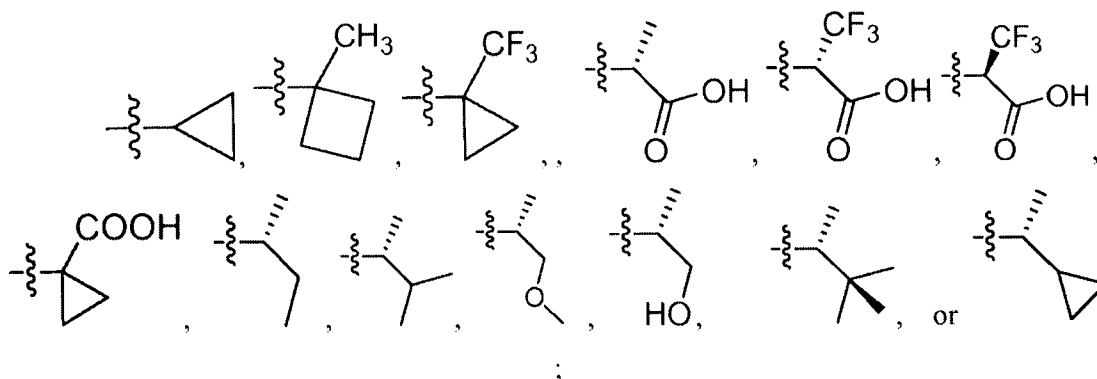
[0413] Embodiment 23. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 2, or any one of Embodiments 5 to 18, the compound comprising a structure:



wherein y is 0, 1, or 2.

[0414] Embodiment 24. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 22, wherein

R¹ is isopropyl, tert-butyl,

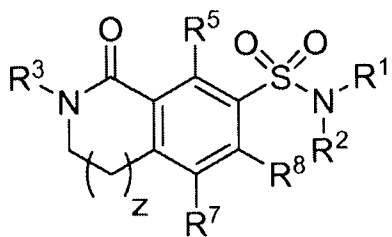


R³ is

R⁴, R⁵, and R⁷ are H; and

R⁶ is H or F.

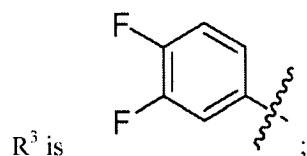
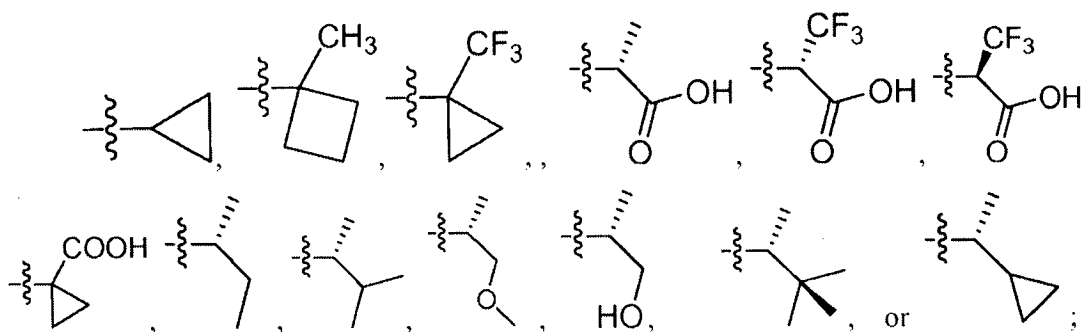
[0415] Embodiment 25. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 2, or any one of Embodiments 5 to 18, the compound comprising a structure:



wherein z is 0 or 1.

[0416] Embodiment 26. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 24, wherein

R^1 is isopropyl, *tert*-butyl,

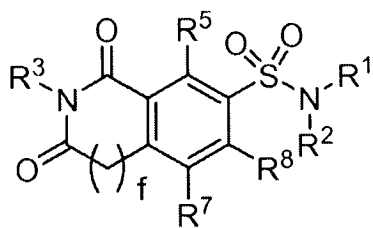


R^3 is

R^5 , and R^7 are H; and

R^8 is H or F.

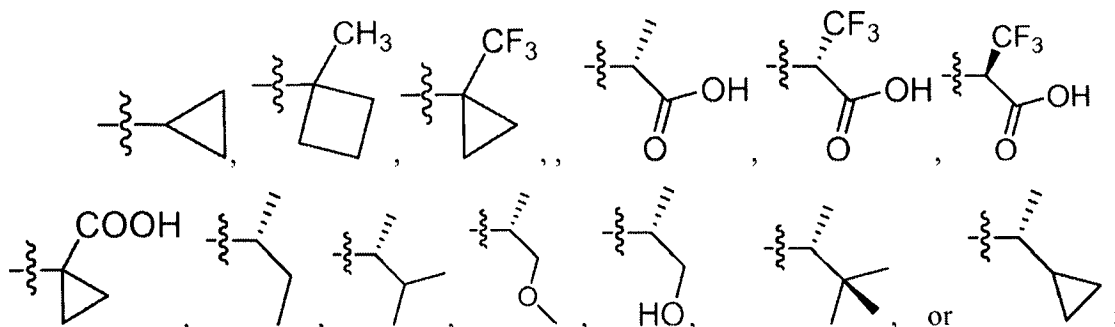
[0417] Embodiment 27. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 2, and any one of Embodiments 5 to 18, the compound comprising a structure:



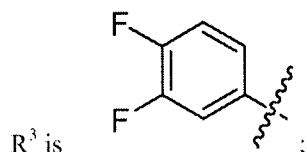
wherein f is 0 or 1.

[0418] Embodiment 28. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 26, wherein

R^1 is isopropyl, *tert*-butyl,



R^2 is H;

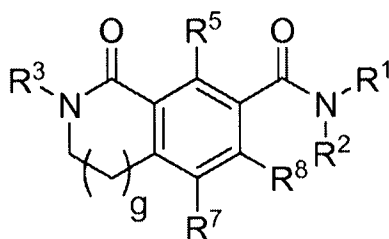


R^3 is

R^5 , and R^7 are H; and

R^8 is H or F.

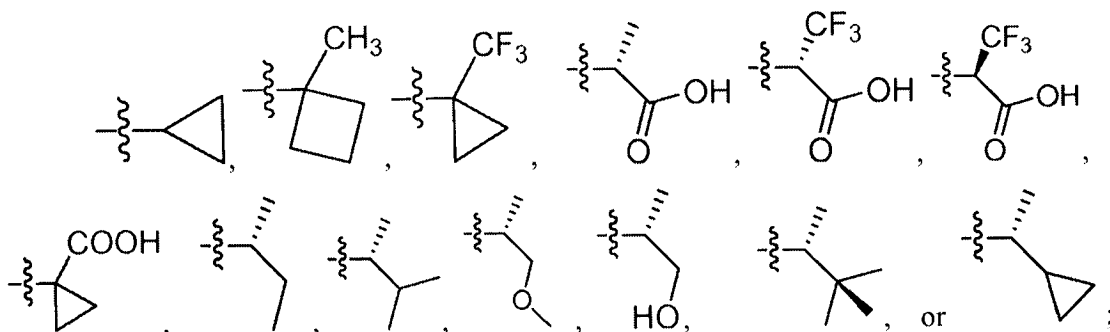
[0419] Embodiment 29. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 3, or any one of Embodiments 6 to 19, the compound comprising a structure:



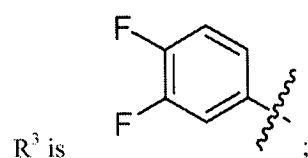
wherein g is 0 or 1.

[0420] Embodiment 30. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 29, wherein

R^1 is isopropyl, tert-butyl,



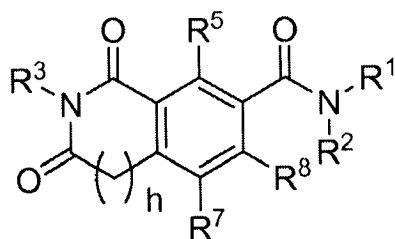
R^2 is H;



R^5 , and R^7 are H; and

R^8 is H or F.

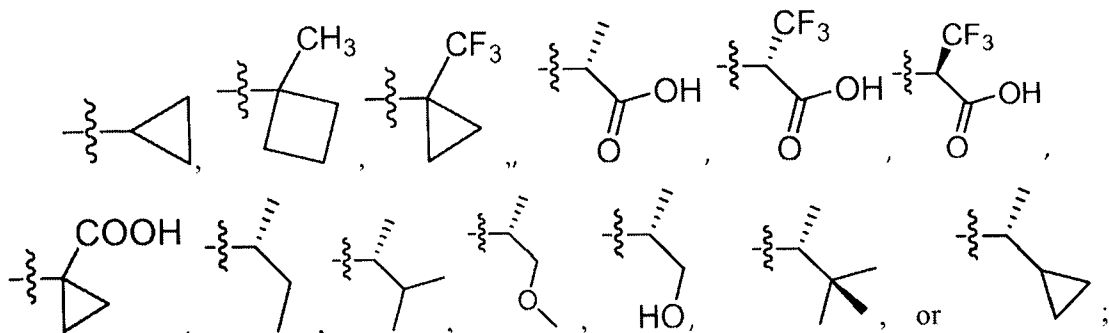
[0421] Embodiment 31. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 3, or any one of Embodiments 6 to 19, the compound comprising a structure:



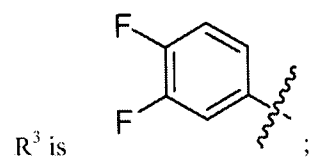
wherein h is 0 or 1.

[0422] Embodiment 32. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 31, wherein

R^1 is isopropyl, tert-butyl,



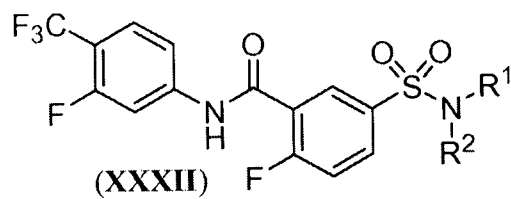
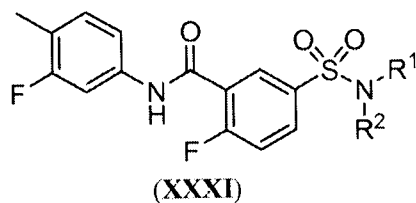
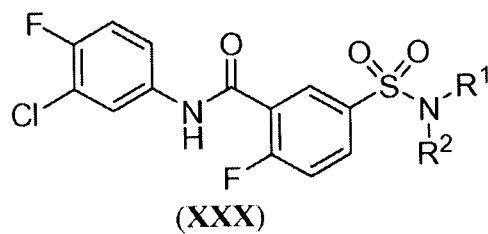
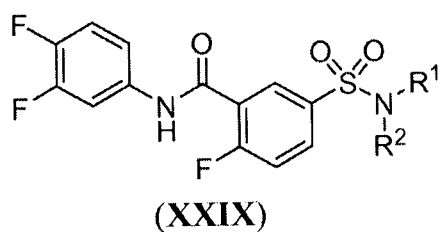
R^2 is H;

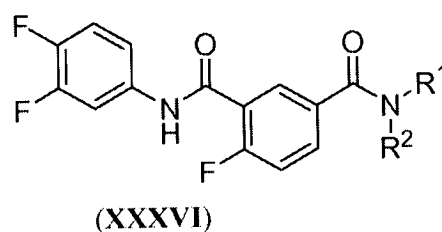
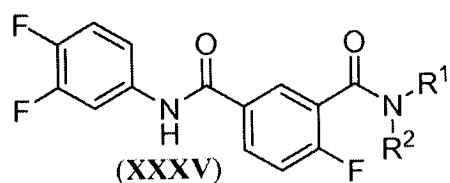
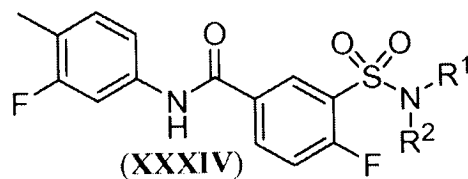
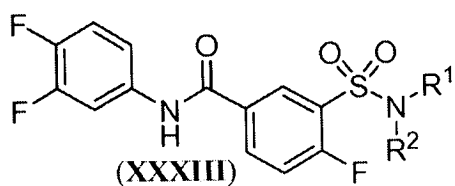


R^5 , and R^7 are H; and

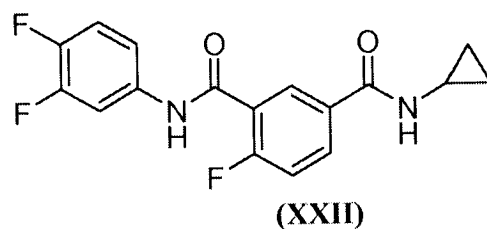
R^8 is H or F.

[0423] Embodiment 33. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of Embodiment 1, the compound comprising a structure of any one of:

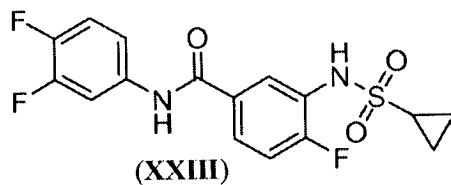




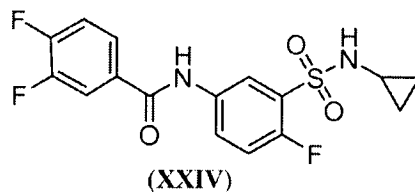
[0424] Embodiment 34. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 1, the compound comprising a structure of Formula (XXII):



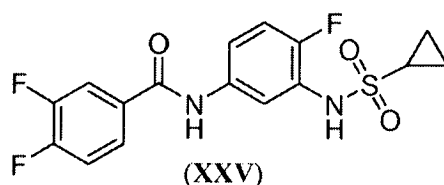
[0425] Embodiment 35. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 1, the compound comprising a structure of Formula (XXIII):



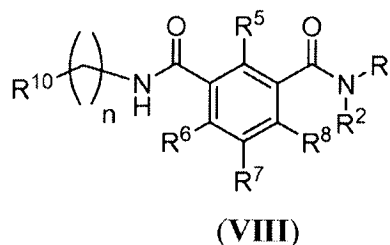
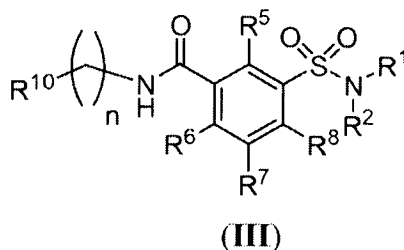
[0426] Embodiment 36. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 1, the compound comprising a structure of Formula (XXIV):



[0427] Embodiment 37. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 1, the compound comprising a structure of Formula (XXV):



[0428] Embodiment 38. A compound comprising a structure of Formula (III) or Formula (VIII), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted C_{1-6} haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy- C_{1-6} -alkoxide, $-SO_2$ - C_{1-6} alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R^2 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl; R^2 may also alternatively or additionally optionally include optionally substituted C_{3-7} cycloalkyl or optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms; and

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

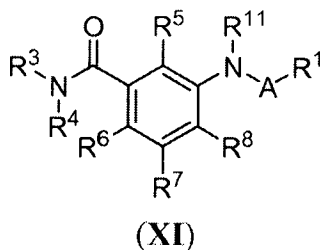
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted ring with 5 to 6 atoms; and

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{1-6} haloalkyl; R^9 may also alternatively or additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and

n is 0 or 1.

[0429] Embodiment 39. A compound comprising a structure of Formula (XI), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted C_{1-6} haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy- C_{1-6} -alkoxide, $-SO_2-C_{1-6}$ alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R^3 is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, optionally substituted alkylheteroaryl, and optionally substituted C_{1-6} linear alkyl;

R^4 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

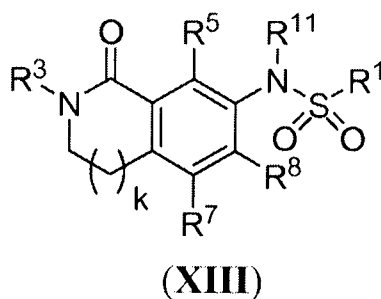
R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl, and optionally substituted C_{1-6} haloalkyl; R^9 may also alternatively or additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

R^{11} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl.

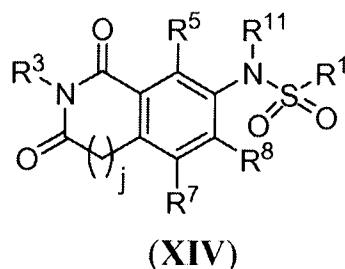
[0430] Embodiment 40. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, wherein A is SO_2 .

[0431] Embodiment 41. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of Formula (XIII):



wherein k is 0 or 1.

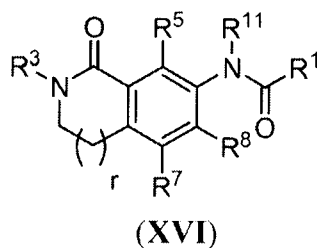
[0432] Embodiment 42. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of Formula (XIV),



where j is 0 or 1.

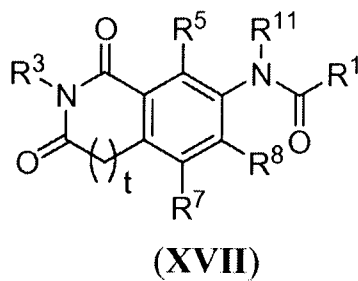
[0433] Embodiment 43. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, wherein A is carbonyl, CO.

[0434] Embodiment 44. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of Formula (XVI):



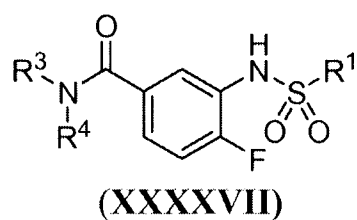
wherein r is 0 or 1.

[0435] Embodiment 45. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of Formula (XVII),

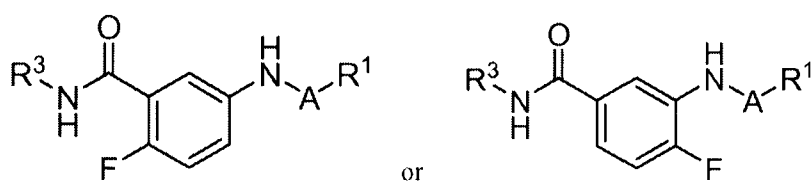


wherein t is 0 or 1.

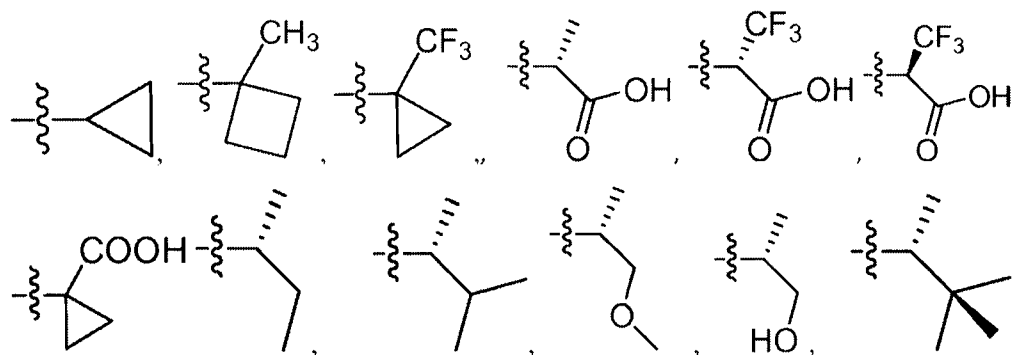
[0436] Embodiment 46. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of Formulae XXXXVII:

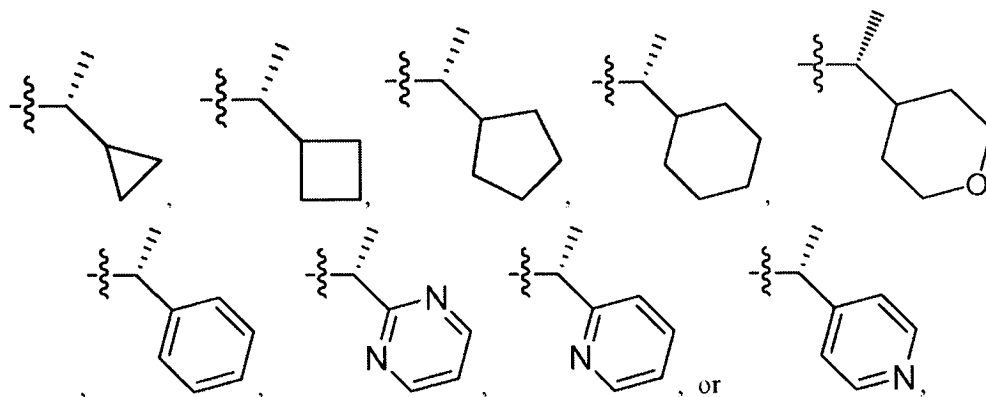


[0437] Embodiment 47. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 39, the compound comprising a structure of

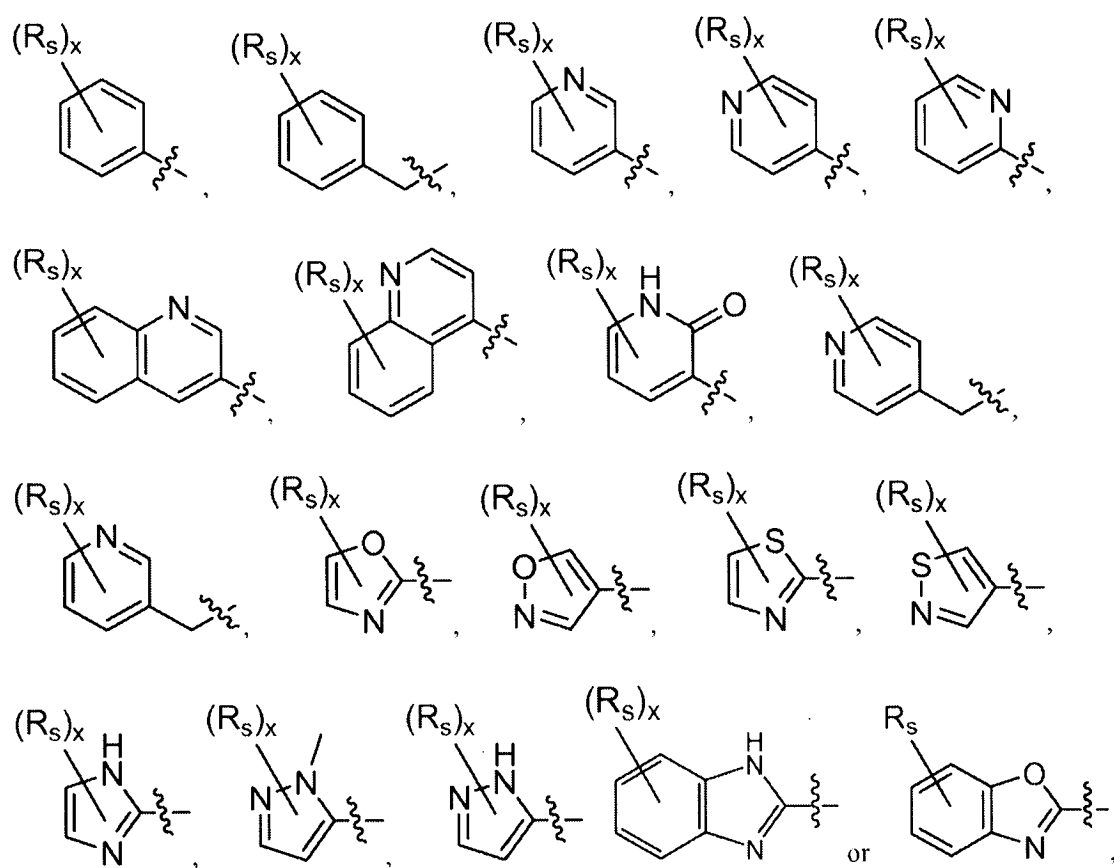


wherein R¹ is isopropyl, t-butyl,



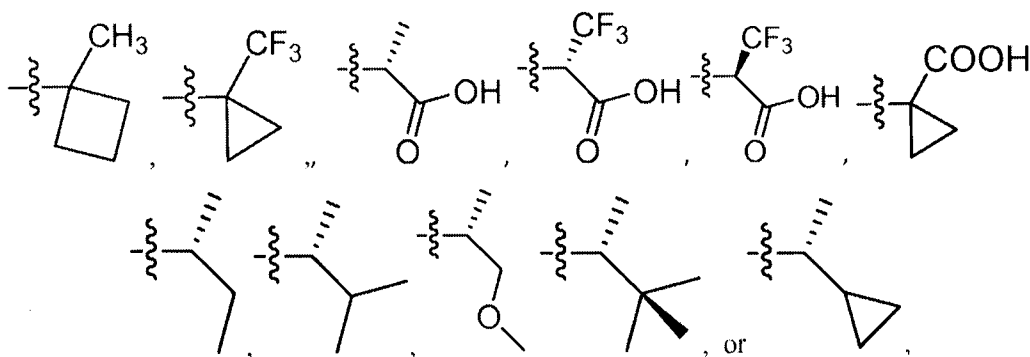


R^3 is

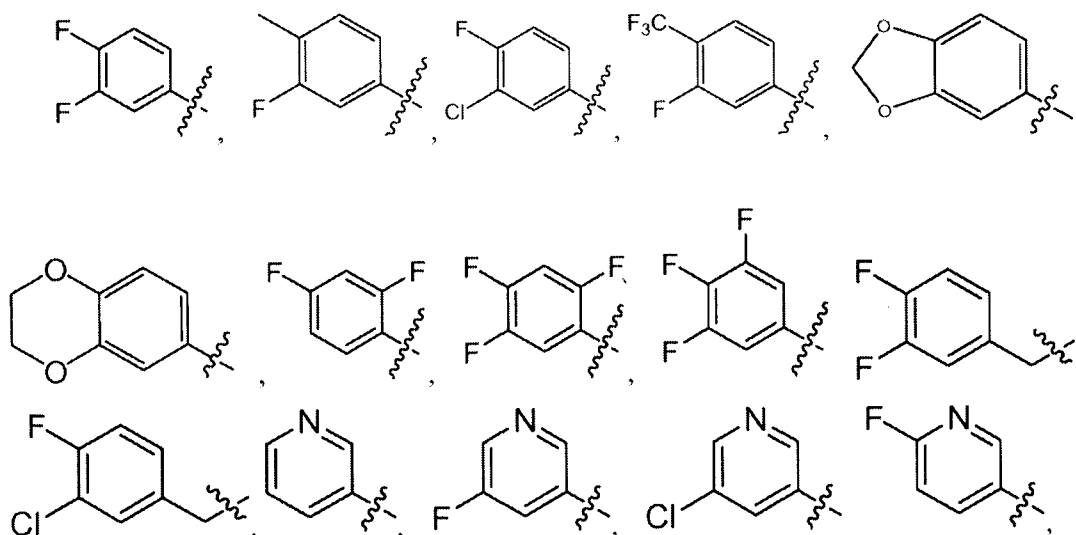


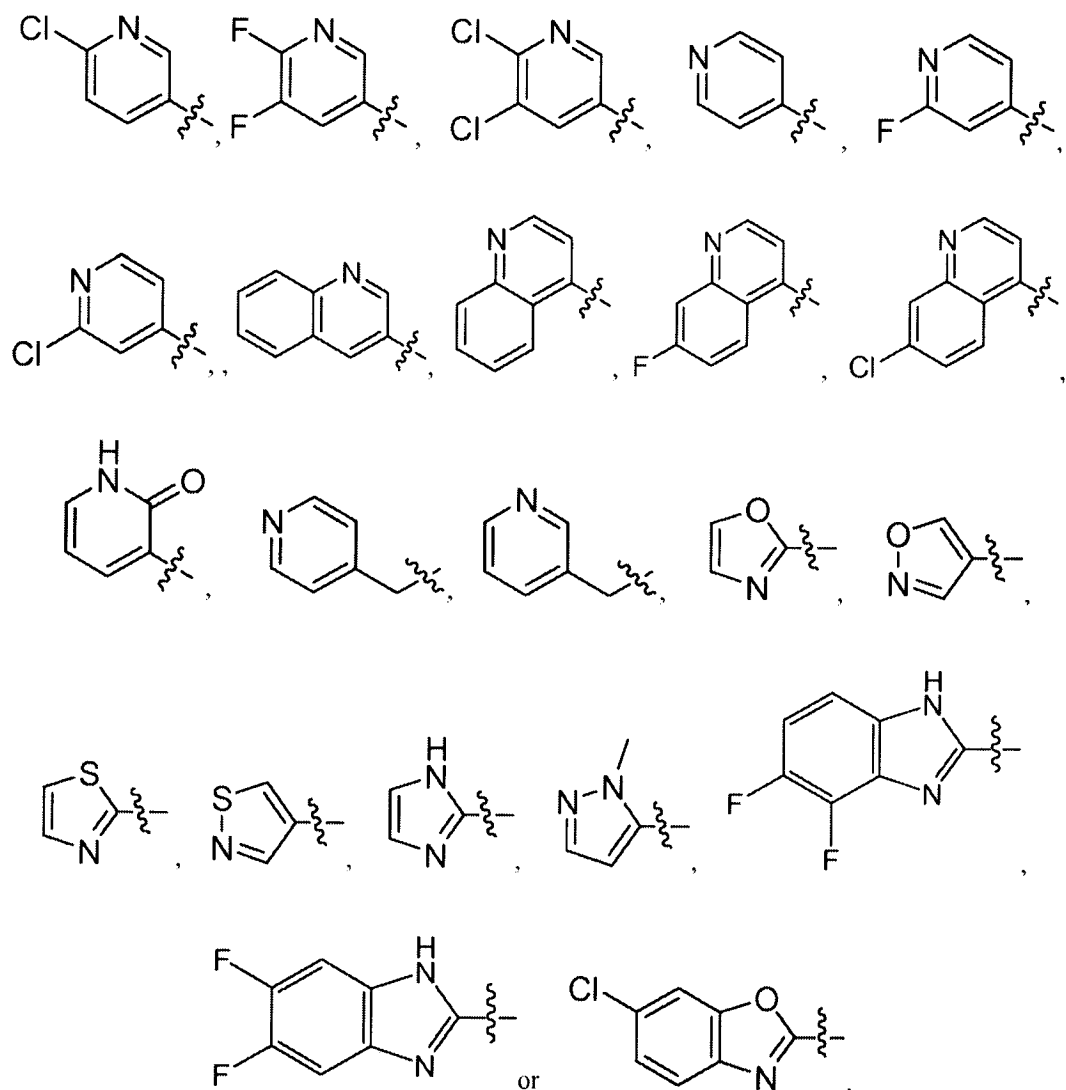
R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl (e.g., $-CH_3$, $-CH_2F$, $-CF_2H$, $-CF_3$), $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

[0438] Embodiment 48. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 47, wherein R^1 is

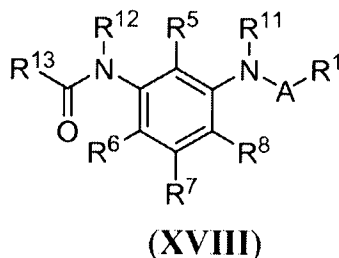


and R^3 is





[0439] Embodiment 49. A compound comprising a structure of Formula (XVIII), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R¹ may also alternatively or additionally optionally include optionally substituted C₁₋₆ haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁵ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁶ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁶ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁷ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁷ may also alternatively or additionally optionally include cyano or N(R⁹)₂;

R⁸ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, and OR⁹; R⁸ may also alternatively or additionally optionally include cyano or N(R⁹)₂; or

R⁹ is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, and optionally substituted C₃₋₇ cycloalkyl, and optionally substituted C₁₋₆ haloalkyl; R⁹ may also alternatively or

additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

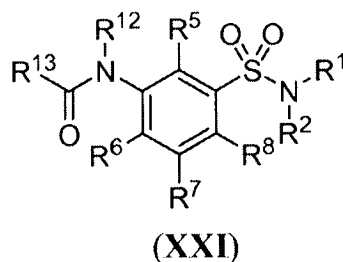
R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

[0440] Embodiment 50. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 49, wherein A is SO_2 .

[0441] Embodiment 51. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 49, wherein A is carbonyl, CO.

[0442] Embodiment 52. A compound comprising a structure of Formula (XXI), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl; R^1 may also alternatively or additionally optionally include optionally substituted C_{1-6} haloalkyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy- C_{1-6} -alkoxide, $-SO_2-C_{1-6}$ alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R^2 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl; R^2 may also alternatively or additionally optionally include optionally substituted C_{3-7} cycloalkyl or optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle (including bicyclic or adamantyl structures) with 3 to 10 atoms;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^5 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^6 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^7 may also alternatively or additionally optionally include cyano or $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, and OR^9 ; R^8 may also alternatively or additionally optionally include cyano or $N(R^9)_2$; or

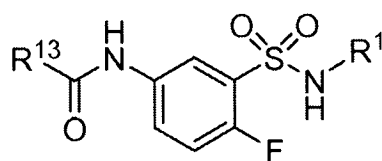
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted ring with 5 to 6 atoms;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; R^9 may also alternatively or additionally optionally include, independently at each occurrence, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

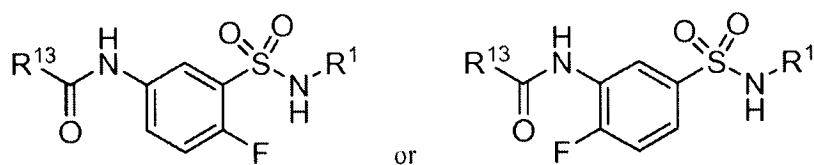
R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

[0443] Embodiment 53. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 52, the compound comprising a structure of Formula XXXXVIII:

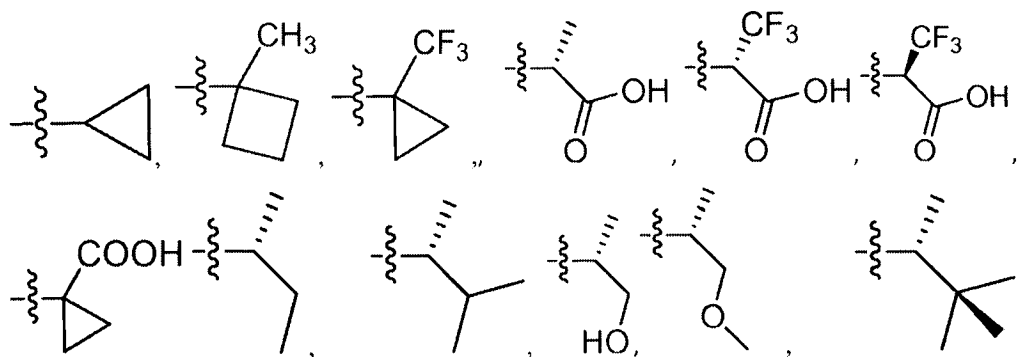


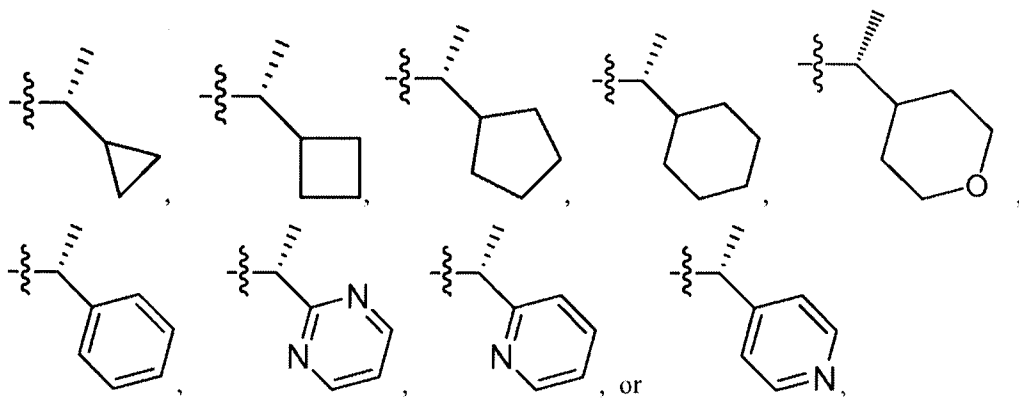
(XXXXVIII)

[0444] Embodiment 54. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 53, the compound comprising a structure of

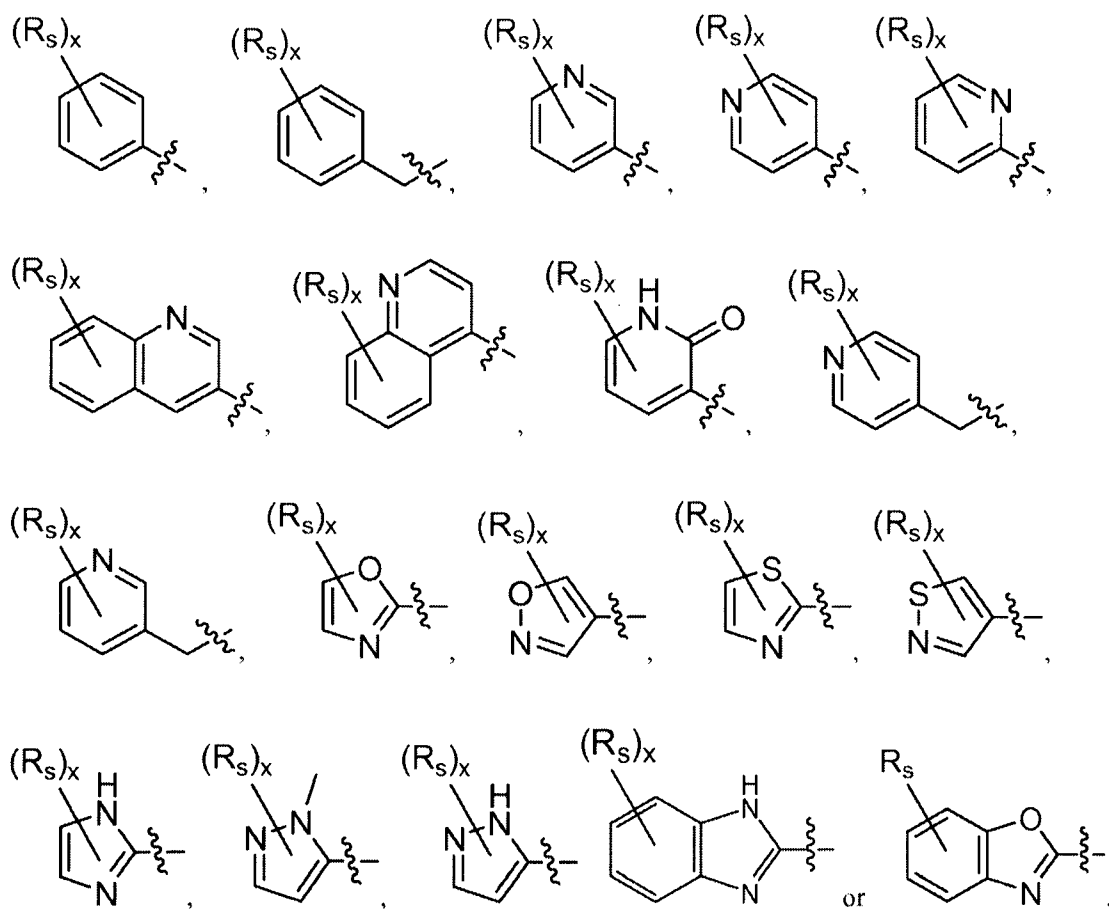


wherein R¹ is isopropyl, t-butyl,



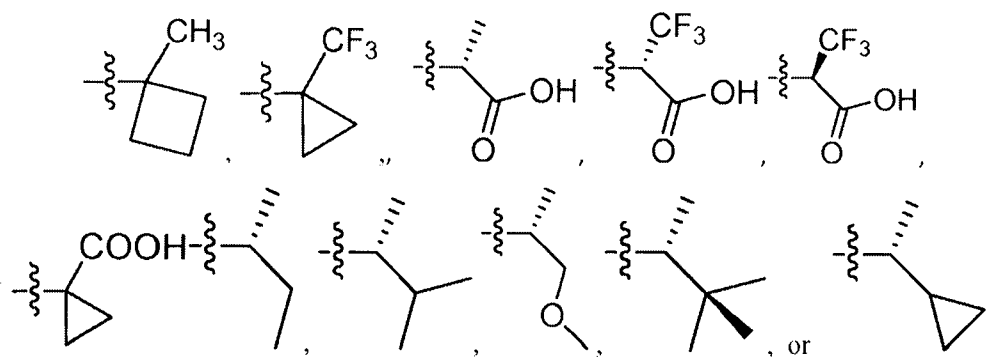


R^{13} is

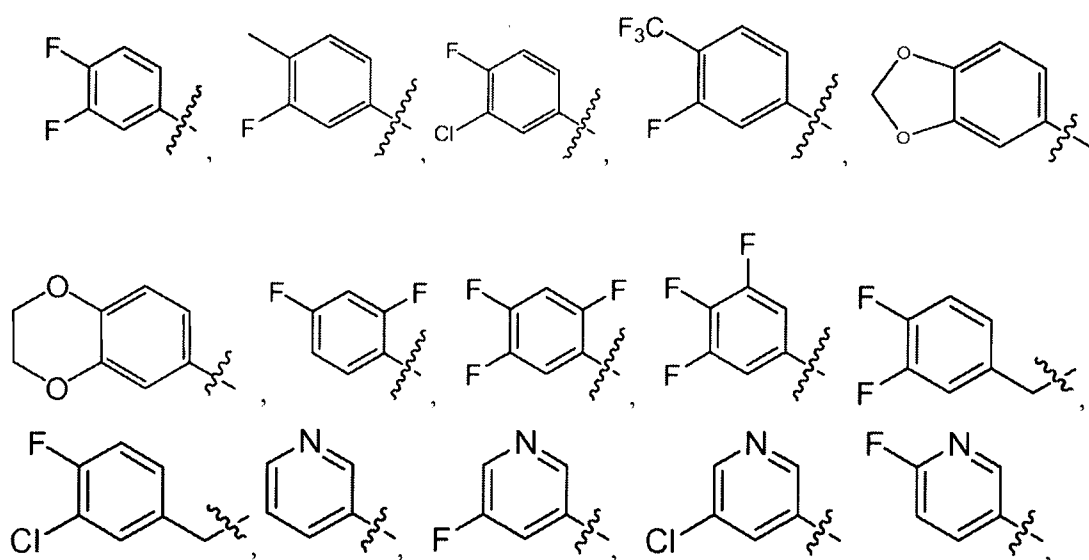


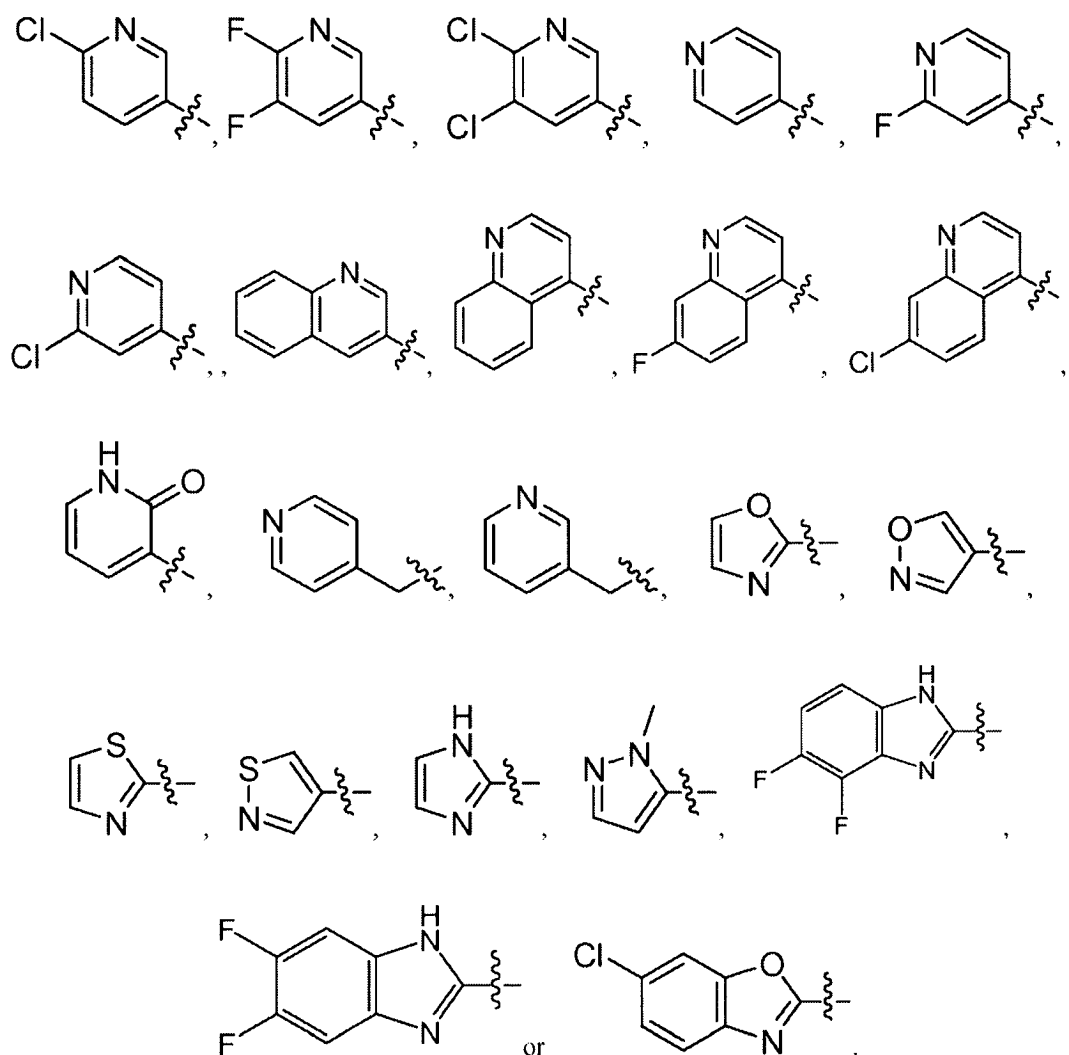
R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl (e.g., $-CH_3$, $-CH_2F$, $-CF_2H$, $-CF_3$), $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

[0445] Embodiment 55. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of Embodiment 54, wherein R^1 is



and R^{13} is





[0446] Embodiment 56. A pharmaceutical composition comprising a compound of any one of Embodiments 1 to 55, or any compound recited within this specification, and a pharmaceutically acceptable excipient.

[0447] Embodiment 57. A method of treating a disease that involves pregenomic RNA encapsidation, said method comprising administering to a patient in need of such treatment an effective amount of at least one compound of any one of Embodiments 1 to 55 or a composition of Embodiment 56.

[0448] Embodiment 58. The method of Embodiment 57, wherein the disease that involves pregenomic RNA encapsidation is a Hepatitis B virus infection.

[0449] Embodiment 59. A method of treating a Hepatitis B viral infection, said method comprising administering to a patient in need of such treatment an effective amount of at least one compound of any one of claim Embodiments 1 to 55 or any individual compound recited in this specification or a composition of Embodiment 56.

[0450] Embodiment 60. The method of Embodiment 59, wherein the treatment controls or ameliorates a condition associated with liver disease, including cirrhosis and hepatocellular carcinoma.

Embodiment 61. A method of repressing viral replication, morphogenesis, or both replication and morphogenesis comprising administering to a patient in need thereof a compound, enantiomer, diastereomer or pharmaceutically accepted salt of any one of Embodiments 1 to 55 or a composition of Embodiment 56.

[0451] Embodiment 62. The method of any one of Embodiments 57 to 61, wherein the compound, or pharmaceutically acceptable salt is administered in combination with one or more additional therapeutic agents.

[0452] Embodiment 63. The method of Embodiment 62, wherein the additional therapeutic agent comprises an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, literature-described capsid assembly modulator, 5 reverse transcriptase inhibitor, a TLR-agonist, or an agents of distinct or unknown mechanism, or a combination thereof.

[0453] Embodiment 64. The method of Embodiment 62, wherein the additional therapeutic agent comprises an immune modulator or immune stimulator therapy, comprising a biological agent belonging to the interferon class, such as interferon alpha 2a or 2b or modified interferons such as pegylated interferon, alpha 2a, alpha 2b, lamda; or TLR modulators such as TLR-7 agonists or TLR-9 agonists, or antiviral agents that block viral entry or maturation or target the HBV polymerase such as nucleoside or nucleotide or non-nucleos(t)ide polymerase inhibitors, and agents of distinct or unknown mechanism including agents that disrupt the function of other essential viral protein(s) or host proteins required for HB V replication or persistence.

[0454] Embodiment 65. The method of Embodiment 62, wherein the reverse transcriptase inhibitor comprises at least one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

[0455] Embodiment 66. The method of Embodiment 62, wherein the the TLR- agonist comprises SM360320 (9-benzyl-8-hydroxy-2-(2-methoxyethoxy) adenine) or AZD 8848 (methyl [3-({ [3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl] [3 -(4-morpholinyl)propyl]amino} methyl)phenyl]acetate).

[0456] Embodiment 67. The method of any one of Embodiments 60 to 66, wherein the compound, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are co-formulated, co-administered, or both co-formulated and co-administered.

[0457] Embodiment 68. The method of any one of Embodiments 60 to 64, wherein the compound, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are separately formulated, separately administered, or both separately formulated and separately administered.

[0458] Embodiment 69. The method of any one of Embodiments 57 to 68, wherein administering the compound, or pharmaceutically acceptable salt of the present invention allows for administering of the additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

[0459] Embodiment 70. The method of any one of Embodiments 57 to 69, wherein, before administering the therapeutically effective amount of the compound, or pharmaceutically acceptable salt, the patient is known to be refractory to an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, an antiviral compound of distinct or unknown mechanism, or a combination thereof.

[0460] Embodiment 71. The method of any one of Embodiments 57 to 70, wherein administering a compound, or pharmaceutically acceptable salt reduces viral load in the individual to a greater extent compared to the administering of a a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, an antiviral compound of distinct or unknown mechanism, or a combination thereof.

EXAMPLES

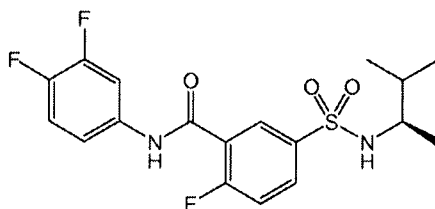
[0461] The following Examples are provided to illustrate some of the concepts described within this disclosure. While each Example is considered to provide specific individual embodiments of composition, methods of preparation and use, none of the Examples should be considered to limit the more general embodiments described herein.

[0462] In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C, pressure is at or near atmospheric.

[0463] The examples below provide non-limiting methods for preparing representative compounds of the disclosure. The skilled practitioner will know how to substitute the appropriate reagents, starting materials and purification methods known to those skilled in the art, in order to prepare additional compounds of the present invention.

[0464] ¹H NMR spectra were recorded on a 300 MHz INOVA VARIAN spectrometer. Chemical shifts values are given in ppm and referred as the internal standard to TMS (tetramethylsilane). The peak patterns are indicated as follows: b, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; qint, quintet; m, multiplet; dd, doublet of doublets; and dt, doublet of triplets. The coupling constants (*J*) are reported in Hertz (Hz). Mass Spectra were obtained on a 1200 Agilent LC-MS spectrometer (ES-API, Positive). Silica gel column chromatography was performed over silica gel 100-200 mesh, and the eluent was a mixture of ethyl acetate and hexanes, or a mixture of methanol and dichloromethane. Analytical HPLC was run on the Agilent 1100 HPLC instrument, equipped with Agilent, ZORBAX SB-C18 column and UV detection at 210 nm.

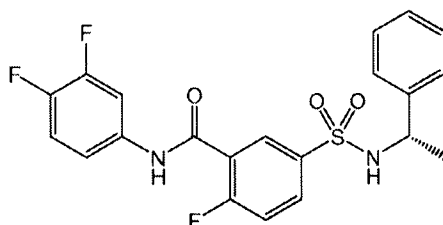
[0465] **Example 1: General Procedure A**



[0466] **(R)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(3-methylbutan-2-yl)sulfamoyl)benzamide:** To a 0°C solution of 5-chlorosulfonyl-2-fluorobenzoic acid (150 mg, 0.62

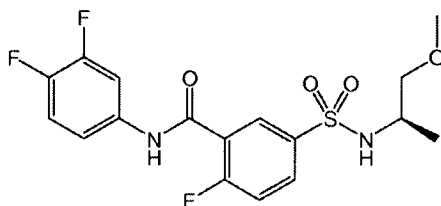
mmol) in THF (3 mL) was added NEt₃ (125 mg, 1.24 mmol) and (R)-(-)-2-amino-3-methylbutane (54 mg, 0.62 mmol). The reaction was warmed to 20°C, and was stirred for 20 minutes. The mixture was concentrated, and the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The material was used without further purification.

[0467] To the material from the previous step was added thionyl chloride (2 mL), and this mixture was heated at reflux for 2 hours. The mixture was concentrated, and the residue was treated with THF (1 mL). This solution was added to a 0 °C solution of NEt₃ (144 mg, 1.43 mmol) and 3,4-difluoroaniline (60 mg, 0.48 mmol) in THF (3 mL). The reaction was warmed to 20 °C, and was stirred for 16 hours. The mixture was concentrated, and the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (10 mL), water (10 mL), dilute NaHCO₃ (10 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (20 -50% EtOAc/ Hexane) to give the desired product (44 mg, 18% over 3 steps) as an off-white solid. MS: M+H⁺ 401. ¹H NMR (300 MHz, MeOH-d₄): δ 8.23-8.20 (m, 1H), 8.07-8.04 (m, 1H), 7.85-7.77 (m, 1H), 7.47-7.35 (m, 2H), 7.26 (q, *J* = 9.0 Hz, 1H), 3.15-3.12 (m, 1H), 1.65-1.59 (m, 1H), 0.90-0.82 (m, 6H).

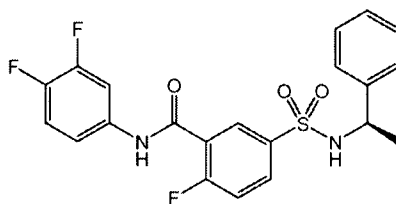


[0468] (S)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-phenylethyl)sulfamoyl)benzamide:

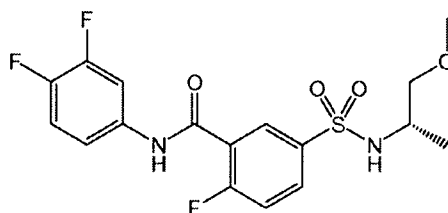
General procedure A was followed using (S)-(+)-1-methyl-benzylamine (75 mg, 0.62 mmol) to give the desired product (106 mg, 39% over 3 steps) as an off-white solid. MS: M+H⁺ 435. ¹H NMR (300 MHz, CDCl₃): δ 8.41 (dd, *J* = 2.6, 7.6 Hz, 1H), 8.25 (d, *J* = 14.0 Hz, 1H), 7.78-7.71 m, 2H), 7.20-7.05 (m, 9H), 5.11 (d, *J* = 7.3 Hz, 1H), 4.56 (dq, *J* = 6.7, 7.0 Hz, 1H), 1.47 (d, *J* = 6.7 Hz, 3H).



[0469] (R)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-methoxypropan-2-yl)sulfamoyl)benzamide: General procedure A was followed using (R)-(-)-1-methoxy-2-aminopropane.HCl (78 mg, 0.62 mmol) to give the desired product (60 mg, 24% over 3 steps) as an off-white solid. MS: $M+H^+$ 403. 1H NMR (300 MHz, $CDCl_3$): δ 8.63 (dd, $J = 2.4, 7.0$ Hz, 1H), 8.42 (d, $J = 13.2$ Hz, 1H), 8.07-8.02 (m, 1H), 7.80-7.73 (m, 1H), 7.36-7.71 (m, 3H), 5.08 (d, $J = 6.7$ Hz, 1H), 3.54-3.50 (m, 1H), 3.29-3.21 (m, 5H), 1.13 (d, $J = 6.7$ Hz, 1H).



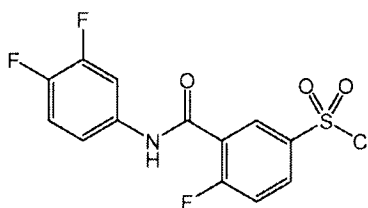
[0470] (R)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-phenylethyl)sulfamoyl)benzamide: General procedure A was followed using (R)-(-)-1-methyl-benzylamine (75 mg, 0.62 mmol) to give the desired product (136 mg, 51% over 3 steps) as an off-white solid. MS: $M+H^+$ 436. 1H NMR (300 MHz, $CDCl_3$): δ 8.41 (dd, $J = 2.6, 7.3$ Hz, 1H), 8.27 (d, $J = 13.5$ Hz, 1H), 7.79-7.72 (m, 2H), 7.9 (d, $J = 4.4$ Hz, 1H), 7.26-7.03 (m, 8 H), 5.18 (d, $J = 7.0$ Hz, 1H), 4.58 (dq, $J = 6.7, 7.0$ Hz, 1H), 1.48 (d, $J = 7.0$ Hz, 1H).



[0471] (S)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-methoxypropan-2-yl)sulfamoyl)benzamide. General procedure A was followed using (S)-(-)-1-methoxy-2-aminopropane (55 mg, 0.62 mmol) to give the desired product (64 mg, 26% over 3 steps) as a white

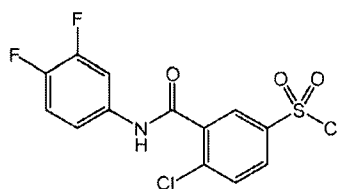
solid. MS: $M+H^+$ 403. 1H NMR (300 MHz, MeOH- d_4): δ 8.22 (dd, $J = 2.6, 6.5$ Hz, 1H), 8.07-8.02 (m, 1H), 7.85-7.78 (m, 1H), 7.47-7.20 (m, 3H), 3.49-3.73 (m, 1H), 3.32-3.15 (m, 5H), 1.04 (d, $J = 6.7$ Hz, 3H).

[0472] Example 2: General Procedure B

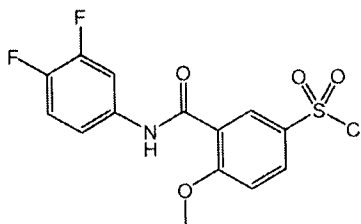


[0473] 3-(3,4-Difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride: A mixture of 5-chlorosulfonyl-2-fluorobenzoic acid (1.00 g, 4.19 mmol), thionyl chloride (3.5 mL), and 1,2-dichloroethane (3.5 mL) was heated at reflux for 1 h. The reaction was concentrated, then the residue was treated with toluene (5 mL), then the mixture was concentrated. The crude material was used without further purification.

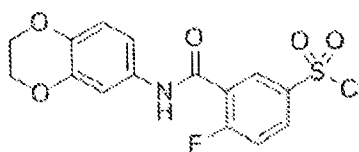
[0474] To a solution of 3,4-difluoroaniline (0.55 g, 4.24 mmol) in toluene (10 mL) was added the material from the previous step. The reaction was stirred for 16 hours then was filtered. The concentrated filtrate was purified by silica column (0 – 100% EtOAc/ Hexane) to give the desired product (0.38 g, 27%) as a white solid. 1H NMR (300 MHz, DMSO- d_6): δ 10.72 (s, 1H), 7.90-7.72 (m, 2H), 7.46-7.26 (m, 4H).



[0475] 3-(3,4-Difluorophenyl-carbamoyl)-4-chlorobenzene-1-sulfonyl chloride: General Procedure B was followed, using of 5-chlorosulfonyl-2-chlorobenzoic acid (0.50 g, 2.06 mmol) to give the desired product (0.29 g, 40% over 2 steps) as an off-white solid. 1H NMR (300 MHz, DMSO- d_6): δ 10.81 (s, 1H), 7.89-7.80 (m, 1H), 7.70-7.66 (m, 2H), 7.46 (d, $J = 17.3$ Hz, 1H), 7.44-7.36 (m, 1H).

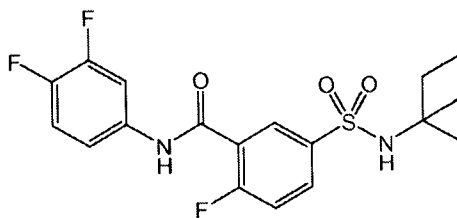


[0476] **3-(3,4-Difluorophenyl-carbamoyl)-methoxybenzene-1-sulfonyl chloride.** General Procedure B was followed, using of 5-chlorosulfonyl-2-methoxybenzoic acid (0.50 g, 2.00 mmol) to give the desired product (0.33 g, 45% over 2 steps) as an off-white solid. MS: $M+H^+$ 362. 1H NMR (300 MHz, DMSO- d_6): δ 10.33 (s, 1H), 7.94-7.78 (m, 2H), 7.69 (dd, $J = 2.2, 8.5$ Hz, 1H), 7.50-7.34 (m, 2H), 7.10 (d, $J = 8.8$ Hz, 1H), 3.87 (s, 3H).



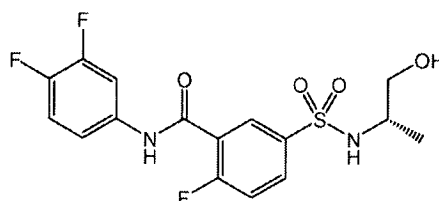
[0477] **3-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)carbamoyl)-4-fluorobenzene-1-sulfonyl chloride:** In a similar procedure as General Procedure B, final compound was obtained as a white solid (0.95 g, 61 %). MS (ES) m/z : 372.1 ($M+H^+$), calculated 372.00.

[0478] **Example 3: General Procedure C**

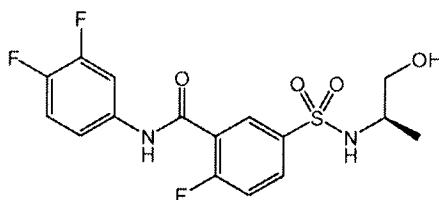


[0479] ***N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-tert-pentylsulfamoyl)benzamide:** To a 0 °C solution of 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol) in CH_2Cl_2 (1 mL) was added NEt_3 (17 mg, 0.17 mmol) and tert-amylamine (8 mg, 0.086 mmol). The reaction was warmed to 20 °C, and was stirred for 1.5 hours. The mixture was concentrated, and the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and

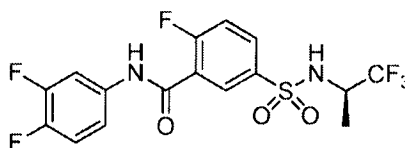
concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (26 mg, 76%) as a clear gum. MS: $M+H^+$ 403. 1H NMR (300 MHz, MeOH- d_4): δ 8.55 (dd, $J = 2.4, 6.5$ Hz, 1H), 8.08-8.03 (m, 1H), 7.86-7.78 (m, 1H), 7.46-7.21 (m, 3H), 1.54 (q, $J = 7.6$ Hz, 2H), 1.14 (s, 6H), 0.84 (t, $J = 7.3$ Hz, 3H).



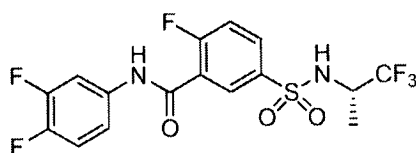
[0480] (S)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-hydroxypropan-2-yl)sulfamoyl)benzamide: General Procedure C was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (14 mg, 0.14 mmol), and (S)-2-amino-1-propanol (6 mg, 0.072 mmol) to give the desired product (20 mg, 72%) as a white solid. MS: $M+H^+$ 389. 1H NMR (300 MHz, MeOH- d_4): δ 8.22 (dd, $J = 2.4, 6.2$ Hz, 1H), 8.09-8.04 (m, 1H), 7.86-7.80 (m, 1H), 7.48-7.21 (m, 3H), 3.44-3.31 (m, 3H), 1.02 (d, $J = 6.4$ Hz, 3H).



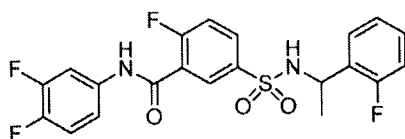
[0481] (R)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-hydroxypropan-2-yl)sulfamoyl)benzamide: General Procedure C was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (14 mg, 0.14 mmol), and (R)-2-amino-1-propanol (6 mg, 0.072 mmol) to give the desired product (26 mg, 93%) as a clear gum. MS: $M+H^+$ 389. 1H NMR (300 MHz, MeOH- d_4): δ 8.22 (dd, $J = 2.4, 6.2$ Hz, 1H), 8.09-8.04 (m, 1H), 7.86-7.78 (m, 1H), 7.49-7.21 (m, 3H), 3.44-3.29 (m, 3H), 1.02 (d, $J = 6.5$ Hz, 3H).



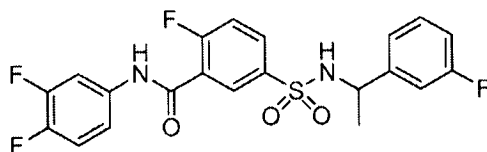
[0482] (R)-N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1,1,1-trifluoropropan-2-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained in 13.4% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.68 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.40 (bd, $J = 14.1$ Hz, 1H), 8.05 (ddd, $J = 8.8, 4.7, 2.6$ Hz, 1H), 7.36 (dd, $J = 11.4, 8.8$ Hz, 1H), 7.26-7.10 (m, 2H), 5.24 (d, $J = 9.4$ Hz, 1H), 4.12-3.98 (m, 1H), 1.37 (d, $J = 7.0$ Hz, 3H); Calculated for $\text{C}_{16}\text{H}_{12}\text{F}_6\text{N}_2\text{O}_3\text{S}$, 426.05; observed MS (ESI) (m/z) 427.2 ($M + 1$) $^+$.



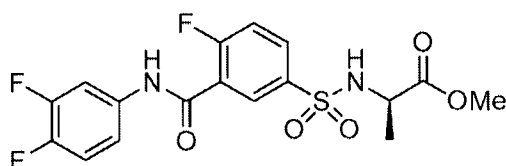
[0483] (S)-N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1,1,1-trifluoropropan-2-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained in 21% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.68 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.40 (bd, $J = 14.1$ Hz, 1H), 8.05 (ddd, $J = 8.8, 4.7, 2.6$ Hz, 1H), 7.36 (dd, $J = 11.4, 8.8$ Hz, 1H), 7.26-7.10 (m, 2H), 5.24 (d, $J = 9.4$ Hz, 1H), 4.12-3.98 (m, 1H), 1.37 (d, $J = 7.0$ Hz, 3H); Calculated for $\text{C}_{16}\text{H}_{12}\text{F}_6\text{N}_2\text{O}_3\text{S}$, 426.05; observed MS (ESI) (m/z) 427.1 ($M + 1$) $^+$.



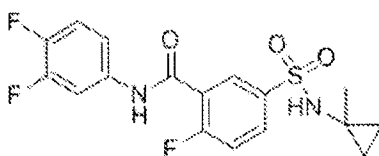
[0484] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1-(2-fluorophenyl)ethyl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained in 78% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.40 (dd, $J = 7.0, 2.3$ Hz, 1H), 8.22 (bd, $J = 14.1$ Hz, 1H), 7.84-7.72 (m, 2H), 7.24-7.06 (m, 5H), 6.99-6.92 (m, 1H), 6.86-6.76 (m, 1H), 5.16 (d, $J = 8.5$ Hz, 1H), 4.73 (dt, $J = 15.5, 7.0$ Hz, 1H), 1.53 (d, $J = 7.0$ Hz, 3H); Calculated for $\text{C}_{21}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_3\text{S}$, 452.08; observed MS (ESI) (m/z) 453.2 ($M + 1$) $^+$.



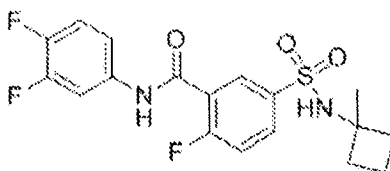
[0485] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1-(3-fluorophenyl)ethyl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained in 84% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.46 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.28 (bd, $J = 14.1$ Hz, 1H), 7.82-7.70 (m, 2H), 7.24-7.10 (m, 4H), 6.94-6.88 (m, 1H), 6.83 (ddt, $J = 8.5, 2.6, 0.9$ Hz, 1H), 6.75 (td, $J = 9.7, 2.0$ Hz, 1H), 5.10 (d, $J = 6.7$ Hz, 1H), 4.64-4.52 (m, 1H), 1.46 (d, $J = 7.0$ Hz, 3H); Calculated for $\text{C}_{21}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_3\text{S}$, 452.08; observed MS (ESI) (m/z) 453.2 ($M + 1$) $^+$.



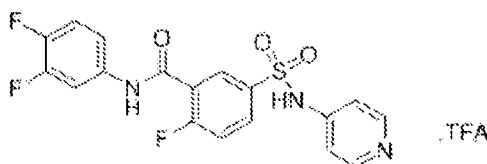
[0486] (R)-methyl-2-(3-((3,4-difluorophenyl)carbamoyl)-4-fluorophenylsulfonamido)propanoate: ^1H NMR (300 MHz, CDCl_3): δ 8.56 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.42 (bd, $J = 12.3$ Hz, 1H), 8.01 (ddd, $J = 8.7, 4.5, 2.6$ Hz, 1H), 7.76 (ddd, $J = 12.4, 7.0, 2.0$ Hz, 1H), 7.32 (dd, $J = 11.1, 8.8$ Hz, 1H), 7.26-7.10 (m, 2H), 5.57 (d, $J = 7.0$ Hz, 1H), 4.16-4.02 (m, 1H), 3.61 (s, 3H), 1.42 (d, $J = 7.3$ Hz, 3H); Calculated for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_5\text{S}$, 416.07; observed MS (ESI) (m/z) 417.2 ($M + 1$) $^+$.



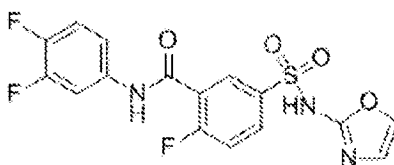
[0487] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1-methylcyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained as a white solid (60 mg, 78 %). ^1H NMR (300 MHz, CD_3OD): 8.21-8.18 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.07-8.01 (m, 1H), 7.86-7.79 (m, 1H), 7.49-7.37 (m, 2H), 7.31-7.22 (m, 1H), 1.17 (s, 3H), 0.74-0.70 (t, $J = 5.7$ Hz, 2H), 0.48-0.46 (m, 2H); MS (ES) m/z : 385.2 ($M + \text{H}^+$), calculated 385.08.



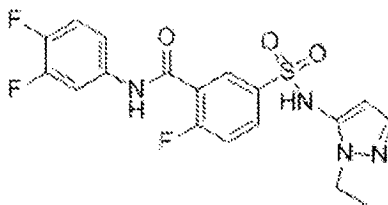
[0488] **N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1-methylecyclobutyl)sulfamoyl)benzamide**: In a similar procedure as General Procedure C, final compound was obtained as a white solid (123 mg, 88.5 %). ¹H NMR (300 MHz, CD₃OD): 8.22-8.19 (dd, *J* = 6.3, 2.3 Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.48-7.36 (m, 2H), 7.31-7.22 (m, 1H), 2.27-2.19 (m, 2H), 1.84-1.67 (m, 4H), 1.36 (s, 3H); MS (ES) *m/z*: 399.2 (*M*+ *H*⁺), calculated 399.09.



[0489] **N-(3,4-difluorophenyl)-2-fluoro-5-(N-(pyridin-4-yl)sulfamoyl)benzamide**: In a similar procedure as General Procedure C, final compound was obtained as a TFA salt beige solid (20 mg, 28 %). ¹H NMR (300 MHz, CD₃OD): 8.38 (bs, 1H), 8.31-8.29 (m, 1H), 8.18-8.13 (m, 1H), 7.77-7.70 (m, 1H), 7.48-7.42 (m, 3H), 7.27-7.14 (m, 3H); MS (ES) *m/z*: 408.2 (*M*+ *H*⁺), calculated 408.06.

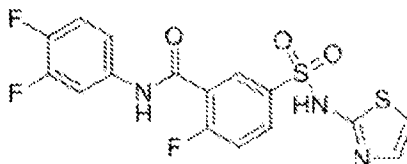


[0490] **N-(3,4-difluorophenyl)-2-fluoro-5-(N-(oxazol-2-yl)sulfamoyl)benzamide**: In a similar procedure as General Procedure C, final compound was obtained as a beige TFA salt (7 mg, 12 %). ¹H NMR (300 MHz, CD₃OD): 8.26-8.23 (m, 1H), 8.13-8.07 (m, 1H), 7.94 (s, 1H), 7.77-7.70 (m, 1H), 7.46-7.40 (m, 1H), 7.41-7.17 (m, 3H); MS (ES) *m/z*: 398.2 (*M*+ *H*⁺), calculated 398.03.

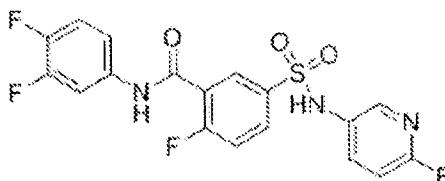


[0491] **N-(3,4-difluorophenyl)-5-(N-(1-ethyl-1H-pyrazol-5-yl)sulfamoyl)-2-fluorobenzamide**: In a similar procedure as General Procedure C, final compound was obtained as a

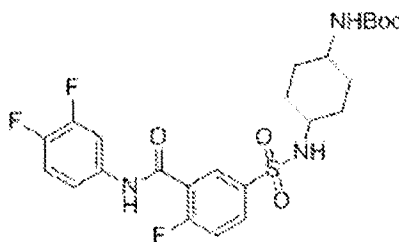
beige solid (13.5 mg, 23 %). ^1H NMR (300 MHz, CD_3OD): 8.15-8.13 (m, 1H), 7.96-7.93 (m, 1H), 7.86-7.79 (m, 1H), 7.47-7.24 (m, 5H), 3.20-3.17 (m, 2H), 1.34-1.29 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 425.2 ($\text{M} + \text{H}^+$), calculated 425.08.



[0492] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(thiazol-2-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained as a beige solid (7 mg, 12 %). ^1H NMR (300 MHz, CD_3OD): 8.15-8.12 (m, 1H), 8.10-7.93 (m, 1H), 7.76-7.70 (m, 1H), 7.34-7.23 (m, 2H), 7.22-7.16 (m, 1H), 7.03 (bs, 1H), 6.64 (bs, 1H); MS (ES) m/z : 414.1 ($\text{M} + \text{H}^+$), calculated 414.01.

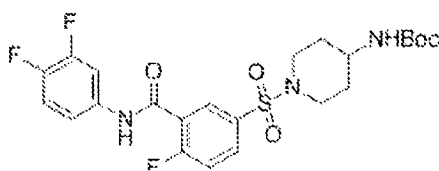


[0493] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(6-fluoropyridin-3-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained as a beige solid (8.3 mg, 14 %). ^1H NMR (300 MHz, CD_3OD): 8.15-8.12 (m, 1H), 7.94-7.92 (m, 1H), 7.82-7.70 (m, 3H), 7.42-7.23 (m, 3H), 6.97-6.94 (m, 1H); MS (ES) m/z : 426.2 ($\text{M} + \text{H}^+$), calculated 426.05.

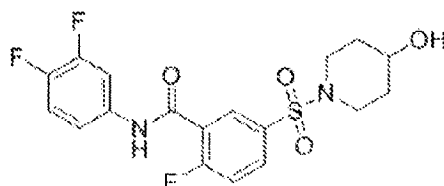


[0494] tert-Butyl (4-(3-((3,4-difluorophenyl)carbamoyl)-4-fluorophenylsulfonamido)cyclohexyl) carbamate: In a similar procedure as General Procedure C,

final compound was obtained as a white solid (128 mg, 85 %). ^1H NMR (300 MHz, d_6 -DMSO): 10.82 (s, 1H), 8.10-8.08 (m, 1H), 8.04-7.99 (m, 1H), 7.88-7.82 (m, 1H), 7.70 (m, 1H), 7.62-7.57 (m, 1H), 7.49-7.42 (m, 2H), 6.73 (m, 1H), 3.22 (m, 1H), 3.00 (bs, 1H), 1.55-1.39 (m, 8H), 1.35 (s, 9H); MS (ES) m/z : 528.3 ($\text{M} + \text{H}^+$), calculated 528.17.

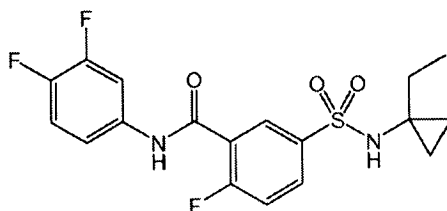


[0495] tert-Butyl 1-((3-((3,4-difluorophenyl)carbamoyl)-4-fluorophenyl)sulfonyl)piperidin-4-yl)carbamate: In a similar procedure as General Procedure C, final compound was obtained as a white solid (120 mg, 82 %). ^1H NMR (300 MHz, d_4 -MeOH): 8.11-8.00 (m, 1H), 8.09-7.95 (m, 1H), 7.86-7.79 (m, 1H), 7.54-7.40 (m, 1H), 7.40-7.31 (m, 1H), 7.28-7.22 (m, 1H), 3.69-3.65 (m, 2H), 2.57-2.50 (m, 2H), 1.93-1.89 (m, 2H), 1.57-1.49 (m, 3H), 1.41 (m, 9H); MS (ES) m/z : 536.3 ($\text{M} + \text{Na}^+$), calculated 536.15.



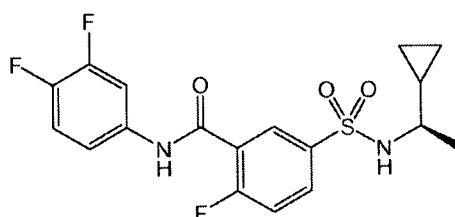
[0496] N-(3,4-Difluorophenyl)-2-fluoro-5-((4-hydroxypiperidin-1-yl)sulfonyl)benzamide: In a similar procedure as General Procedure C, final compound was obtained as a white solid (31 mg, 41 %). ^1H NMR (300 MHz, d_4 -MeOH): 8.12-8.09 (m, 1H), 8.01-7.95 (m, 1H), 7.86-7.78 (m, 1H), 7.54-7.48 (m, 1H), 7.40-7.37 (m, 1H), 7.31-7.22 (m, 1H), 3.69-3.63 (m, 1H), 3.41-3.30 (m, 2H), 2.89-2.82 (m, 2H), 1.92-1.86 (m, 2H), 1.64-1.54 (m, 2H); MS (ES) m/z : 415.2 ($\text{M} + \text{H}^+$), calculated 415.09.

[0497] Example 4: General Procedure D



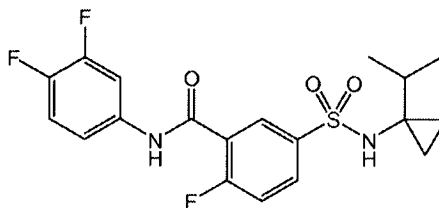
[0498] *N*-(3,4-Difluorophenyl)-5-(*N*-(1-ethylcyclopropyl)sulfamoyl)-2-

fluorobenzamide: To a 0 °C solution of 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol) in THF (1 mL) was added NEt₃ (17 mg, 0.17 mmol), and 1-ethylcyclopropylamine.HCl (9 mg, 0.072 mmol). The reaction was warmed to 20°C, and was stirred for 1.5 hours. The mixture was concentrated, and residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (13 mg, 45%) as a clear gum. MS: M+H⁺ 399. ¹H NMR (300 MHz, MeOH-d₄): δ 10.47 (s, 1H), 8.20 (dd, *J* = 2.4, 6.5 Hz, 1H), 8.06-8.00 (m, 1H), 7.86-7.78 (m, 1H), 7.48-7.12 (m, 4H), 1.42 (q, *J* = 7.6 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.64 (dd, *J* = 1.8, 5.3 Hz, 2H), 0.46-0.64 (dd, *J* = 2.1, 5.0 Hz, 2H).

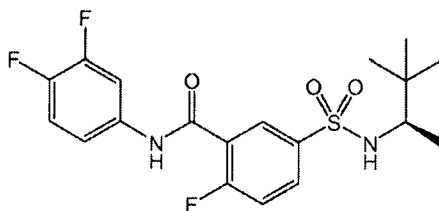


[0499] (*R*)-5-(*N*-(1-cyclopropylethyl)sulfamoyl)-*N*-(3,4-Difluorophenyl)-2-

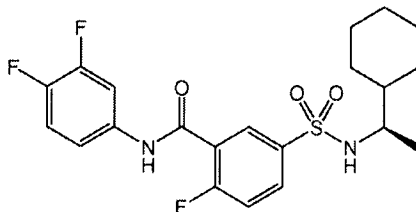
fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (14 mg, 0.14 mmol), and (*R*)-1-cyclopropylethylamine (9 mg, 0.11 mmol) to give the desired product (16 mg, 56%) as a white solid. MS: M+H⁺ 399. ¹H NMR (300 MHz, CDCl₃): δ 8.64 (dd, *J* = 2.6, 7.0 Hz, 1H), 8.46 (d, *J* = 13.2 Hz, 1H), 8.08-8.03, 1H), 7.80-7.73 (m, 1H), 7.36-7.11 (m, 3H), 5.03 (d, *J* = 6.7 Hz, 1H), 2.75 (dt, *J* = 1.8, 6.5, 1H), 1.17 (d, *J* = 26.5 Hz, 3H), 0.82-0.74 (m, 1H), 0.50-0.43 (m, 1H), 0.38-0.32 (m, 1H), 0.18-0.04 (m, 2H).



[0500] *N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-isopropylcyclopropyl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (28 mg, 0.28 mmol), and isopropylcyclopropylamine.HCl (15 mg, 0.11 mmol) to give the desired product (22 mg, 74%) as a white solid. MS: $M+H^+$ 413. ¹H NMR (300 MHz, CDCl₃): δ 8.56 (dd, J = 2.4, 6.7 Hz, 1H), 8.48 (d, J = 12.9 Hz, 1H), 8.05-7.99 (m, 1H), 7.80-7.72 (m, 1H), 7.34-7.11 (m, 3H), 5.57 (s, 1H), 1.54 (qint, J = 6.7 Hz, 1H), 0.87 (d, J = 6.7 Hz, 6H), 0.69-0.58 (m, 4H).

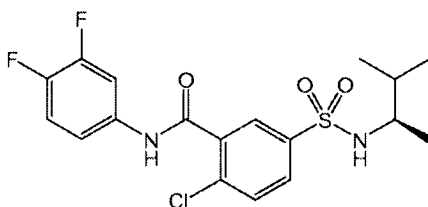


[0501] (*R*)-*N*-(3,4-Difluorophenyl)-5-(*N*-(3,3-dimethylbutan-2-yl)sulfamoyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (14 mg, 0.14 mmol), and (*R*)-(-)-3,3-dimethyl-2-aminopropane (11 mg, 0.11 mmol) to give the desired product (12 mg, 40%) as a white solid. MS: $M+H^+$ 415. ¹H NMR (300 MHz, MeOH-*d*₄): δ 8.21 (dd, J = 2.4, 6.5 Hz, 1H), 8.08-8.03 (m, 1H), 7.86-7.79 (m, 1H), 7.49-7.21 (m, 3H), 3.07 (q, J = 6.7 Hz, 1H), 0.87 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H).

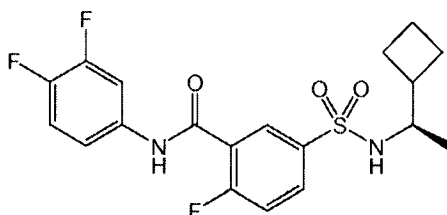


[0502] (*R*)-5-(*N*-(1-cyclohexylethyl)sulfamoyl)-*N*-(3,4-Difluorophenyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-

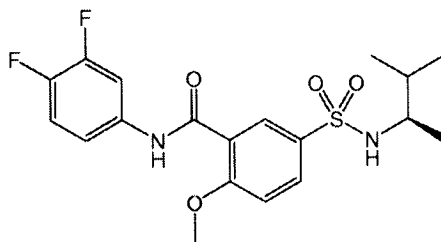
fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (14 mg, 0.14 mmol), and (R)-(-)-cyclohexylethylamine (14 mg, 0.11 mmol) to give the desired product (15 mg, 47%) as a white solid. MS: $\text{M}+\text{H}^+$ 441. ^1H NMR (300 MHz, CDCl_3): δ 8.63 (dd, $J = 2.4, 7.0$ Hz, 1H), 8.45 (d, $J = 13.2$ Hz, 1H), 8.06-8.01 (m, 1H), 7.80-7.73 (m, 1H), 7.36-7.11 (m, 3H), 4.73 (d, $J = 8.8$ Hz, 1H), 3.25-3.18 (m, 1H), 1.72-1.53 (m, 4H), 1.31-1.01 (m, 5H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.96-0.80 (m, 1H).



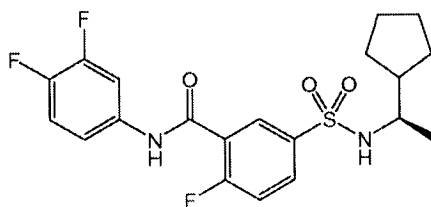
[0503] (R)-2-chloro-N-(3,4-Difluorophenyl)-5-(N-(3-methylbutan-2-yl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-chlorobenzene-1-sulfonyl chloride (25 mg, 0.068 mmol), NEt_3 (13 mg, 0.14 mmol), and (R)-(-)-2-amino-3-methylbutane (9 mg, 0.10 mmol) to give the desired product (23 mg, 81%) as an off-white solid. MS: $\text{M}+\text{H}^+$ 417. ^1H NMR (300 MHz, CDCl_3): δ 8.38 (s, 1H), 8.12 (d, $J = 2.1$ Hz, 1H), 7.81-7.68 (m, 2H), 7.53 (d, $J = 8.5$ Hz, 1H), 7.19-7.12 (m, 2H), 4.83 (d, $J = 8.8$ Hz, 1H), 3.23-3.16 (m, 1H), 1.70-1.62 (m, 1H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.82 (d, $J = 6.7$ Hz, 6H).



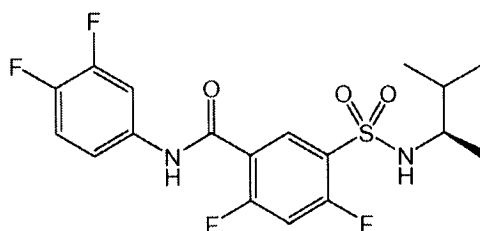
[0504] (R)-5-(N-(1-cyclobutylethyl)sulfamoyl)-N-(3,4-Difluorophenyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (28 mg, 0.28 mmol), and (R)-(-)-cyclobutylethylamine.HCl (15 mg, 0.11 mmol) to give the desired product (19 mg, 64%) as a white solid. MS: $\text{M}+\text{H}^+$ 417. ^1H NMR (300 MHz, CDCl_3): δ 8.64 (dd, $J = 2.4, 7.0$ Hz, 1H), 8.44 (d, $J = 13.8$ Hz, 1H), 8.08-8.03 (m, 1H), 7.80-7.73 (m, 1H), 7.37-7.11 (m, 3H), 4.69 (d, $J = 8.2$ Hz, 1H), 3.29-3.22 (m, 1H), 2.19 (q, $J = 8.2$ Hz, 1H), 1.94-1.60 (m, 5H), 0.96 (d, $J = 6.5$ Hz, 1H), 0.88-0.83 (m, 1H).



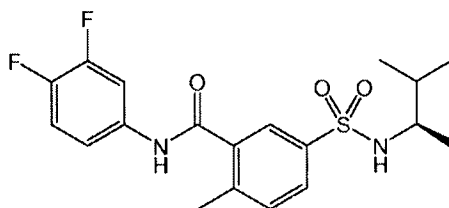
[0505] (R)-N-(3,4-Difluorophenyl)-2-methoxy-5-(N-(3-methylbutan-2-yl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-methoxybenzene-1-sulfonyl chloride (25 mg, 0.069 mmol), NEt_3 (13 mg, 0.13 mmol), and (R)-(-)-2-amino-3-methylbutane (9 mg, 0.10 mmol) to give the desired product (12 mg, 42%) as a white solid. MS: $\text{M}+\text{H}^+$ 413. ^1H NMR (300 MHz, CDCl_3): 9.60 (s, 1H), 8.72 (d, $J = 2.6$ Hz, 1H), 7.99 (dd, $J = 2.6, 8.8$ Hz, 1H), 7.81-7.74 (m, 1H), 7.22-7.08 (m, 3H), 4.61 (d, $J = 8.5$ Hz, 1H), 3.23-3.17 (m, 1H), 1.68-1.61 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 1H), 0.82 (d, $J = 7.0$ Hz, 1H).



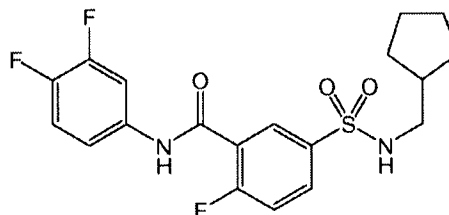
[0506] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-N-(3,4-Difluorophenyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (28 mg, 0.28 mmol), and (R)-(-)-cyclopentylethylamine.HCl (17 mg, 0.11 mmol) to give the desired product (24 mg, 78%) as a white solid. MS: $\text{M}+\text{H}^+$ 427. ^1H NMR (300 MHz, CDCl_3): 8.62 (dd, $J = 2.4, 7.0$ Hz, 1H), 8.47 (d, $J = 13.2$ Hz, 1H), 8.06-8.01 (m, 1H), 7.79-7.72 (m, 1H), 7.35-7.11 (m, 3H), 4.84 (d, $J = 8.5$ Hz, 1H), 3.26-3.19 (m, 1H), 1.84-1.43 (m, 5H), 1.39-1.06 (m, 3H), 1.03 (d, $J = 6.5$ Hz, 1H), 0.88-0.83 (m, 1H).



[0507] (R)-N-(3,4-Difluorophenyl)-2,4-difluoro-5-(N-(3-methylbutan-2-yl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-2,4-difluorobenzene-1-sulfonyl chloride (25 mg, 0.068 mmol), NEt₃ (13 mg, 0.13 mmol), and (R)-(-)-2-amino-3-methylbutane (9 mg, 0.10 mmol) to give the desired product (10 mg, 35%) as a white solid. MS: M+H⁺ 419. ¹H NMR (300 MHz, CDCl₃): 8.68 (t, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 12.3 Hz, 1H), 7.78-7.71 (m, 1H), 7.25-7.07 (m, 3H), 7.70 (m, 1H), 3.33-3.26 (m, 1H), 1.73-1.64 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 1H), 0.86 (dd, *J* = 1.8, 7.0 Hz, 1H).

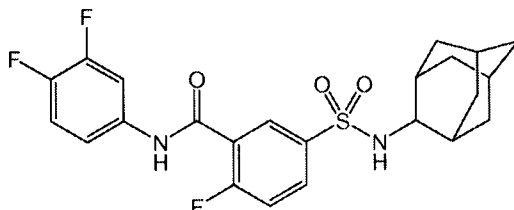


[0508] (R)-N-(3,4-Difluorophenyl)-2-methyl-5-(N-(3-methylbutan-2-yl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-methylbenzene-1-sulfonyl chloride (25 mg, 0.068 mmol), NEt₃ (13 mg, 0.13 mmol), and (R)-(-)-2-amino-3-methylbutane (9 mg, 0.10 mmol) to give the desired product (10 mg, 35%) as a white solid. MS: M+H⁺ 397. ¹H NMR (300 MHz, CDCl₃): 8.23 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.74-7.70 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.26-7.12 (m, 2H), 4.59 ((d, *J* = 8.5 Hz, 1H), 3.17-3.15 (m, 1H), 2.56 (s, 3H), 1.66-1.62 (m, 1H), 0.93 (d, *J* = 6. Hz, 1H), 0.81 (d, *J* = 6.7 Hz, 1H).



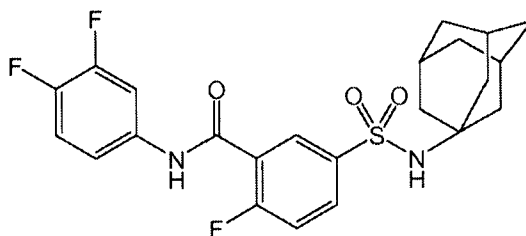
[0509] 5-(N-(cyclopentylmethyl)sulfamoyl)-N-(3,4-Difluorophenyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (28 mg, 0.28 mmol), and C-cyclopentyl-methylamine (11 mg, 0.11 mmol) to give the desired product (14 mg, 47%) as a white solid. MS: M+H⁺ 413. ¹H NMR (300 MHz, DMSO-d₆): 10.82 (s, 1H), 8.06-7.96 (m, 2H), 7.90-7.76 (m, 2H), 7.61 (t, *J* = 9.2 Hz,

1H), 7.50-7.42 (m, 2H), 2.67 (t, $J = 6.2$ Hz, 2H), 1.98-1.86 (m, 1H), 1.64-1.43 (m, 6H), 1.14-1.08 (m, 2H).



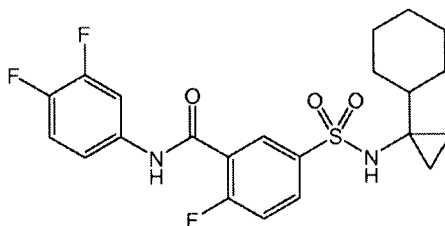
[0510] 5-(N-(2-adamantyl)sulfamoyl)-N-(3,4-Difluorophenyl)-2-fluorobenzamide:

General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol), NEt_3 (28 mg, 0.28 mmol), and 2-amino-adamantane.HCl (24 mg, 0.13 mmol) to give the desired product (31 mg, 78%) as a white solid. MS: $\text{M}+\text{H}^+$ 465. ^1H NMR (300 MHz, CDCl_3): 8.66-8.63 (m, 1H), 8.44 (d, $J = 13.5$ Hz, 1H), 8.08-8.03 (m, 1H), 7.79-7.72 (m, 1H), 7.36-7.11 (m, 3H), 5.23 (d, $J = 7.3$ Hz, 1H), 3.44 (d, $J = 7.0$ Hz, 1H), 1.80-1.16 (m, 14H).

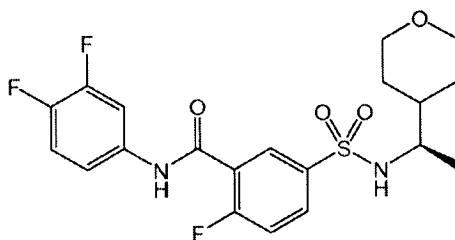


[0511] 5-(N-(1-adamantyl)sulfamoyl)-N-(3,4-Difluorophenyl)-2-fluorobenzamide:

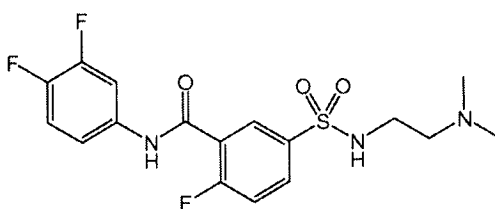
General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol), NEt_3 (17 mg, 0.17 mmol), and 1-amino-adamantane.HCl (20 mg, 0.13 mmol) to give the desired product (26 mg, 65%) as a white solid. MS: $\text{M}+\text{Na}^+$ 487. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): 10.81 (s, 1H), 8.11-8.09 (m, 1H), 8.05-8.00 (m, 1H), 7.90-7.83 (m, 1H), 7.70 (s, 1H), 7.60 (d, $J = 9.4$ Hz, 1H), 7.47-7.42 (m, 2H), 1.97-1.92 (m, 3H), 1.69 (s, 6H), 1.55-1.45 (m, 6H).



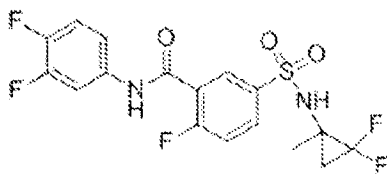
[0512] 5-(*N*-(1-cyclohexylcyclopropyl)sulfamoyl)-*N*-(3,4-Difluorophenyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol), NEt₃ (17 mg, 0.17 mmol), and (1-cyclohexylcyclopropyl)amine.HCl (18 mg, 0.13 mmol) to give the desired product (11 mg, 28%) as a white solid. MS: M+H⁺ 453. ¹H NMR (300 MHz, CDCl₃): 8.61-8.58 (m, 1H), 8.38 (d, *J* = 14.1 Hz, 1H), 8.06-8.01 (m, 1H), 7.80-7.74 (m, 1H), 7.35-7.12 (m, 4H), 5.20 (s, 1H), 1.70-1.58 (m, 3H), 1.43-0.93 (m, 8H), 0.64 (d, *J* = 4.7 Hz, 4H).



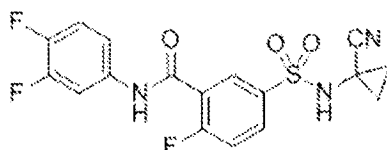
[0513] (*R*)-*N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-(tetrahydro-2*H*-pyran-4-yl)ethyl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt₃ (42 mg, 0.42 mmol), and (*R*)-1-(tetrahydro-2*H*-pyran-4-yl)ethanamine.HCl (35 mg, 0.21 mmol) to give the desired product (36 mg, 58%) as a white solid. MS: M+H⁺ 443. ¹H NMR (300 MHz, DMSO-*d*₆): 10.81 (s, 1H), 8.08-8.05 (m, 1H), 8.02-7.96 (m, 1H), 7.90-7.82 (m, 1H), 7.65 (d, *J* = 12.9 Hz, 1H), 7.60 (t, *J* = 9.7 Hz, 1H), 7.47-7.39 (m, 2H), 3.83-3.78 (m, 2H), 3.20-2.99 (m, 3H), 1.53-1.38 (m, 3H), 1.25-0.97 (m, 3H), 0.80 (d, *J* = 6.7 Hz, 1H).



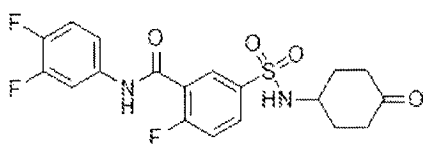
[0514] *N*-(3,4-difluorophenyl)-5-(*N*-(2-(dimethylamino)ethyl)sulfamoyl)-2-fluorobenzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt₃ (28 mg, 0.28 mmol), and *N,N*-dimethylethylenediamine (19 mg, 0.22 mmol) to give the desired product (46 mg, 82%) as a white solid. MS: M+H⁺ 402.



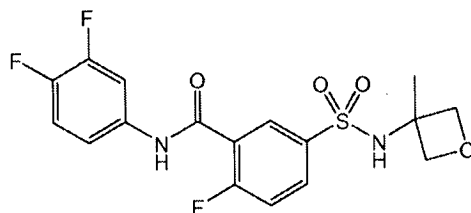
[0515] 5-(N-(2,2-Difluoro-1-methylcyclopropyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure D, final compound was obtained as a white solid (29.8 mg, 50 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.23-8.20 (m, 1H), 8.08-8.03 (m, 1H), 7.86-7.78 (m, 1H), 7.50-7.44 (t, $J = 9.2$ Hz, 1H), 7.40-7.22 (m, 2H), 1.67-1.57 (m, 1H), 1.45-1.30 (m, 1H), 1.29 (s, 3H); MS (ES) m/z : 421.2 ($\text{M} + \text{H}^+$), calculated 421.06.



[0516] 5-(N-(1-Cyanocyclopropyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure D, final compound was obtained as a white solid (30.6 mg, 75 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.30-8.27 (m, 1H), 8.15-8.10 (m, 1H), 7.86-7.79 (m, 1H), 7.55-7.49 (m, 1H), 7.40-7.22 (m, 2H), 143 (s, 4H); MS (ES) m/z : 396.2 ($\text{M} + \text{H}^+$), calculated 396.06.

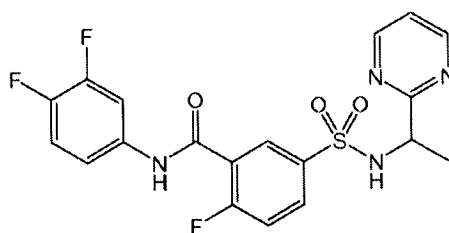


[0517] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(4-oxocyclohexyl)sulfamoyl)benzamide: In a similar procedure as General Procedure D, final compound was obtained as a white solid (45 mg, 46 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.27-8.19 (m, 1H), 8.13-8.03 (m, 1H), 7.85-7.79 (m, 1H), 7.52-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.61-3.53 (m, 1H), 2.01-1.97 (m, 2H), 1.81-1.76 (m, 3H), 1.68-1.62 (m, 1H), 1.49-1.45 (m, 2H); MS (ES) m/z : 427.2 ($\text{M} + \text{H}^+$), calculated 427.09.

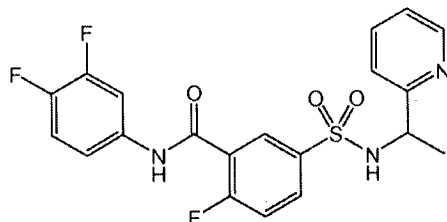


[0518] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(3-methyloxetan-3-yl)sulfamoyl)benzamide: General Procedure D was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt_3 (28 mg, 0.28 mmol), and 3-amino-3-methyl-oxetane (19 mg, 0.22 mmol) to give the desired product (41 mg, 73%) as a white solid. MS: $\text{M}+\text{H}^+$ 401.

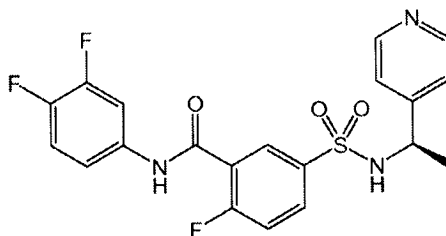
[0519] Example 5: General Procedure E



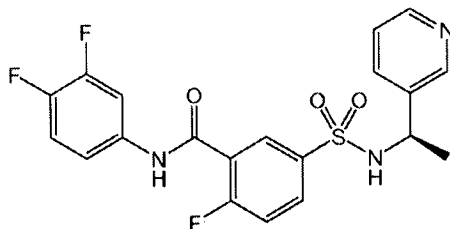
[0520] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-(pyrimidin-2-yl)ethyl)sulfamoyl)benzamide: To a 0°C solution of 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol) in THF (1 mL) was added NEt_3 (14 mg, 0.14 mmol) and 1-pyrimidin-2-yl-ethylamine.HCl (18 mg, 0.11 mmol). The reaction was warmed to 20°C , and was stirred for 3 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and dilute NaHCO_3 (5 mL). The organic layer was washed with water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by silica column (20 -100% EtOAc/ Hexane) to give the desired product (11 mg, 35%) as an off-white solid. MS: $\text{M}+\text{H}^+$ 436. ^1H NMR (300 MHz, CDCl_3): δ 8.59 (d, $J = 5.0$ Hz, 1H), 8.46-8.40 (m, 1H), 7.97-7.92 (m, 1H), 7.79-7.72 (m, 1H), 7.26-7.11 (m, 4H), 6.32 (d, $J = 8.2$ Hz, 1H), 4.68 (dq, $J = 1.2, 7.0$ Hz, 1H), 1.54 (d, $J = 6.7$ Hz, 1H).



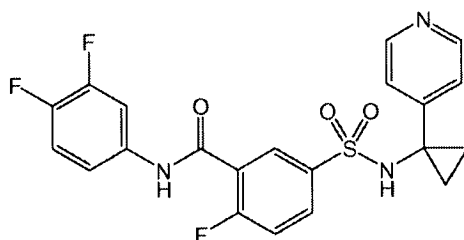
[0521] *N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-pyridin-2-yl)ethyl)sulfamoyl)benzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (14 mg, 0.14 mmol), and 1-pyridin-2-yl-ethylamine (13 mg, 0.11 mmol) to give the desired product (24 mg, 77%) as a white solid. MS: M+H⁺ 436. ¹H NMR (300 MHz, DMSO-d₆): 10.72 (s, 1H), 8.44 (d, *J* = 7.3 Hz, 1H), 8.35-8.33 (m, 1H), 7.92-7.80 (m, 3H), 7.66-7.60 (m, 1H), 7.50-7.42 (m, 3H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.17-7.12 (m, 2H), 4.44 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 1H).



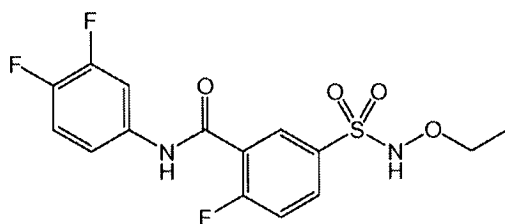
[0522] (*R*)-*N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-pyridin-4-yl)ethyl)sulfamoyl)benzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt₃ (14 mg, 0.14 mmol), and (*R*)-1-pyridin-4-ylethanamine (13 mg, 0.11 mmol) to give the desired product (16 mg, 51%) as a white solid. MS: M+H⁺ 436. ¹H NMR (300 MHz, DMSO-d₆): 10.75 (s, 1H), 8.55 (d, *J* = 7.9 Hz, 1H), 8.39 (dd, *J* = 1.2, 4.4 Hz, 2H), 8.00-7.97 (m, 1H), 7.90-7.82 (m, 1H), 7.51-7.42 (m, 3H), 7.24 (dd, *J* = 1.5, 4.7 Hz, 1H), 4.44-4.39 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 1H).



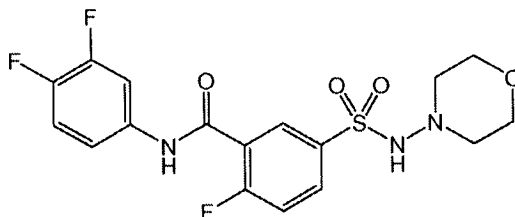
[0523] (*R*)-*N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-(pyridin-3-yl)ethyl)sulfamoyl)benzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (25 mg, 0.072 mmol), NEt_3 (42 mg, 0.42 mmol), and (1*R*)-pyridin-3-yl-ethylamine.2 HCl (21 mg, 0.11 mmol) to give the desired product (21 mg, 67%) as a white solid. MS: $\text{M}+\text{H}^+$ 436. ^1H NMR (300 MHz, DMSO-d_6): 10.71 (s, 1H), 8.48 (d, $J = 7.9$ Hz, 1H), 8.39-8.34 (m, 1H), 7.93-7.80 (m, 3H), 7.61-7.57 (m, 1H), 7.50-7.42 (m, 2H), 7.23-7.18 (m, 1H), 4.51-4.41 (m, 1H), 1.27 (d, $J = 7.0$ Hz, 1H).



[0524] *N*-(3,4-difluorophenyl)-2-fluoro-5-(*N*-(1-(pyridin-4-yl)cyclopropyl)sulfamoyl)benzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt_3 (56 mg, 0.56 mmol), and 1-pyridin-4-yl-cyclopropylamine.2 HCl (44 mg, 0.22 mmol) to give the desired product (15 mg, 24%) as an off-white solid. MS: $\text{M}+\text{H}^+$ 448. ^1H NMR (300 MHz, MeOH-d_4): 8.30 (bs, 2H), 8.07-8.04 (m, 1H), 7.89-7.78 (m, 2H), 7.39-7.22 (m, 5H), 1.40-1.36 (m, 2H), 1.33-1.21 (m, 2H).

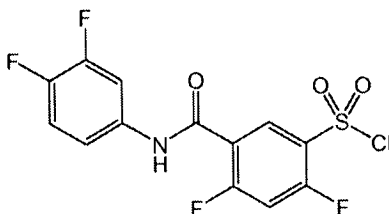


[0525] *N*-(3,4-difluorophenyl)-5-(*N*-ethoxysulfamoyl)-2-fluorobenzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt_3 (42 mg, 0.42 mmol), and *O*-ethylhydroxylamine.HCl (21 mg, 0.22 mmol) to give the desired product (24 mg, 46%) as a white solid. MS: $\text{M}+\text{H}^+$ 375.



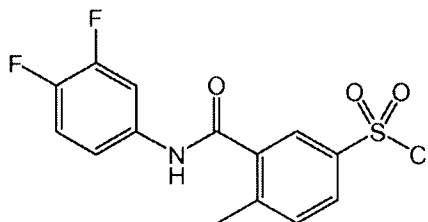
[0526] *N*-(3,4-difluorophenyl)-2-fluoro-5-(*N*-morpholinosulfamoyl)benzamide: General Procedure E was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), NEt₃ (28 mg, 0.28 mmol), and *N*-amino-morpholine (22 mg, 0.22 mmol) to give the desired product (28 mg, 48%) as a white solid. MS: M+H⁺ 416. ¹H NMR (300 MHz, MeOH-d₄): 8.28 (dd, *J* = 2.4, 6.5 Hz, 1H), 8.15-8.09 (m, 1H), 7.86-7.79 (m, 1H), 7.48 (t, *J* = 9.3 Hz, 1H), 7.40-7.37 (m, 1H), 7.26(q, *J* = 9.0 Hz, 1H), 3.60-3.57 (m, 2H), 2.60-2.58 (m, 2H).

[0527] Example 6: General Procedure F

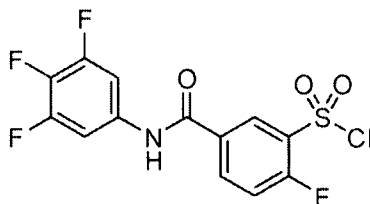


[0528] 3-(3,4-Difluorophenyl-carbamoyl)-2,4-difluorobenzene-1-sulfonyl chloride: A mixture of 5-chlorosulfonyl-2,4-difluorobenzoic acid (0.50 g, 1.96 mmol), thionyl chloride (2 mL), and 1,2-dichloroethane (1 mL) was heated at reflux for 3 h. The reaction was concentrated, then the residue was treated with toluene (5 mL), then the mixture was concentrated. The crude material was used with further purification.

[0529] To a 0°C solution of 3,4-difluoroaniline (0.51 g, 3.92 mmol) in toluene (5 mL) was added a solution of the material from the previous step in toluene (1 mL). The reaction was stirred for 16 hours then was filtered. The residue was partitioned between CH₂Cl₂ (25 mL) and a mixture of ice and 2N HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (0.53 g, 74%) as a white solid. MS: M+H⁺ 368.

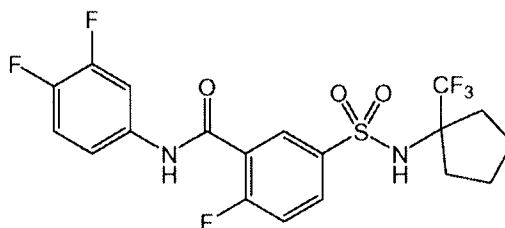


[0530] 3-(3,4-Difluorophenylcarbamoyl)-4-methylbenzene-1-sulfonyl chloride: General Procedure F was followed, using 5-chlorosulfonyl-2-methylbenzoic acid (0.50 g, 2.13 mmol) to give the desired product (0.48 g, 65% over two steps) as a white solid. MS: $M+H^+$ 346.



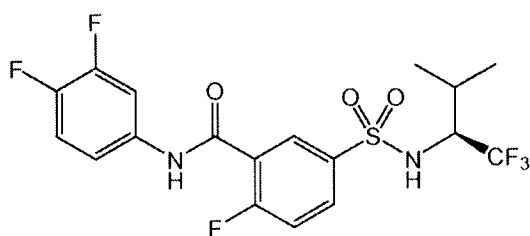
[0531] 2-Fluoro-5-(3,4,5-trifluorophenylcarbamoyl)-benzene-1-sulfonyl chloride: In a similar procedure to General Procedure F, the final compound was obtained as a white solid (0.85 g, 53 %). MS (ES) m/z : 367.70 ($M+H^+$), calculated 367.97.

[0532] Example 7: General Procedure G

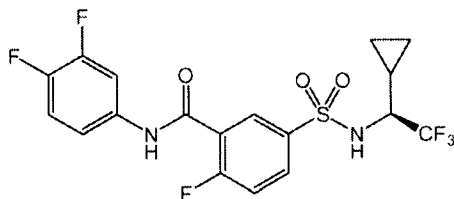


[0533] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-(trifluoromethyl)cyclopentylamine)sulfamoyl)benzamide: To a 0°C solution of 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (75 mg, 0.22 mmol) and DMAP (10 mg) in pyridine (0.2 mL) was added 1-trifluoromethyl-cyclopentane (67 mg, 0.44 mmol). The reaction was warmed to 20 °C, and was stirred for 4 hours. The mixture was concentrated, and the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated. The crude

material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (56 mg, 55%) as a white solid. MS: $M+H^+$ 467. 1H NMR (300 MHz, DMSO- d_6): 10.82 (s, 1H), 8.51 (s, 1H), 8.11-8.08 (m, 1H), 8.03-7.98 (m, 1H), 7.90-7.83 (m, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.47-7.42 (m, 2H), 2.17-2.13 (m, 2H), 1.80-1.75 (m, 2H), 1.59 (bs, 4H), 1.31-1.29 (m, 2H).

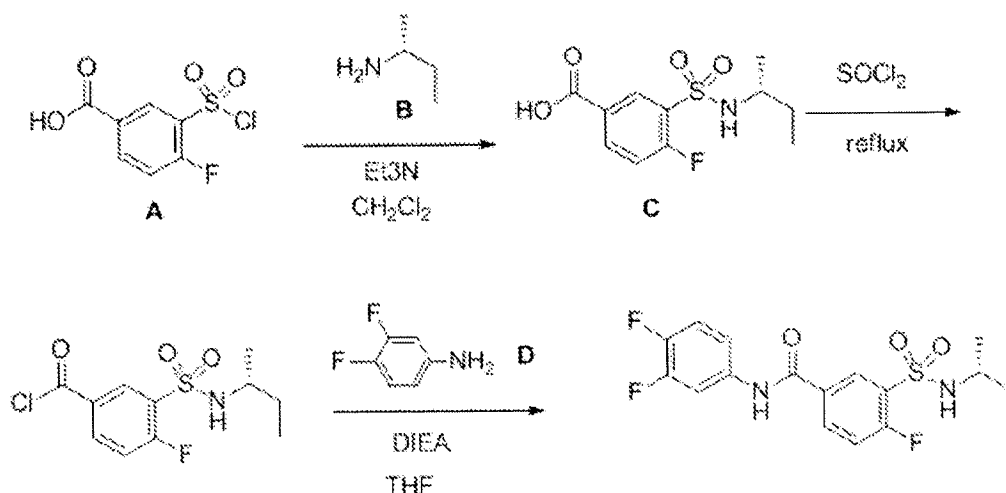


[0534] (S)-N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1,1,1-trifluoro-3-methylbutan-2-yl)sulfamoyl)benzamide: General Procedure G was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), and (S)-1,1,1,-trifluoro-3-methyl-2-butylamine (40 mg, 0.28 mmol) to give the desired product (19 mg, 30%) as a white solid. MS: $M+H^+$ 455. 1H NMR (300 MHz, $CDCl_3$): 8.63-8.60 (m, 1H), 8.31 (d, $J = 14.4$ Hz, 1H), 7.98-7.93 (m, 1H), 7.71-7.65 (m, 1H), 7.29-7.04 (m, 3H), 5.16 (d, $J = 10.3$ Hz, 1H), 3.88-3.81 (m, 1H), 2.17-2.06 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.90 (d, $J = 6.7$ Hz, 1H).

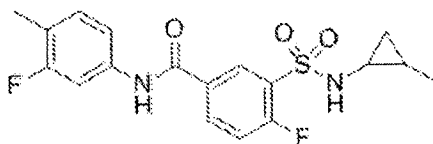


[0535] (S)-5-(N-(1-Cyclopropyl-2,2,2-trifluoroethyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide. General Procedure G was followed, using 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol), and (S)-1-cyclopropyl-2,2,2-trifluoromethylethylamine.HCl (49 mg, 0.28 mmol) to give the desired product (25 mg, 40%) as a white solid. MS: $M+H^+$ 453.

[0536] Example 8: General Procedure H

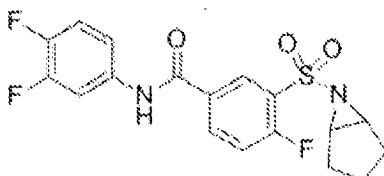


[0537] **A** (1.007 g, 0.0042 mol), **B** (0.3086 g, 0.0042 mol) and Et₃N (1.28 g, 0.01266 mol) in CH₂Cl₂ (20 mL) were stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography to give compound **C** (0.462 g, 40 %). After drying overnight under vacuum, **C** (0.176 g, 0.64 mmol) in SOCl₂ was heated at 80°C for 8h. After which the reagent was evaporated, dried overnight. The residue was then dissolved in THF (5mL), **D** (0.15 g, 1.16 mmol) was added followed by DIEA (0.5 mL) (where DIEA is N,N-diisopropylethylamine). The mixture was heated to 70°C overnight. The solvent was evaporated, followed by EtOAc extraction. After purification by column chromatography on silica gel (EtOAc/hexane), 199 mg (80%) of final product was obtained. ¹H NMR (300 MHz, CDCl₃): δ 8.25 (dd, *J* = 6.7, 2.4 Hz, 1H), 8.14 (m, 1H), 8.01 (m, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 4.63 (d, *J* = 8.2 Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z*: 387.1 (M+ H⁺), calculated 387.09.



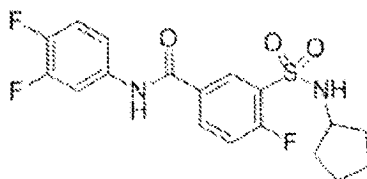
[0538] **4-fluoro-N-(3-fluoro-4-methylphenyl)-3-(N-(2-methylcyclopropyl)sulfamoyl)benzamide**: In a similar procedure as General Procedure H, final compound was obtained as a white solid (108 mg, 100 %). ¹H NMR (300 MHz, CDCl₃): δ 8.28 (dd, *J*

= 6.4, 2.3 Hz, 1H), 8.15 (m, 1H), 8.10 (s, 1H), 7.46 (m, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 5.21 (s, 1H), 2.19 (d, $J = 1.8$ Hz, 3H), 1.89 (m, 1H), 0.95 (m, 1H), 0.87 (d, $J = 5.6$ Hz, 3H), 0.74 (m, 1H), 0.35 (m, 1H); MS (ES) m/z : 381.1 ($M + H^+$), calculated 381.10.



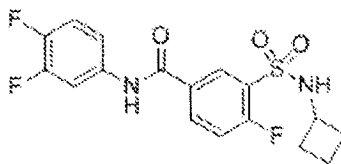
[0539] 3-(6-azabicyclo[3.1.0]hexan-6-ylsulfonyl)-N-(3,4-difluorophenyl)-4-

fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (37 mg, 13%). ^1H NMR (300 MHz, CDCl_3): δ 8.62 (dd, $J = 6.4, 2.5$ Hz, 1H), 8.17 (m, 1H), 7.96 (s, 1H), 7.68 (m, 1H), 7.30 (t, $J = 9.0$ Hz, 1H), 7.15 (m, 2H), 4.99 (m, 1H), 3.96 (m, 1H), 3.56 (m, 1H), 2.14 (m, 2H), 1.74 (m, 3H), 1.44 (m, 2H); MS (ES) m/z : 397.1 ($M + H^+$), calculated 397.08.



[0540] 3-(N-cyclopentylsulfonyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide:

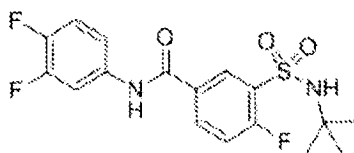
In a similar procedure as General Procedure H, final compound was obtained as a white solid (168 mg, 40%). ^1H NMR (300 MHz, CDCl_3): δ 8.31 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.20 (m, 1H), 8.06 (s, 1H), 7.74 (m, 1H), 7.33 (t, $J = 9.0$ Hz, 1H), 7.19 (m, 2H), 4.80 (d, $J = 7.6$ Hz, 1H), 3.65 (m, 1H), 1.78 (m, 2H), 1.63 (m, 2H), 1.53 (m, 2H), 1.39 (m, 2H); MS (ES) m/z : 399.2 ($M + H^+$), calculated 399.09.



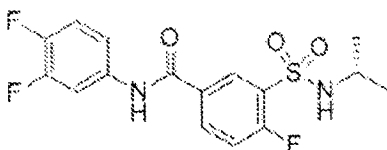
[0541] 3-(N-cyclobutylsulfonyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide:

In a similar procedure as General Procedure H, final compound was obtained as a white solid (328 mg, 78%). ^1H NMR (300 MHz, CDCl_3): δ 8.24 (dd, $J = 6.7, 2.4$ Hz, 1H), 8.14 (m, 2H), 7.68 (m, 1H), 7.22

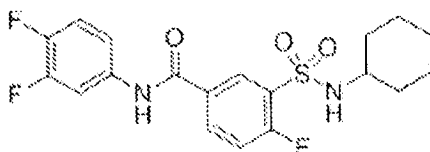
(m, 1H), 7.17 (m, 2H), 5.05 (d, $J = 9.4$ Hz, 1H), 3.79 (m, 1H), 2.06 (m, 2H), 1.79 (m, 2H), 1.67 (m, 1H); MS (ES) m/z : 385.1 ($M + H^+$), calculated 385.08.



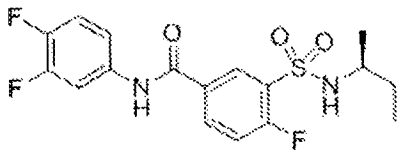
[0542] 3-(N-(*tert*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (261 mg, 37 %). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, $J = 6.5, 2.4$ Hz, 1H), 8.12 (m, 1H), 7.97 (s, 1H), 7.68 (m, 1H), 7.21 (m, 1H), 7.17 (m, 1H), 4.83 (s, 1H), 1.19 (s, 9H); MS (ES) m/z : 387.1 ($M + H^+$), calculated 387.09.



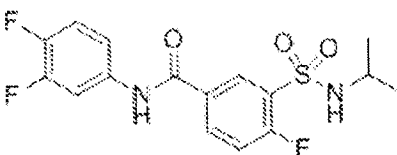
[0543] (R)-3-(N-(*sec*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (199 mg, 80 %). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, $J = 6.7, 2.4$ Hz, 1H), 8.14 (m, 1H), 8.01 (m, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 4.63 (d, $J = 8.2$ Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.78 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 387.1 ($M + H^+$), calculated 387.09.



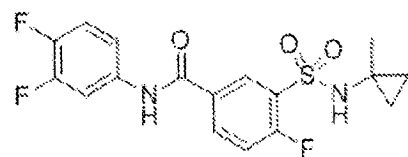
[0544] 3-(N-cyclohexylsulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (106 mg, 43 %). ^1H NMR (300 MHz, CDCl_3): δ 8.26 (dd, $J = 6.6, 2.5$ Hz, 1H), 8.14 (m, 2H), 7.69 (m, 1H), 7.22 (m, 1H), 7.14 (m, 2H), 4.76 (d, $J = 5.9$ Hz, 1H), 3.18 (m, 1H), 1.65 (m, 2H), 1.58 (m, 2H), 1.48 (m, 2H), 1.17 (m, 4H); MS (ES) m/z : 413.2 ($M + H^+$), calculated 413.11.



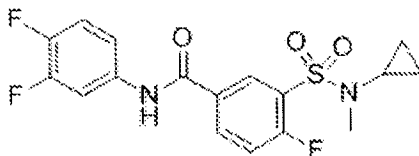
[0545] (S)-3-(N-(*sec*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (66 mg, 24 %). ^1H NMR (300 MHz, CDCl_3): δ 8.26 (dd, J = 6.7, 2.3 Hz, 1H), 8.15 (m, 1H), 8.01 (m, 1H), 7.70 (m, 1H), 7.22 (m, 1H), 7.17 (m, 2H), 4.62 (d, J = 7.2 Hz, 1H), 3.29 (m, 1H), 1.40 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H); MS (ES) m/z : 387.1 ($\text{M} + \text{H}^+$), calculated 387.09.



[0546] 3-(N-(*sec*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (120 mg, 43 %). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, J = 6.5, 2.3 Hz, 1H), 8.14 (m, 1H), 7.90 (s, 1H), 7.68 (m, 1H), 7.20 (m, 1H), 7.17 (m, 2H), 4.57 (d, J = 8.2 Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); MS (ES) m/z : 387.1 ($\text{M} + \text{H}^+$), calculated 387.09.

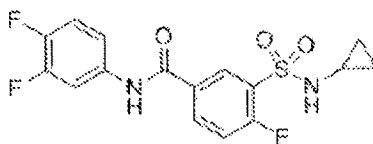


[0547] N-(3,4-difluorophenyl)-4-fluoro-3-(N-(1-methylcyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (63 mg, 15 %). ^1H NMR (300 MHz, CDCl_3): δ 8.28 (dd, J = 6.5, 2.5 Hz, 1H), 8.16 (m, 1H), 7.89 (s, 1H), 7.70 (m, 1H), 7.21 (m, 1H), 7.16 (m, 2H), 5.23 (d, J = 2.3 Hz, 1H), 1.17 (m, 5H), 0.80 (m, 2H); MS (ES) m/z : 385.1 ($\text{M} + \text{H}^+$), calculated 385.08.



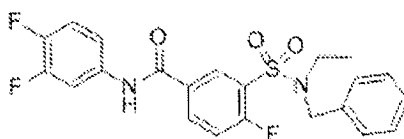
[0548] 3-(N-cyclopropyl-N-methylsulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide:

In a similar procedure as General Procedure H, final compound was obtained as a white solid (158 mg, 83 %). ^1H NMR (300 MHz, CDCl_3): δ 8.24 (dd, $J = 6.2, 2.6$ Hz, 1H), 8.13 (m, 1H), 8.01 (s, 1H), 7.69 (m, 1H), 7.21 (m, 1H), 7.17 (m, 2H), 2.85 (d, $J = 2.1$ Hz, 3H), 2.06 (m, 1H), 0.77 (m, 2H), 0.67 (m, 2H); MS (ES) m/z : 385.1 ($\text{M} + \text{H}^+$), calculated 385.08.



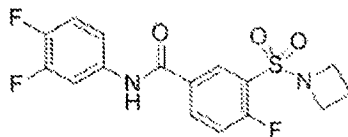
[0549] 3-(N-cyclopropylsulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide:

In a similar procedure as General Procedure H, final compound was obtained as a white solid (118 mg, 35 %). ^1H NMR (300 MHz, CDCl_3): δ 8.30 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.19 (m, 1H), 7.98 (s, 1H), 7.70 (m, 1H), 7.31 (t, $J = 8.9$ Hz, 1H), 7.16 (m, 2H), 5.18 (s, 1H), 2.23 (m, 1H), 0.61 (m, 4H); MS (ES) m/z : 371.1 ($\text{M} + \text{H}^+$), calculated 371.35.

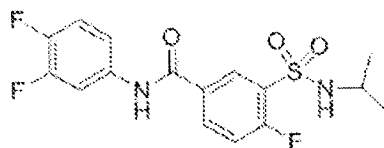


[0550] 3-(N-benzyl-N-ethylsulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide:

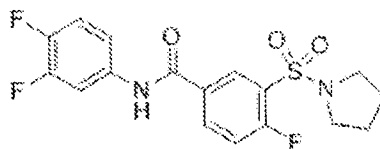
In a similar procedure as General Procedure H, final compound was obtained as a white solid (60 mg, 11 %). ^1H NMR (300 MHz, CDCl_3): δ 8.21 (dd, $J = 6.2, 2.4$ Hz, 1H), 8.11 (m, 1H), 7.94 (s, 1H), 7.69 (m, 1H), 7.25 (m, 1H), 7.18 (m, 7H), 4.45 (s, 2H), 3.26 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H); MS (ES) m/z : 449.2 ($\text{M} + \text{H}^+$), calculated 449.11.



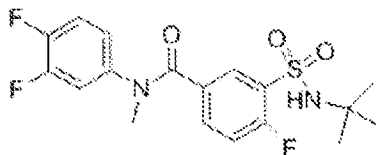
[0551] 3-(azetidin-1-ylsulfonyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (5 mg, 2 %). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, $J = 6.2, 2.3$ Hz, 1H), 8.16 (m, 2H), 7.68 (m, 1H), 7.21 (m, 1H), 7.15 (m, 2H), 3.54 (m, 4H), 2.08 (m, 2H); MS (ES) m/z : 371.1 ($\text{M} + \text{H}^+$), calculated 371.06.



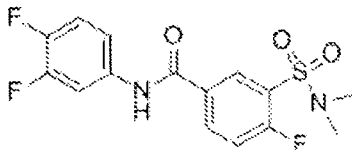
[0552] N-(3,4-difluorophenyl)-4-fluoro-3-(N-isopropylsulfamoyl)benzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (410 mg, 87 %). ^1H NMR (300 MHz, CDCl_3): δ 8.26 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.14 (m, 1H), 8.02 (s, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 4.64 (d, $J = 7.6$ Hz, 1H), 3.50 (m, 1H), 1.07 (d, $J = 6.4$ Hz, 2H); MS (ES) m/z : 373.1 ($\text{M} + \text{H}^+$), calculated 373.08.



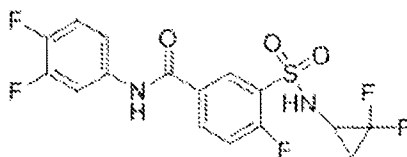
[0553] N-(3,4-difluorophenyl)-4-fluoro-3-(pyrrolidin-1-ylsulfonyl)benzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (350 mg, 70 %). ^1H NMR (300 MHz, CDCl_3): δ 8.25 (dd, $J = 6.2, 2.3$ Hz, 1H), 8.11 (m, 2H), 7.69 (m, 1H), 7.22 (m, 1H), 7.11 (m, 2H), 3.32 (m, 4H), 1.80 (m, 4H); MS (ES) m/z : 385.1 ($\text{M} + \text{H}^+$), calculated 385.08.



[0554] 3-(N-(*tert*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluoro-N-methylbenzamide: In a similar procedure as General Procedure H, final compound was obtained as a beige solid (118 mg, 43.4 %). ¹H NMR (300 MHz, CD₃OD): 7.73-7.67 (m, 2H), 7.31-7.14 (m, 3H), 7.04-7.02 (m, 1H), 3.45 (s, 3H), 1.06 (s, 9H); MS (ES) m/z: 401.2 (M+ H⁺), calculated 401.11.

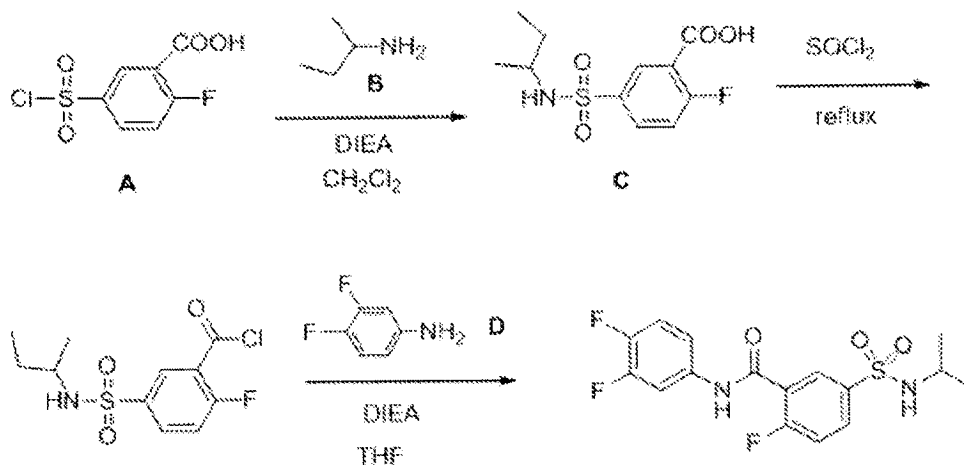


[0555] N-(3,4-difluorophenyl)-3-(N,N-dimethylsulfamoyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (128 mg, 44 %). ¹H NMR (300 MHz, CD₃OD): 8.13-8.10 (dd, *J* = 6.1, 2.3 Hz, 1H), 8.02-7.97 (m, 1H), 7.86-7.79 (m, 1H), 7.55-7.49 (dd, *J* = 10, 8.8 Hz, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 2.73 (s, 6H); MS (ES) m/z: 359.1 (M+ H⁺), calculated 359.06.

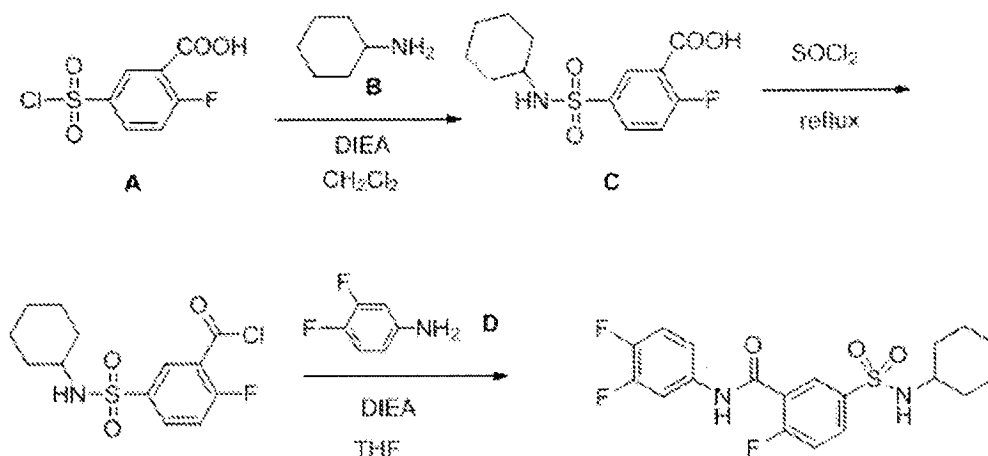


[0556] 3-(N-(2,2-Difluorocyclopropyl)sulfamoyl)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure H, final compound was obtained as a white solid (3 mg, 3 %). ¹H NMR (300 MHz, CDCl₃): δ 8.32 (m, 1H), 8.20 (m, 1H), 7.98 (s, 1H), 7.70 (m, 1H), 7.30 (m, 1H), 7.16 (m, 2H), 5.18 (s, 1H), 2.06 (m, 1H), 0.77 (m, 1H), 0.68 (m, 1H); MS (ES) m/z: 407.1 (M+ H⁺), calculated 407.04.

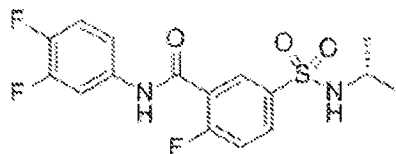
[0557] Example 9: General Procedure I:



[0558] **A** (0.506 g, 0.0021 mol), **B** (0.155 g, 0.00212 mol) and DIEA (1.1 mL, 0.00636 mol) (where DIEA is N,N-diisopropylethylamine) in CH_2Cl_2 were stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography on silica gel to give compound **C** (0.56g, 96%). After drying overnight under vacuum, **C** (0.56 g, 0.0020 mol) in SOCl_2 was heated at 80°C for 8h. After which the reagent was evaporated, dried under vacuum. The residue was then dissolved in THF (5mL), **D** (0.26g, 0.0020 mol) was added followed by DIEA (0.8 mL). The mixture was heated to 70°C overnight. The solvent was evaporated, followed by EtOAc extraction. After purification by column chromatography on silica gel (EtOAc/hexane), 0.45g (57%) of final product was obtained. ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.30 (d, $J = 14.1$ Hz, 1H), 8.00 (m, 1H), 7.70 (m, 1H), 7.26 (m, 1H), 7.15 (m, 2H), 4.46 (d, $J = 8.2$ Hz, 1H), 3.25 (m, 1H), 1.34 (m, 2H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 387.2 ($\text{M} + \text{H}^+$), calculated 387.09.

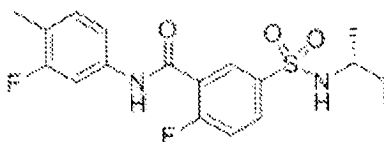


[0559] A (0.508 g, 0.0021 mol), B (0.211 g, 0.00212 mol) and DIEA (1.1 mL, 0.00636 mol) (where DIEA is N,N-diisopropylethylamine) in CH_2Cl_2 were stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography on silica gel to give compound C (0.6 g, 95%). After drying overnight under vacuum, C (0.22 g, 0.737 mmol) in SOCl_2 (5 mL) was heated at 80°C for overnight. After which the reagent was evaporated, dried under vacuum. The residue was then dissolved in THF (5 mL), D (95 mg, 0.737 mmol) was added followed by DIEA (0.8 mL). The mixture was heated to 70°C overnight. The solvent was evaporated, followed by EtOAc extraction. After purification by column chromatography on silica gel (EtOAc/hexane), 0.192 g (63%) of final product **18083** was obtained and submitted. ^1H NMR (300 MHz, CDCl_3): δ 8.59 (dd, $J = 7.2, 2.4$ Hz, 1H), 8.33 (d, $J = 13.4$ Hz, 1H), 8.00 (m, 1H), 7.70 (m, 1H), 7.20 (m, 1H), 7.12 (m, 2H), 4.62 (d, $J = 7.9$ Hz, 1H), 3.12 (m, 1H), 1.72 (m, 2H), 1.59 (m, 2H), 1.46 (m, 2H), 1.17 (m, 4H); MS (ES) m/z : 413.2 ($\text{M} + \text{H}^+$), calculated 413.11.

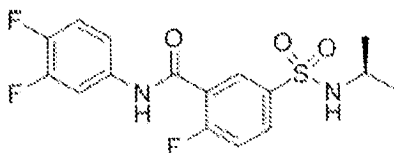


[0560] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (137 mg, 75%). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.32 (d, $J = 13.8$ Hz, 1H), 8.00

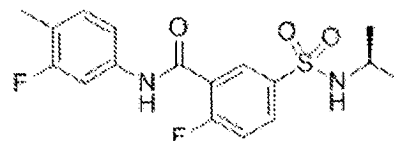
(m, 1H), 7.70 (m, 1H), 7.24 (m, 1H), 7.13 (m, 2H), 4.45 (d, $J = 8.2$ Hz, 1H), 3.26 (m, 1H), 1.37 (m, 2H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 3H); MS (ES) m/z : 387.1 ($M + H^+$), calculated 387.09.



[0561] (R)-5-(N-(*sec*-butyl)sulfamoyl)-2-fluoro-N-(3-fluoro-4-methylphenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (117 mg, 65 %). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.0, 2.4$ Hz, 1H), 8.29 (d, $J = 13.8$ Hz, 1H), 7.99 (m, 1H), 7.47 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.46 (m, 1H), 3.25 (m, 1H), 2.20 (d, $J = 2.0$ Hz, 3H), 1.36 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 383.2 ($M + H^+$), calculated 383.12.

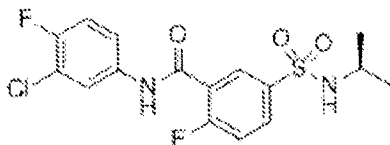


[0562] (S)-5-(N-(*sec*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (134 mg, 45%). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.29 (d, $J = 14.9$ Hz, 1H), 8.00 (m, 1H), 7.71 (m, 1H), 7.23 (m, 1H), 7.15 (m, 2H), 4.31 (d, $J = 8.2$ Hz, 1H), 3.26 (m, 1H), 1.37 (m, 2H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 3H); MS (ES) m/z : 387.1 ($M + H^+$), calculated 387.09.



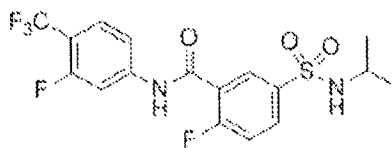
[0563] (S)-5-(N-(*sec*-butyl)sulfamoyl)-2-fluoro-N-(3-fluoro-4-methylphenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (86 mg, 44 %). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.29 (d, $J = 14.4$ Hz, 1H), 8.00 (m, 1H), 7.49 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.40 (m, 1H), 3.26 (m, 1H), 2.20 (d, $J = 2.0$ Hz,

3H), 1.36 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 383.2 ($M + H^+$), calculated 383.12.



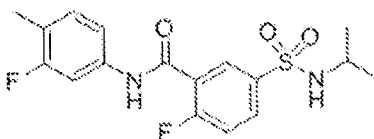
[0564] (S)-5-(N-(*sec*-butyl)sulfamoyl)-N-(3-chloro-4-fluorophenyl)-2-fluorobenzamide:

In a similar procedure as General Procedure I, final compound was obtained as a white solid (97 mg, 47 %). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.2, 2.5$ Hz, 1H), 8.27 (d, $J = 14.1$ Hz, 1H), 8.00 (m, 1H), 7.78 (dd, $J = 6.6, 2.8$ Hz, 1H), 7.39 (m, 1H), 7.25 (m, 1H), 7.09 (t, $J = 8.7$ Hz, 1H), 4.40 (d, $J = 8.2$ Hz, 1H), 3.26 (m, 1H), 1.35 (m, 2H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 403.1 ($M + H^+$), calculated 403.06.



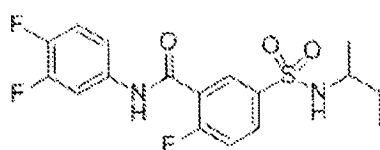
[0565] 5-(N-(*sec*-butyl)sulfamoyl)-2-fluoro-N-(3-fluoro-4-

(trifluoromethyl)phenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (68 mg, 38 %). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.2, 2.4$ Hz, 1H), 8.48 (d, $J = 14.4$ Hz, 1H), 8.02 (m, 1H), 7.77 (d, $J = 11.7$ Hz, 1H), 7.53 (t, $J = 8.2$ Hz, 1H), 7.27 (m, 1H), 4.38 (d, $J = 8.2$ Hz, 1H), 3.25 (m, 1H), 1.38 (m, 2H), 1.01 (m, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 437.2 ($M + H^+$), calculated 437.09.

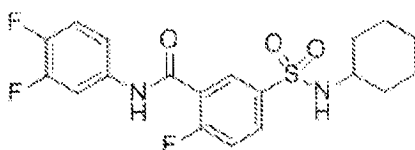


[0566] 5-(N-(*sec*-butyl)sulfamoyl)-2-fluoro-N-(3-fluoro-4-methylphenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (113 mg, 72 %). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.29 (d, $J = 13.5$ Hz, 1H), 7.99 (m,

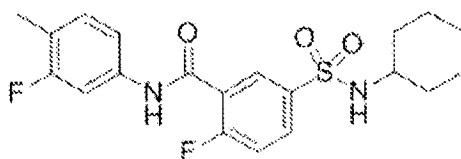
1H), 7.47 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.46 (m, 1H), 3.25 (m, 1H), 2.20 (d, $J = 2.0$ Hz, 3H), 1.36 (m, 2H), 1.00 (m, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 383.2 ($M + H^+$), calculated 383.12.



[0567] 5-(N-(*sec*-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (101 mg, 63%). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.30 (d, $J = 14.1$ Hz, 1H), 8.00 (m, 1H), 7.70 (m, 1H), 7.26 (m, 1H), 7.15 (m, 2H), 4.46 (d, $J = 8.2$ Hz, 1H), 3.25 (m, 1H), 1.34 (m, 2H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 387.2 ($M + H^+$), calculated 387.09.

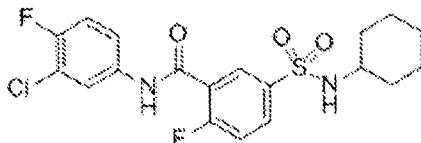


[0568] 5-(N-cyclohexylsulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (238 mg, 46 %). ^1H NMR (300 MHz, CDCl_3): δ 8.59 (dd, $J = 7.2, 2.4$ Hz, 1H), 8.33 (d, $J = 13.4$ Hz, 1H), 8.00 (m, 1H), 7.70 (m, 1H), 7.20 (m, 1H), 7.12 (m, 2H), 4.62 (d, $J = 7.9$ Hz, 1H), 3.12 (m, 1H), 1.72 (m, 2H), 1.59 (m, 2H), 1.46 (m, 2H), 1.17 (m, 4H); MS (ES) m/z : 413.2 ($M + H^+$), calculated 413.11.

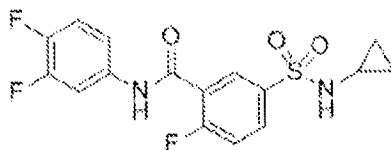


[0569] 5-(N-cyclohexylsulfamoyl)-2-fluoro-N-(3-fluoro-4-methylphenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (131 mg, 34 %). ^1H NMR (300 MHz, CDCl_3): δ 8.59 (dd, $J = 7.2, 2.4$ Hz, 1H), 8.33 (d, $J = 14.1$ Hz, 1H), 8.00 (m, 1H), 7.48 (m, 1H), 7.25 (m, 1H), 7.11 (m, 2H), 4.59 (d, $J = 7.9$ Hz, 1H), 3.12 (m, 1H), 2.20 (s,

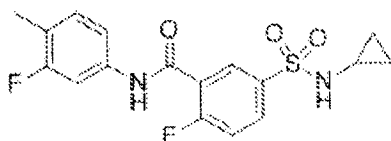
3H), 1.72 (m, 2H), 1.59 (m, 2H), 1.46 (m, 2H), 1.15 (m, 4H); MS (ES) m/z : 409.2 ($M+H^+$), calculated 409.13.



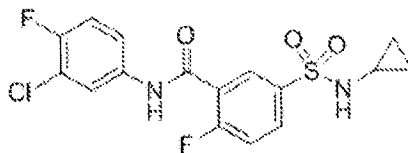
[0570] N-(3-chloro-4-fluorophenyl)-5-(N-cyclohexylsulfamoyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (139 mg, 35 %). ^1H NMR (300 MHz, CDCl_3): δ 8.59 (dd, $J = 7.1, 2.6$ Hz, 1H), 8.33 (d, $J = 13.7$ Hz, 1H), 8.00 (m, 1H), 7.78 (m, 1H), 7.39 (m, 1H), 7.26 (m, 1H), 7.18 (m, 1H), 4.67 (d, $J = 7.9$ Hz, 1H), 3.12 (m, 1H), 1.71 (m, 2H), 1.59 (m, 2H), 1.46 (m, 2H), 1.12 (m, 4H); MS (ES) m/z : 429.1 ($M+H^+$), calculated 429.08.



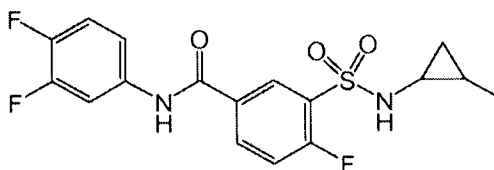
[0571] 5-(N-cyclopropylsulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (238 mg, 26 %). ^1H NMR (300 MHz, CDCl_3): δ 8.60 (dd, $J = 7.0, 2.4$ Hz, 1H), 8.30 (d, $J = 13.7$ Hz, 1H), 8.00 (m, 1H), 7.71 (m, 1H), 7.32 (m, 1H), 7.15 (m, 2H), 4.97 (s, 1H), 2.23 (m, 1H), 0.78 (m, 2H); MS (ES) m/z : 371.1 ($M+H^+$), calculated 371.06.



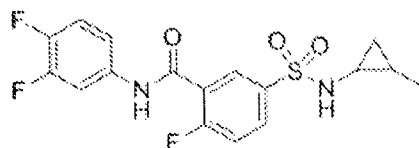
[0572] 5-(N-cyclopropylsulfamoyl)-2-fluoro-N-(3-fluoro-4-methylphenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (156 mg, 32 %). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.30 (d, $J = 13.8$ Hz, 1H), 8.00 (m, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 7.11 (m, 2H), 4.99 (s, 1H), 2.23 (m, 1H), 2.21 (s, 3H), 0.80 (m, 1H), 0.58 (m, 3H); MS (ES) m/z : 367.1 ($M+H^+$), calculated 367.08.



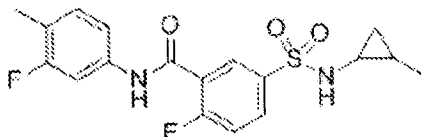
[0573] N-(3-chloro-4-fluorophenyl)-5-(N-cyclopropylsulfamoyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (119 mg, 26 %). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.0, 2.5$ Hz, 1H), 8.29 (d, $J = 13.7$ Hz, 1H), 8.00 (m, 1H), 7.78 (m, 1H), 7.41 (m, 1H), 7.30 (m, 1H), 7.11 (m, 1H), 4.99 (s, 1H), 2.22 (m, 1H), 0.78 (m, 1H), 0.58 (m, 3H); MS (ES) m/z : 387.1 ($\text{M} + \text{H}^+$), calculated 387.03.



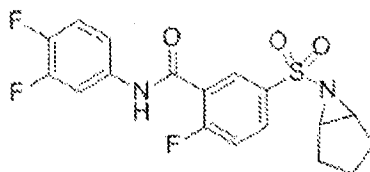
[0574] N-(3,4-difluorophenyl)-4-fluoro-3-(N-(2-methylcyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (90 mg, 85 %). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 6.5, 2.3$ Hz, 1H), 8.17 (m, 1H), 8.01 (s, 1H), 7.69 (m, 1H), 7.29 (m, 1H), 7.17 (m, 1H), 5.17 (s, 1H), 1.89 (m, 1H), 1.52 (d, $J = 9.0$ Hz, 3H), 0.88 (m, 2H), 0.75 (m, 1H); MS (ES) m/z : 385.1 ($\text{M} + \text{H}^+$), calculated 385.08.



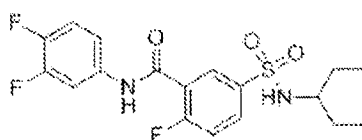
[0575] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(2-methylcyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (4 mg, 2 %). ^1H NMR (300 MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.30 (d, $J = 13.5$ Hz, 1H), 8.02 (m, 1H), 7.70 (m, 1H), 7.30 (m, 1H), 7.15 (m, 2H), 4.93 (s, 1H), 1.88 (m, 1H), 0.91 (m, 3H), 0.81 (m, 1H), 0.70 (m, 1H), 0.37 (m, 1H); MS (ES) m/z : 385.1 ($\text{M} + \text{H}^+$), calculated 385.08.



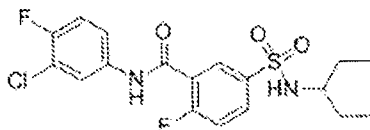
[0576] 2-fluoro-N-(3-fluoro-4-methylphenyl)-5-(N-(2-methylcyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure 1, final compound was obtained as a white solid (5 mg, 5 %). ^1H NMR (300 MHz, CDCl_3): δ 8.62 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.26 (d, $J = 14.1$ Hz, 1H), 8.01 (m, 1H), 7.49 (d, $J = 12.0$ Hz, 1H), 7.29 (dd, $J = 11.7, 8.2$ Hz, 1H), 7.11 (m, 2H), 4.84 (s, 1H), 2.20 (d, $J = 2.2$ Hz, 3H), 1.89 (m, 1H), 0.90 (m, 3H), 0.74 (m, 2H), 0.35 (m, 1H); MS (ES) m/z : 381.2 ($\text{M} + \text{H}^+$), calculated 381.10.



[0577] 5-(6-azabicyclo[3.1.0]hexan-6-ylsulfonyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (27 mg, 12 %). ^1H NMR (300 MHz, CDCl_3): δ 8.62 (dd, $J = 7.0, 2.3$ Hz, 1H), 8.29 (d, $J = 14.4$ Hz, 1H), 8.04 (m, 1H), 7.69 (m, 1H), 7.30 (dd, $J = 11.4, 8.8$ Hz, 1H), 7.16 (m, 2H), 4.78 (d, $J = 6.2$ Hz, 1H), 3.94 (m, 1H), 3.54 (m, 1H), 2.15 (m, 2H), 1.78 (m, 2H), 1.66 (m, 1H), 1.41 (m, 2H); MS (ES) m/z : 397.2 ($\text{M} + \text{H}^+$), calculated 397.08.

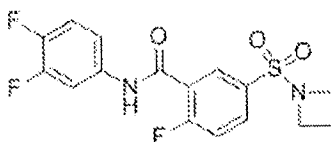


[0578] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(pentan-3-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (239 mg, 74 %). ^1H NMR (300 MHz, CD_3OD): δ 8.22-8.19 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.48-7.36 (m, 2H), 7.31-7.21 (m, 1H), 3.11-3.06 (m, 1H), 1.51-1.42 (m, 2H), 1.40-1.28 (m, 2H), 0.79-0.74 (t, $J = 7.3$ Hz, 6H); MS (ES) m/z : 401.2 ($\text{M} + \text{H}^+$), calculated 401.11.

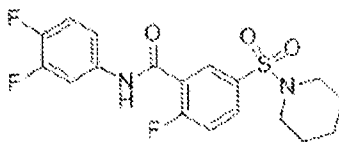


[0579] N-(3-chloro-4-fluorophenyl)-2-fluoro-5-(N-(pentan-3-yl)sulfonyl)benzamide:

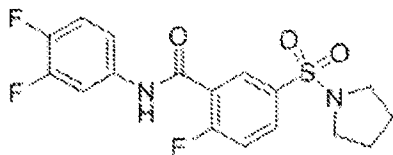
In a similar procedure as General Procedure I, final compound was obtained as a beige solid (244 mg, 72%). ¹H NMR (300 MHz, CD₃OD): δ 8.23-8.20 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.07-8.02 (m, 1H), 7.98-7.94 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.61-7.56 (m, 1H), 7.48-7.42 (dd, *J* = 9.9, 8.8 Hz, 1H), 7.28-7.22 (t, *J* = 9.1 Hz, 1H), 3.11-3.06 (m, 1H), 1.51-1.40 (m, 2H), 1.38-1.28 (m, 2H), 0.79-0.74 (t, *J* = 7.6 Hz, 6H); MS (ES) *m/z*: 417.1 (M+ H⁺), calculated 417.08.



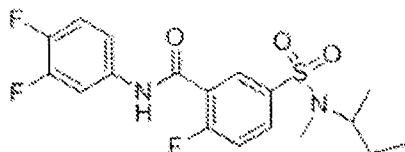
[0580] 5-(azetidin-1-ylsulfonyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (34 mg, 12 %). ¹H NMR (300 MHz, CD₃OD): δ 8.56 (bs, 1H), 8.10-8.07 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.89-7.84 (m, 1H), 7.38-7.32 (dd, *J* = 10, 8.6 Hz, 1H), 7.18-7.02 (m, 2H), 6.89-6.83 (m, 1H), 3.66-3.62 (t, *J* = 6.5 Hz, 2H), 3.56-3.50 (m, 2H), 2.11-2.01 (m, 2H); MS (ES) *m/z*: 371.1 (M+ H⁺), calculated 371.06.



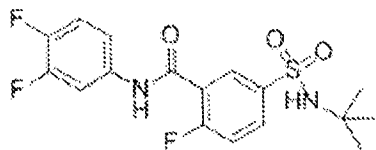
[0581] N-(3,4-difluorophenyl)-2-fluoro-5-(piperidin-1-ylsulfonyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (74 mg, 26 %). ¹H NMR (300 MHz, CD₃OD): δ 8.10-8.07 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.99-7.94 (m, 1H), 7.85-7.79 (m, 1H), 7.54-7.47 (dd, *J* = 9.6, 8.6 Hz, 1H), 7.40-7.36 (m, 1H), 7.31-7.22 (m, 1H), 3.04-3.01 (t, *J* = 5.3 Hz, 4H), 1.68-1.61 (m, 4H), 1.50-1.44 (m, 2H); MS (ES) *m/z*: 399.2 (M+ H⁺), calculated 399.09.



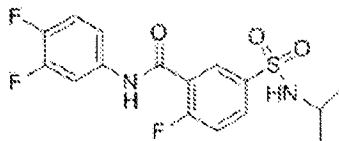
[0582] N-(3,4-difluorophenyl)-2-fluoro-5-(pyrrolidin-1-ylsulfonyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (164 mg, 58%). ¹H NMR (300 MHz, CD₃OD): 8.17-8.14 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.54-7.47 (dd, *J* = 9.8, 8.8 Hz, 1H), 7.40-7.37 (m, 1H), 7.31-7.22 (m, 1H), 3.29-3.25 (m, 4H), 1.81-1.76 (m, 4H); MS (ES) *m/z*: 385.1 (*M* + *H*⁺), calculated 385.08.



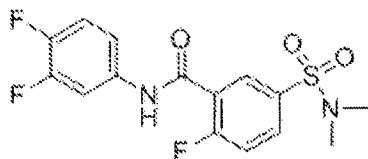
[0583] 5-(N-(sec-butyl)-N-methylsulfonyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (31 mg, 12 %). ¹H NMR (300 MHz, CD₃OD): 7.93-7.70 (m, 1H), 7.69-7.66 (m, 1H), 7.42-7.34 (m, 1H), 7.19-7.03 (m, 2H), 6.89-6.83 (m, 1H), 4.69-4.59 (m, 1H), 2.92 (s, 3H), 1.64-1.48 (m, 2H), 1.22-1.20 (d, *J* = 6.7 Hz, 3H), 0.98-0.90 (m, 3H); MS (ES) *m/z*: 401.2 (*M* + *H*⁺), calculated 401.11.



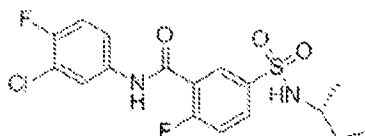
[0584] 5-(N-(tert-butyl)sulfonyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (171 mg, 52 %). ¹H NMR (300 MHz, CD₃OD): 8.23-8.20 (dd, *J* = 6.5, 2.3 Hz, 1H), 8.09-8.03 (m, 1H), 7.86-7.79 (m, 1H), 7.47-7.36 (m, 2H), 7.31-7.21 (m, 1H), 1.21 (s, 9H); MS (ES) *m/z*: 387.2 (*M* + *H*⁺), calculated 387.09.



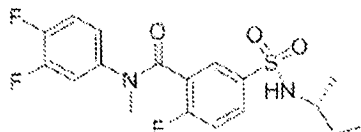
[0585] N-(3,4-difluorophenyl)-2-fluoro-5-(N-isopropylsulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (262 mg, 72 %). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.49-7.43 (dd, $J = 10.0, 8.8$ Hz, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 3.45-3.36 (m, 1H), 1.06-1.04 (d, $J = 6.4$ Hz, 6H); MS (ES) m/z : 373.1 ($\text{M} + \text{H}^+$), calculated 373.08.



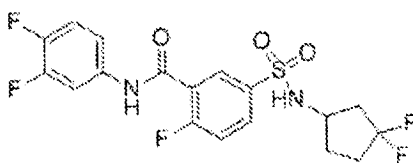
[0586] N-(3,4-difluorophenyl)-5-(N,N-dimethylsulfamoyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (196 mg, 66 %). ^1H NMR (300 MHz, CD_3OD): 8.13-8.10 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.02-7.97 (m, 1H), 7.87-7.80 (m, 1H), 7.79-7.49 (m, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 2.73 (s, 6H); MS (ES) m/z : 359.1 ($\text{M} + \text{H}^+$), calculated 359.06.



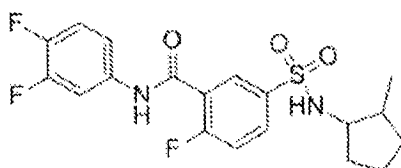
[0587] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(3-chloro-4-fluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (59 mg, 24 %). ^1H NMR (300 MHz, CD_3OD): 8.23-8.20 (m, 1H), 8.07-8.04 (m, 1H), 7.98-7.94 (m, 1H), 7.58-7.57 (m, 1H), 7.49-7.43 (m, 1H), 7.28-7.22 (m, 1H), 3.24-3.20 (m, 1H), 1.43-1.38 (m, 2H), 1.00-0.98 (d, $J = 6.7$ Hz, 3H), 0.84-0.79 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z : 403.1 ($\text{M} + \text{H}^+$), calculated 403.06.



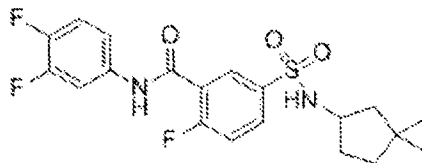
[0588] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluoro-N-methylbenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (67 mg, 24 %). ^1H NMR (300 MHz, CD_3OD): 7.84-7.82 (m, 2H), 7.32-7.06 (m, 4H), 3.46 (s, 3H), 3.01-2.95 (m, 1H), 1.36-1.29 (m, 2H), 0.88-0.86 (d, $J = 6.4$ Hz, 3H), 0.77-0.72 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 401.2 ($\text{M} + \text{H}^+$), calculated 401.11.



[0589] 5-(N-(3,3-difluorocyclopentyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (41 mg, 53%). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (m, 1H), 8.07-8.02 (m, 1H), 7.85-7.79 (m, 1H), 7.49-7.36 (m, 2H), 7.31-7.22 (m, 1H), 3.07-2.99 (m, 1H), 3.79-3.71 (m, 1H), 2.34-2.06 (m, 1H), 2.03-1.87 (m, 2H), 1.71-1.61 (m, 1H), 1.33-1.24 (m, 1H), 0.89-0.79 (m, 1H); MS (ES) m/z : 435.2 ($\text{M} + \text{H}^+$), calculated 435.07

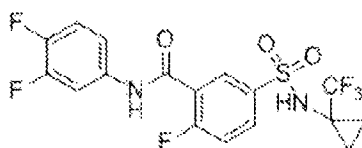


[0590] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(2-methylcyclopentyl)sulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (62 mg, 85 %). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (m, 1H), 8.07-8.02 (m, 1H), 7.85-7.79 (m, 1H), 7.49-7.36 (m, 2H), 7.31-7.22 (m, 1H), 3.07-2.99 (m, 1H), 1. -3.71 (m, 1H), 2.34-2.06 (m, 1H), 2.03-1.87 (m, 2H), 1.71-1.61 (m, 1H), 1.33-1.24 (m, 1H), 0.89-0.79 (m, 1H); MS (ES) m/z : 435.2 ($\text{M} + \text{H}^+$), calculated 435.07.



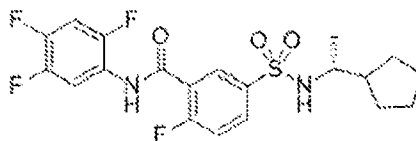
[0591] N-(3,4-difluorophenyl)-5-(N-(3,3-dimethylcyclopentyl)sulfamoyl)-2-

fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (54 mg, 89%). ¹H NMR (300 MHz, CD₃OD): 8.21-8.18 (dd, *J* = 6.4, 2.3 Hz, 1H), 8.07-8.01 (m, 1H), 7.86-7.79 (m, 1H), 7.46-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.72-3.54 (m, 1H), 2.01-1.84 (m, 1H), 1.64-1.53 (m, 1H), 1.50-1.40 (m, 2H), 1.37-1.15 (m, 2H), 1.01 (s, 3H), 0.91 (s, 3H); MS (ES) *m/z*: 427.2 (*M*+ *H*⁺), calculated 427.12.



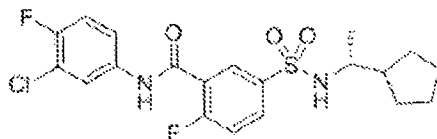
[0592] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(1-

(trifluoromethyl)cyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (22.3 mg, 18 %). ¹H NMR (300 MHz, CD₃OD): 8.20-8.18 (m, 1H), 8.10-8.04 (m, 1H), 7.90-7.79 (m, 1H), 7.49-7.37 (m, 2H), 7.31-7.21 (m, 1H), 1.21 (s, 4H); MS (ES) *m/z*: 439.2 (*M*+ *H*⁺), calculated 439.05.

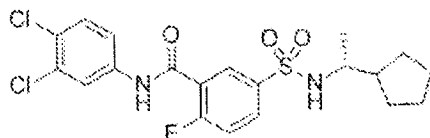


[0593] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-2-fluoro-N-(2,4,5-

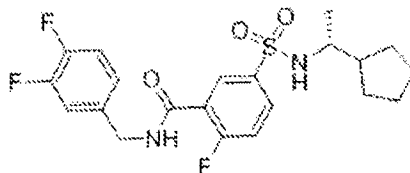
trifluorophenyl)benzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (8.3 mg, 14 %). ¹H NMR (300 MHz, CD₃OD): 8.31-8.28 (dd, *J* = 6.4, 2.3 Hz, 1H), 8.13-8.04 (m, 2H), 7.50-7.43 (m, 1H), 7.37-7.28 (m, 1H), 3.18-3.13 (m, 1H), 1.85-1.74 (m, 1H), 1.68-1.51 (m, 6H), 1.20-1.15 (m, 2H), 0.96-0.94 (d, *J* = 6.4 Hz, 3H); MS (ES) *m/z*: 445.2 (*M*+ *H*⁺), calculated 445.11.



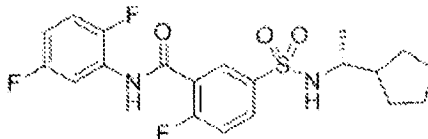
[0594] (R)-N-(3-chloro-4-fluorophenyl)-5-(N-(1-cyclopentylethyl)sulfamoyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (18 mg, 10 %). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.07-8.02 (m, 1H), 7.97-7.94 (m, 1H), 7.61-7.56 (m, 1H), 7.48-7.42 (m, 1H), 7.28-7.25 (m, 1H), 3.18-3.13 (m, 1H), 1.82-1.74 (m, 1H), 1.67-1.51 (m, 6H), 1.29-1.12 (m, 2H), 0.96-0.94 (d, $J = 6.4$ Hz, 3H); MS (ES) m/z : 443.2 ($\text{M} + \text{H}^+$), calculated 443.09.



[0595] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-N-(3,4-dichlorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a beige solid (49 mg, 25%). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.06-8.02 (m, 2H), 7.61-7.57 (m, 1H), 7.52-7.42 (m, 2H), 3.17-3.13 (m, 1H), 1.84-1.47 (m, 7H), 1.28-1.11 (m, 2H), 0.96-0.94 (d, $J = 6.4$ Hz, 3H); MS (ES) m/z : 459.2 ($\text{M} + \text{H}^+$), calculated 459.06.

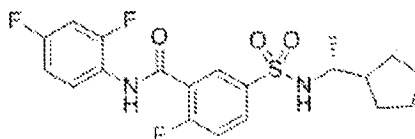


[0596] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-N-(3,4-difluorobenzyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a colorless oil (29.1 mg, 16 %). ^1H NMR (300 MHz, CD_3OD): 8.22-8.19 (dd, $J = 6.6, 2.6$ Hz, 1H), 8.04-7.98 (m, 1H), 7.45-7.38 (m, 1H), 7.31-7.18 (m, 2H), 4.55 (s, 2H), 3.15-3.10 (m, 1H), 1.83-1.75 (m, 1H), 1.68-1.46 (m, 6H), 1.29-1.08 (m, 2H), 0.94-0.92 (d, $J = 6.4$ Hz, 3H); MS (ES) m/z : 441.3 ($\text{M} + \text{H}^+$), calculated 441.14.



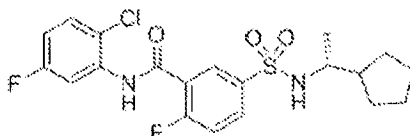
[0597] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-N-(2,5-difluorophenyl)-2-

fluorobenzamide: In a similar procedure as as General Procedure I, final compound was obtained as a white solid (47 mg, 32 %). ^1H NMR (300 MHz, CD_3OD): 8.32-8.30 (dd, $J = 6.4, 2.0$ Hz, 1H), 8.09-8.00 (m, 2H), 7.50-7.44 (m, 1H), 7.27-7.19 (m, 1H), 7.00-6.92 (m, 1H), 3.20-3.11 (m, 1H), 1.85-1.75 (m, 1H), 1.68-1.51 (m, 6H), 1.29-1.14 (m, 2H), 0.97-0.95 (d, $J = 6.4$ Hz, 3H); MS (ES) m/z : 427.2 ($\text{M} + \text{H}^+$), calculated 427.12.



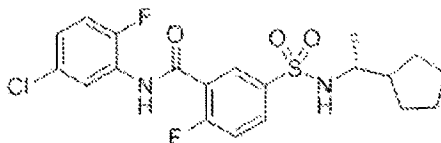
[0598] (R)-5-(N-(1-cyclopentylethyl)sulfamoyl)-N-(2,4-difluorophenyl)-2-

fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (54 mg, 29 %). ^1H NMR (300 MHz, CD_3OD): 8.30-8.27 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.09-8.03 (m, 1H), 7.92-7.87 (m, 1H), 7.50-7.44 (m, 1H), 7.14-7.00 (m, 2H), 3.20-3.13 (m, 1H), 1.85-1.74 (m, 1H), 1.68-1.51 (m, 6H), 1.29-1.12 (m, 2H), 0.97-0.94 (d, $J = 6.7$ Hz, 3H); MS (ES) m/z : 427.3 ($\text{M} + \text{H}^+$), calculated 427.12.

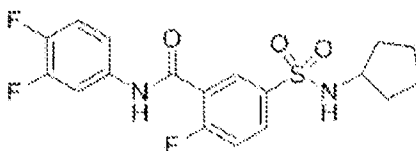


[0599] (R)-N-(2-chloro-5-fluorophenyl)-5-(N-(1-cyclopentylethyl)sulfamoyl)-2-

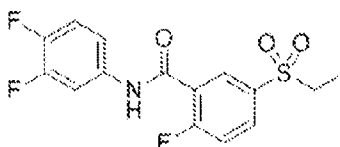
fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (24 mg, 13 %). ^1H NMR (300 MHz, CD_3OD): 8.46-8.43 (dd, $J = 6.7, 2.3$ Hz, 1H), 8.12-8.07 (m, 2H), 7.55-7.47 (m, 2H), 7.04-6.97 (m, 1H), 3.18-3.14 (m, 1H), 1.86-1.77 (m, 1H), 1.68-1.51 (m, 6H), 1.28-1.11 (m, 2H), 0.97-0.95 (d, $J = 6.7$ Hz, 3H); MS (ES) m/z : 443.2 ($\text{M} + \text{H}^+$), calculated 443.09.



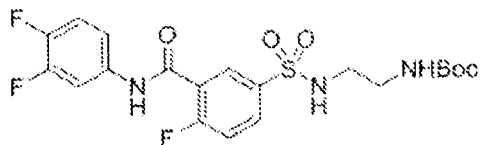
[0600] (R)-N-(5-chloro-2-fluorophenyl)-5-(N-(1-cyclopentylethyl)sulfamoyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (30 mg, 16 %). ^1H NMR (300 MHz, CD_3OD): 8.32-8.29 (dd, $J = 6.5, 2.2$ Hz, 1H), 8.19-8.17 (m, 1H), 8.09-8.04 (m, 1H), 7.50-7.44 (m, 1H), 7.24-7.21 (m, 2H), 3.20-3.11 (m, 1H), 1.85-1.75 (m, 1H), 1.72-1.51 (m, 6H), 1.28-1.12 (m, 2H), 0.97-0.95 (d, $J = 6.5$ Hz, 3H); MS (ES) m/z : 443.2 ($\text{M} + \text{H}^+$), calculated 443.09.



[0601] 5-(N-Cyclopentylsulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (300 mg, 45 %). ^1H NMR (300 MHz, CDCl_3): δ 8.67-8.65 (m, 1H), 8.64-8.37 (m, 1H), 8.10-8.04 (m, 1H), 7.80-7.73 (m, 1H), 7.26-7.12 (m, 3H), 4.72-4.13 (m, 1H), 3.69-3.62 (m, 1H), 1.88-1.78 (m, 2H), 1.69-1.26 (m, 6H); MS (ES) m/z : 399.1 ($\text{M} + \text{H}^+$), calculated 399.09.

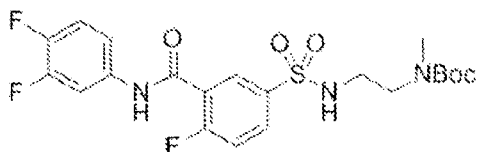


[0602] N-(3,4-Difluorophenyl)-5-(ethylsulfonyl)-2-fluorobenzamide: In a similar procedure as General Procedure I, final compound was obtained as a white solid (155.5 mg, 96.4 %). ^1H NMR (300 MHz, d_4 -MeOH): 8.27-8.24 (m, 1H), 8.14-8.09 (m, 1H), 7.86-7.79 (m, 1H), 7.57-7.51 (t, $J = 9.1$ Hz, 1H), 7.40-7.22 (m, 2H), 3.30-3.24 (m, 2H), 1.28-1.23 (t, $J = 7.6$ Hz, 3H); MS (ES) m/z : 344.2 ($\text{M} + \text{H}^+$), calculated 344.05.



[0603] *tert*-Butyl (2-(3-((3,4-difluorophenyl)carbamoyl)-4-

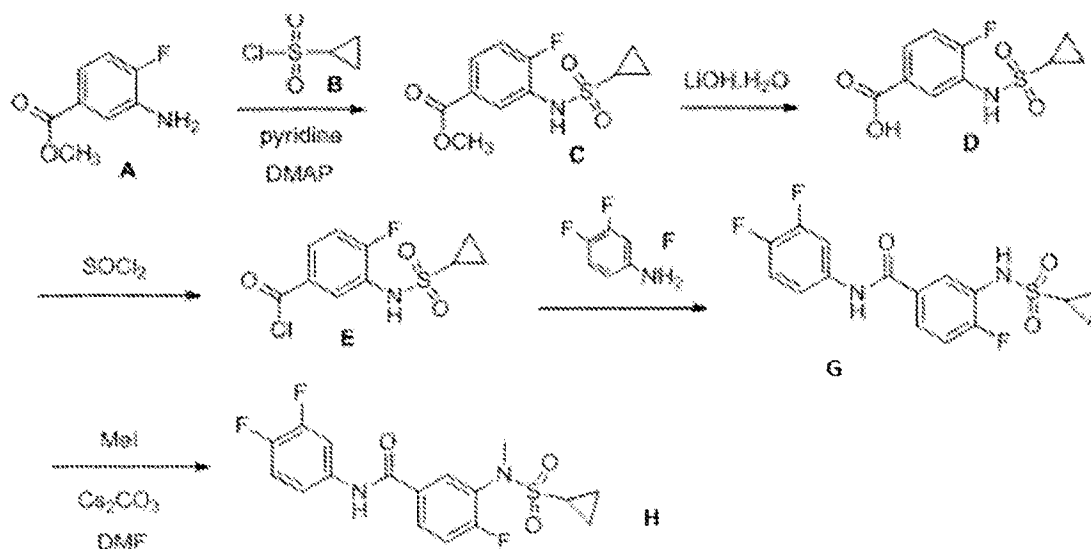
fluorophenylsulfonamido)ethyl) carbamate: In a similar procedure as General Procedure I, final compound was obtained as a white solid (54.6 mg, 40 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.20-8.17 (m, 1H), 8.06-8.01 (m, 1H), 7.86-7.78 (m, 1H), 7.49-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.12-3.07 (m, 2H), 2.98-2.94 (t, $J = 6.3$ Hz, 2H), 1.40 (s, 9H); MS (ES) m/z : 496.2 ($\text{M} + \text{Na}^+$), calculated 496.12.



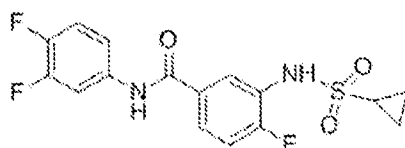
[0604] *tert*-Butyl (2-(3-((3,4-difluorophenyl)carbamoyl)-4-

fluorophenylsulfonamido)ethyl)(methyl) carbamate: In a similar procedure as General Procedure I, final compound was obtained as a white solid (102 mg, 72 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.19-8.18 (m, 1H), 8.06-8.01 (m, 1H), 7.86-7.77 (m, 1H), 7.50-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.06-2.99 (m, 2H), 2.89-2.82 (m, 2H), 1.44 (s, 9H), 1.42 (s, 3H); MS (ES) m/z : 510.2 ($\text{M} + \text{Na}^+$), calculated 510.14.

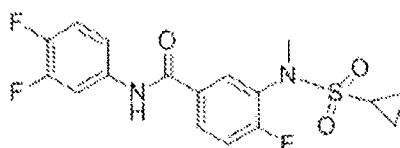
[0605] Example 10: General Procedure J:



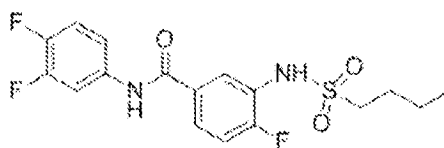
[0606] **A** (0.255 g, 1.51 mmol) was dissolved in pyridine, **B** (0.344 g, 1.88 mmol) and DMAP (92.2 mg, 0.755 mmol) were added and the mixture was stirred at 110 °C overnight. The solvent was evaporated and the crude product was extracted with CH_2Cl_2 and washed with 1N HCl, 2N H_2SO_4 , followed by H_2O and brine, dried (Na_2SO_4) and concentrated to give the crude product **C** which was directly used for the next step. Product **C** was treated with $\text{LiOH} \cdot \text{H}_2\text{O}$ in Dioxane and H_2O overnight. The solvent was evaporated, adjusted pH with 1N HCl to slightly acidic, extracted with EtOAc, dried and concentrated to give product **D**. After dried overnight, **D** (0.37g, 1.4 mmol) was reflux in SOCl_2 (5mL) for 2h, after evaporate excess SOCl_2 , dried to give **E** (0.4188g). The residue **E** was then dissolved in THF (5mL), **F** (195 mg, 1.5 mmol) was added followed by DIEA (0.6 mL) (where DIEA is N,N-diisopropylethylamine). The mixture was stirred at room temperature overnight. The solvent was evaporated, followed by EtOAc extraction. After purified by isco (EtOAc/hexane), 0.337 g (63%) of final product **G** was obtained. Into **G** (20 mg, 0.054 mmol) in DMF (2 mL) was added MeI (1 eq) and Cs_2CO_3 (19.3 mg, 0.059 mmol). The mixture was stirred at room temperature overnight. The solvent was evaporated and prep-TLC to give the product **H** (18.3 mg, 88%).



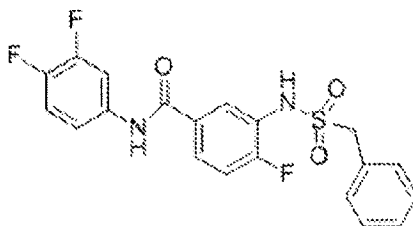
[0607] 3-(cyclopropanesulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure J, final compound was obtained as a white solid (336.7 mg, 63 %). ¹H NMR (300 MHz, CD₃OD): 8.11-8.09 (m, 1H), 7.83-7.80 (m, 2H), 7.40-7.20 (m, 3H), 2.70-2.60 (m, 1H), 1.03-0.98 (m, 4H); MS (ES) m/z: 371.2 (M+ H⁺), calculated 371.06.



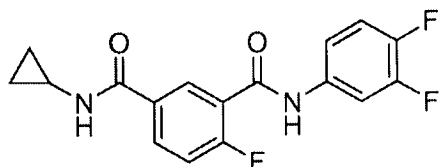
[0608] N-(3,4-difluorophenyl)-4-fluoro-3-(N-ethylcyclopropanesulfonamido)benzamide: In a similar procedure as General Procedure J, final compound was obtained as a white solid (18.3 mg, 88.4 %). ¹H NMR (300 MHz, CD₃OD): 8.11-8.07 (dd, *J* = 7.3, 2.1 Hz, 1H), 8.02-7.97 (m, 1H), 7.85-7.77 (m, 1H), 7.43-7.34 (m, 2H), 7.29-7.20 (m, 1H), 3.36 (s, 3H), 2.76-2.69 (m, 1H), 1.10-1.01 (m, 4H); MS (ES) m/z: 385.2 (M+ H⁺), calculated 385.08.



[0609] 3-(butylsulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide: In a similar procedure as General Procedure J, final compound was obtained as a white solid (94.8 mg, 79 %). ¹H NMR (300 MHz, CD₃OD): 8.09-8.06 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.82-7.74 (m, 2H), 7.39-7.20 (m, 3H), 3.18-3.13 (m, 2H), 1.86-1.76 (m, 2H), 1.49-1.42 (m, 2H), 0.96-0.91 (t, *J* = 7.3 Hz, 3H); MS (ES) m/z: 387.2 (M+ H⁺), calculated 387.09.

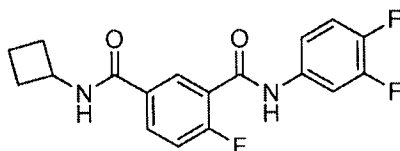


[0610] N-(3,4-Difluorophenyl)-4-fluoro-3-(phenylmethanesulfonyl)benzamide: In a similar procedure as General Procedure J, final compound was obtained as a white solid (30.4 mg, 24 %). ¹H NMR (300 MHz, d₄-MeOH): 7.93-7.90 (m, 1H), 7.83-7.75 (m, 1H), 7.71-7.65 (m, 1H), 7.42-7.35 (m, 3H), 7.32-7.20 (m, 5H), 4.51 (s, 2H); MS (ES) m/z: 421.2 (M+H⁺), calculated 421.08.



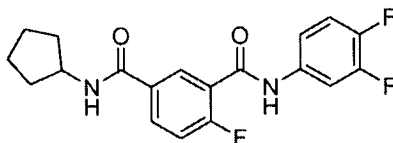
[0611] Example 11: General Procedure K: N¹-cyclopropyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide: In a microwave vial (Biotage) was charged with N-(3,4-difluorophenyl)-2-fluoro-5-iodobenzamide (100.0 mg, 0.26 mmol), palladium acetate (8.9 mg, 0.013 mmol), sodium carbonate (82.7 mg, 0.78 mmol), Mo(CO)₆ (34.3 mg, 0.13 mmol) and water (1 mL). The mixture was sealed, evacuated, and refilled with Ar. cyclopropanamine (0.09 mL, 1.33 mmol) was added into the mixture, which was then heated at 100 °C in microwave reactor for 15 minutes. The mixture was diluted with ethyl acetate, washed with HCl (2N) twice, saturated NaHCO₃, and brine. The organic phase was concentrated, and the residue was purified on silica gel (24 g), eluted with a gradient of ethyl acetate and hexanes from 2 : 8 to 1 : 1 to give the compound as a light yellow solid (22.2 mg, 25%). ¹H NMR (300 MHz, CDCl₃-MeOD): δ 8.21 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.99 (ddd, *J* = 8.5, 5.0, 2.3 Hz, 1H), 7.70 (ddd, *J* = 12.0, 7.3, 2.3 Hz, 1H), 7.25-7.04 (m, 3H), 2.87-2.77 (m, 1H), 0.84-0.75 (m, 2H), 0.62-0.55 (m, 2H); Calculated for C₁₇H₁₃F₃N₂O₂, 334.09; observed MS (ESI) (m/z) 335.1 (M + 1)⁺.

[0612] The following compounds can be prepared by following General Procedure K, the procedure for the synthesis of N¹-cyclopropyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide.

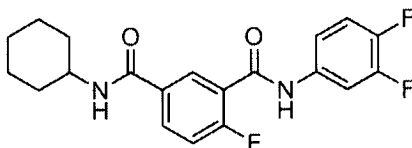


[0613] N¹-cyclobutyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide: yield: 38%; ¹H NMR (300 MHz, CDCl₃-MeOD): δ 8.26 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.98 (ddd, *J* = 8.5, 5.0, 2.3 Hz, 1H), 7.71 (ddd, *J* = 12.0, 7.0, 2.3 Hz, 1H), 7.30-7.14 (m, 3H), 4.55-4.40 (m, 1H), 2.42-2.28 (m, 2H),

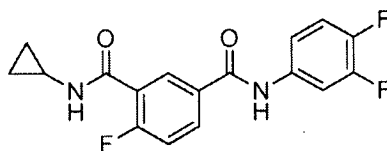
2.06-1.88 (m, 2H), 1.82-1.64 (m, 2H); Calculated for $C_{18}H_{15}F_3N_2O_2$, 348.11; MS (ESI) (m/z) observed 349.1 ($M + 1$)⁺.



[0614] N¹-cyclopentyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide: Yield, 27%; ¹H NMR (300 MHz, CDCl₃-MeOD): δ 8.15 (dd, $J = 6.7, 2.3$ Hz, 1H), 7.92 (ddd, $J = 8.8, 5.0, 2.3$ Hz, 1H), 7.70 (ddd, $J = 12.3, 7.0, 2.3$ Hz, 1H), 7.25-7.04 (m, 3H), 4.36-4.20 (m, 1H), 2.08-1.90 (m, 2H), 1.75-1.38 (m, 6H); Calculated for $C_{19}H_{17}F_3N_2O_2$, 362.12; observed MS (ESI) (m/z) 363.2 ($M + 1$)⁺.

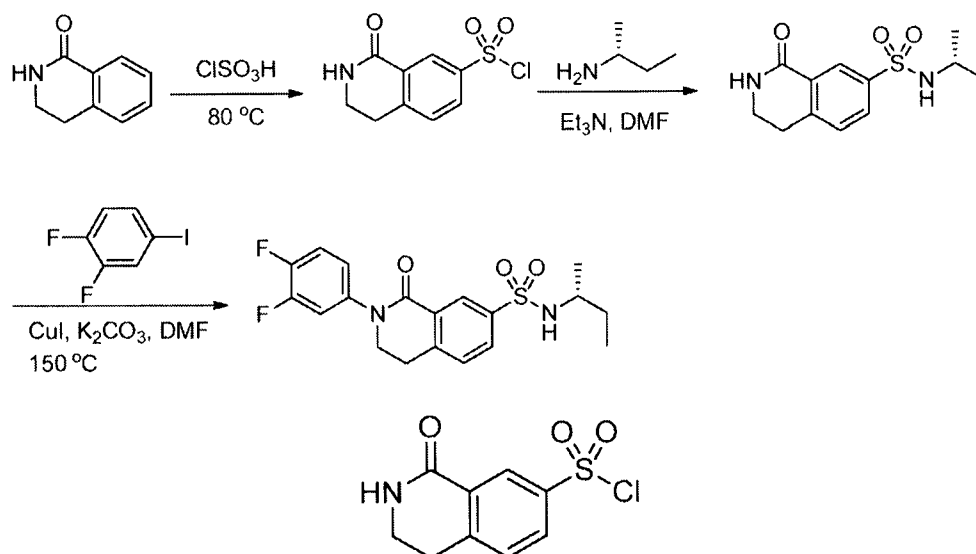


[0615] N¹-cyclohexyl-N³-(3,4-difluorophenyl)-4-fluoroisophthalamide: Yield, 30%; ¹H NMR (300 MHz, CDCl₃-MeOD): δ 8.22-8.15 (m, 1H), 7.98-7.90 (m, 1H), 7.75-7.65 (m, 1H), 7.24-7.04 (m, 3H), 3.92-3.76 (m, 1H), 2.00-1.00 (m, 10H); Calculated for $C_{20}H_{19}F_3N_2O_2$, 376.14; observed MS (ESI) (m/z) 377.2 ($M + 1$)⁺.

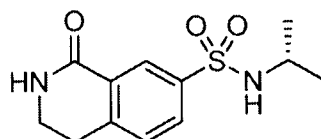


[0616] N³-cyclopropyl-N¹-(3,4-difluorophenyl)-4-fluoroisophthalamide: In a microwave vial (Biotage) was charged with 3-bromo-N-(3,4-difluorophenyl)-4-fluorobenzamide (86.0 mg, 0.26 mmol), palladium acetate (8.9 mg, 0.013 mmol), sodium carbonate (82.7 mg, 0.78 mmol), Xantphos (15.0 mg, 0.026 mmol), Mo(CO)₆ (34.3 mg, 0.13 mmol) and water (2 mL). The mixture was sealed, evacuated, and refilled with Ar. cyclopropanamine (0.09 mL, 1.33 mmol) was added into the mixture, which was then heated at 170 °C in microwave reactor for 15 minutes. The mixture was diluted with ethyl acetate, washed with HCl (2N) twice, saturated NaHCO₃, and brine. The organic phase was concentrated, and the residue was purified on silica gel (24 g), eluted with a gradient of ethyl acetate and hexanes from 1 : 9 to 3 : 7 to give the compound as a light yellow solid (26.0 mg, 30%). ¹H NMR (300 MHz, CDCl₃-MeOD): δ 8.31 (dd, $J = 6.7, 2.3$ Hz, 1H), 8.00 (ddd, $J = 8.5, 4.7, 2.3$ Hz, 1H),

7.73-7.63 (m, 1H), 7.36-7.26 (m, 1H), 7.21-7.02 (m, 2H), 2.87-2.77 (m, 1H), 0.85-0.77 (m, 2H), 0.62-0.55 (m, 2H); Calculated for $C_{17}H_{13}F_3N_2O_2$, 334.09; observed MS (ESI) (m/z) 335.2 ($M + 1$)⁺.

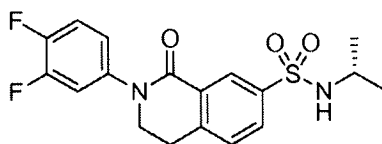


[0617] 1-oxo-1,2,3,4-tetrahydroisoquinoline-7-sulfonyl chloride: 3,4-dihydroisoquinolin-1(2H)-one (300 mg, 2.0 mmol) was dissolved in sulfurochloridic acid (3 mL). The solution was heated at 80°C for 4 hrs and cooled to room temperature. The mixture was poured onto ice in a separatory funnel and extracted with methylene chloride (10 mL x 3). The combined organic phase was washed with water, brine, and dried over Na₂SO₄. Concentration provided a white solid, which was used directly in the next step. Calculated for $C_9H_8ClNO_3S$, 244.99; observed MS (ESI) (m/z) 246.0 ($M + 1$)⁺.



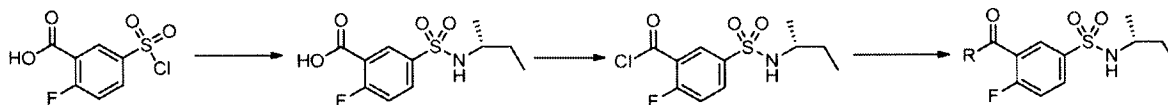
[0618] (R)-N-(sec-butyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide: The white solid obtained above was dissolved in DMF (2 mL) and added to a stirred solution of (R)-butan-2-amine (0.41 mL, 4.0 mmol) and triethyl amine (1.1 mL, 8 mmol) in DMF (3 mL) at rt. After 30 min at this temperature, the mixture was diluted with ethyl acetate, washed with HCl (2N, 5 mL x 2), saturated NaHCO₃, brine, and concentrated. The residue was purified on silica gel (40 g) with a gradient of ethyl acetate : hexanes from 1 : 1 to 1 : 0 gave the desired product as a white solid (300

mg, 52% for two steps). ^1H NMR (300 MHz, DMSO): δ 8.26 (d, $J = 2.0$ Hz, 1H), 8.16 (bs, 1H, CONH), 7.86 (dd, $J = 7.9, 2.0$ Hz, 1H), 7.60 (d, $J = 7.9$ Hz, 1H, SO₂NH), 7.52 (d, $J = 8.0$ Hz, 1H), 3.40 (td, $J = 6.4, 2.9$ Hz, 2H), 3.10-2.95 (m, 3H), 1.30 (dt, $J = 14.1, 7.6$ Hz, 2H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.71 (t, $J = 7.3$ Hz, 3H); Calculated for C₁₃H₁₈N₂O₃S, 282.1; observed MS (ESI) (m/z) 283.2 ($M + 1$)⁺.



[0619] (R)-N-(sec-butyl)-2-(3,4-difluorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide: To a pressure tube was charged with (R)-N-(sec-butyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (135 mg, 0.48 mmol), 1,2-difluoro-4-iodobenzene (230 mg, 0.96 mmol), potassium carbonate (78 mg, 0.56 mmol), CuI (9.5 mg, 0.05 mmol), and DMF (5 mL). The mixture was degassed with vacuum and refilled with He, and then heated at 150°C for 5 days. The mixture was diluted with ethyl acetate, washed with ammonia (10%) and brine, and concentrated. The residue was purified on silica gel (24 g) with a gradient of ethyl acetate : hexanes from 1 : 9 to 1 : 1 gave the desired product as a light yellow solid (82.4 mg, 44%). ^1H NMR (300 MHz, MeOD): δ 8.46 (d, $J = 1.8$ Hz, 1H), 7.95 (dd, $J = 7.9, 2.0$ Hz, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 7.47-7.19 (m, 3H), 4.02 (t, $J = 6.4$ Hz, 2H), 3.26 (t, $J = 6.4$ Hz, 2H), 3.24-3.10 (m, 1H), 1.373 (td, $J = 14.4, 7.0$ Hz, 2H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.78 (t, $J = 7.3$ Hz, 3H); Calculated for C₁₉H₂₀F₂N₂O₃S, 394.1; observed MS (ESI) (m/z) 395.2 ($M + 1$)⁺.

[0620] Example 12: General Procedure L:



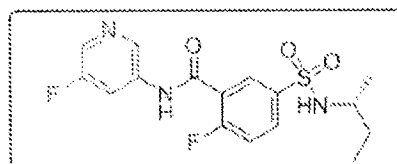
[0621] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluorobenzoic acid, 5-(chlorosulfonyl)-2-fluorobenzoic acid (239 mg) was dissolved in CH₂Cl₂ (20 ml), the reaction mixture was cooled to 0°C. Then Et₃N (405mg) was added, after 15 minutes stirring, (R)-butan-2-amine (73 mg) was added. The resultant mixture was stirred for 3 hours until the reaction was complete. The solvent was

stripped off and the crude product was used without further purification.

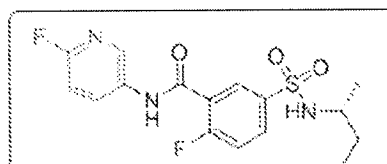
[0622] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluorobenzoyl chloride, (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluorobenzoic acid (300 mg) was added into SOCl_2 (15 ml), the reaction mixture was heated to 75°C and stirred for 1 hour until the reaction is complete. The solvent was stripped off and product, (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluorobenzoyl chloride was used for the next step without purification.

[0623] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-R-benzamide: (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluorobenzoyl chloride (400 mg) was dissolved in THF (20ml), then Et_3N (405 mg) and RNH_2 (224 mg) were added. The reaction mixture was heated to 85°C and stirred for 5 hours until the reaction is complete. The solvent of the reaction mixture was stripped off and the resultant crude product was purified by silica column (EtOAc/ petroleum ether =1:3) to get the product, (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-R-benzamide. The compounds were confirmed by LC-MS.

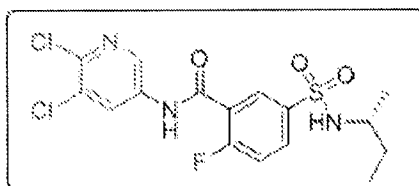
[0624] The following 16 compounds were synthesized using above general procedure:



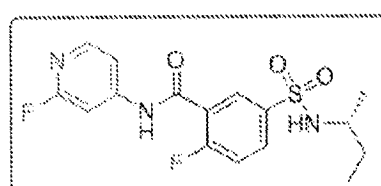
Compound A



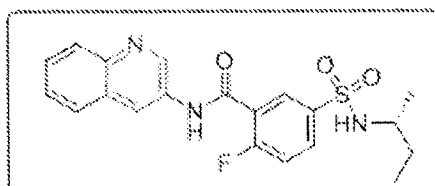
Compound B



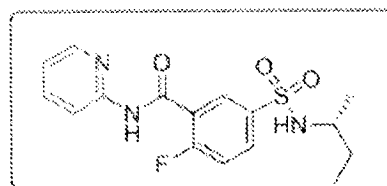
Compound C



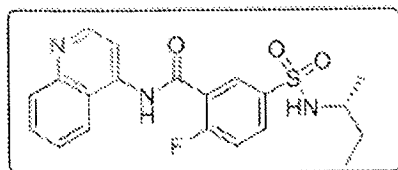
Compound D



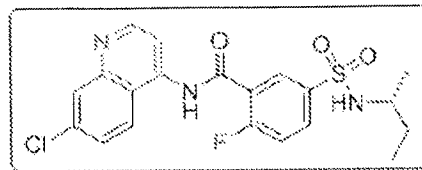
Compound E



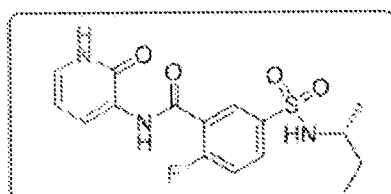
Compound F



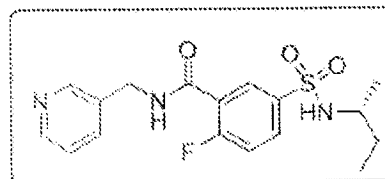
Compound G



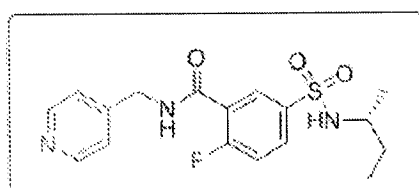
Compound H



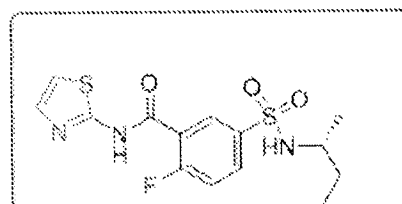
Compound I



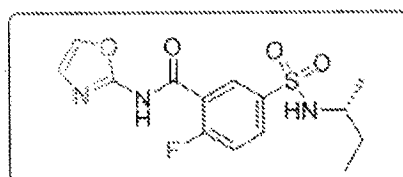
Compound J



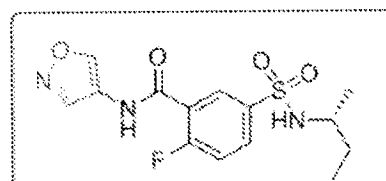
Compound K



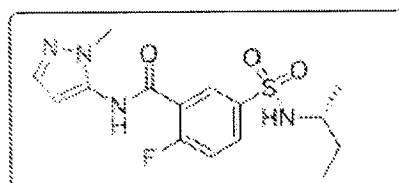
Compound L



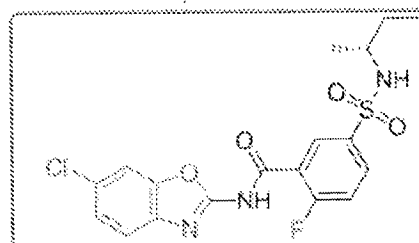
Compound M



Compound N



Compound O



Compound P

[0625] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(5-fluoropyridin-3-yl)benzamide (compound A), 40mg as off-white solid, HPLC purity: 90%. MS Calcd.: 369.1; MS Found: 370.0 $[M+H]^+$.

[0626] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(6-fluoropyridin-3-yl)benzamide (compound B), 50mg as off-white solid, HPLC purity: 90%. MS Calcd.: 369.1; MS Found: 370.0 [M+H]⁺.

[0627] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(5,6-dichloropyridin-3-yl)-2-fluorobenzamide (compound C), 20mg as off-white solid, HPLC purity: 90%.

[0628] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(2-fluoropyridin-4-yl)benzamide (compound D), 14mg as off-white solid, HPLC purity: 90%. MS Calcd.: 369.1; MS Found: 370.0 [M+H]⁺.

[0629] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(quinolin-3-yl)benzamide (compound E), 50mg as off-white solid, HPLC purity: 90%.

[0630] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(pyridin-2-yl)benzamide (compound F), 60mg as off-white solid, HPLC purity: 90%.

[0631] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(quinolin-4-yl)benzamide (compound G), 55mg as off-white solid, HPLC purity: 90%. MS Calcd.: 401.4; MS Found: 402.4 [M+H]⁺.

[0632] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(7-chloroquinolin-4-yl)-2-fluorobenzamide (compound H), 40mg as off-white solid, HPLC purity: 90%.

[0633] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(2-oxo-1,2-dihydropyridin-3-yl)benzamide (compound I), 40mg as off-white solid, HPLC purity: 90%.

[0634] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(pyridin-3-ylmethyl)benzamide (compound J), 50mg as off-white solid, HPLC purity: 90%.

[0635] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(pyridin-4-ylmethyl)benzamide (compound K), 40mg as off-white solid, HPLC purity: 90%. MS Calcd.: 365.4; MS Found: 366.4 [M+H]⁺.

[0636] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(thiazol-2-yl)benzamide (compound L), 40mg as off-white solid, HPLC purity: 90%.

[0637] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(oxazol-2-yl)benzamide (compound M), 22mg as off-white solid, HPLC purity: 90%.

[0638] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(isoxazol-4-yl)benzamide (compound N), 22mg as off-white solid, HPLC purity: 90%.

[0639] (R)-5-(N-(sec-butyl)sulfamoyl)-2-fluoro-N-(1-methyl-1H-pyrazol-5-yl)benzamide (compound O), 40mg as off-white solid, HPLC purity: 90%.

[0640] (R)-5-(N-(sec-butyl)sulfamoyl)-N-(6-chlorobenzo[d]oxazol-2-yl)-2-fluorobenzamide (compound P), 15mg as off-white solid, HPLC purity: 90%.

[0641] Example 13: General Procedure M:

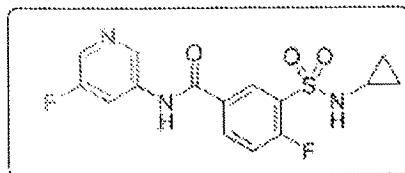


[0642] 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoic acid, 5-(chlorosulfonyl)-2-fluorobenzoic acid (239 mg) was dissolved in CH_2Cl_2 (20 mL), the reaction mixture was cooled to 0°C . Then Et_3N (405mg) was added, after 15 minutes stirring, cyclopropanamine (57.1mg) was added. The resultant mixture was stirred for 3 hours until the reaction was complete. The solvent was stripped off and the crude product 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoic acid was obtained as white solid. It was used without further purification.

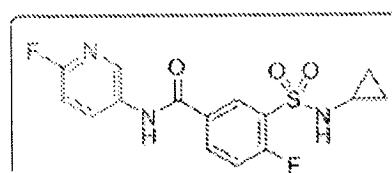
[0643] 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoyl chloride, 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoic acid (300mg) was added into SOCl_2 (15ml), the reaction mixture was heated to 75°C and stirred for 1 hour until the reaction is complete. The solvent was stripped off and product, 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoyl chloride as off white solid was used for the next step without purification.

[0644] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-R-benzamide, 3-(N-cyclopropylsulfamoyl)-4-fluorobenzoyl chloride (400mg) was dissolved in THF (20ml), then Et_3N (405mg) and RNH_2 (112mg) were added. The reaction mixture was heated to 85°C and stirred for 5 hours until the reaction is complete. The solvent of the reaction mixture was stripped off and the resultant crude product was purified by silica column (EtOAc /petroleum ether=1:3) to get the product, 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-R-benzamide. The compounds were confirmed by LC-MS and $^1\text{H-NMR}$.

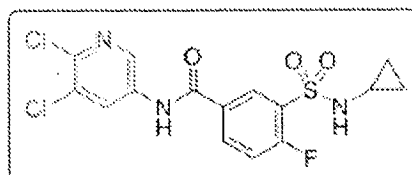
[0645] The following 16 compounds were synthesized using above general procedure:



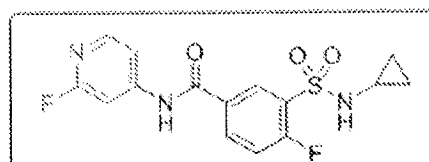
Compound AA



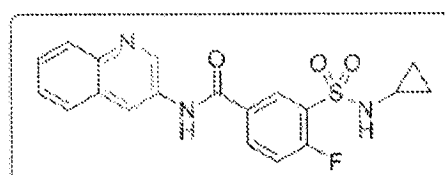
Compound BB



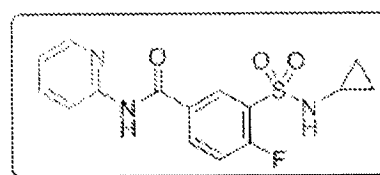
Compound CC



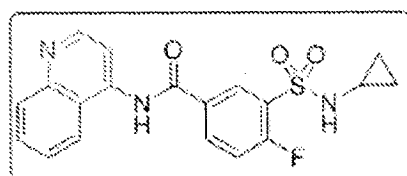
Compound DD



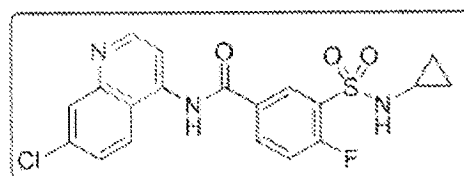
Compound EE



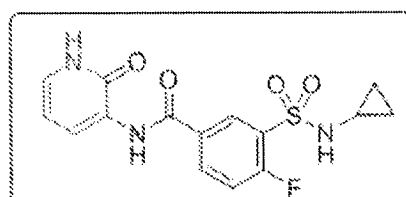
Compound FF



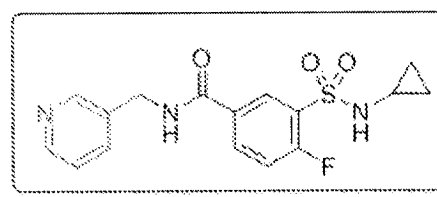
Compound GG



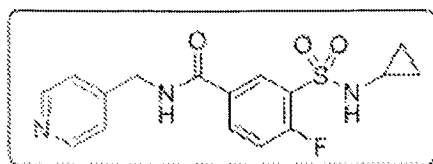
Compound HH



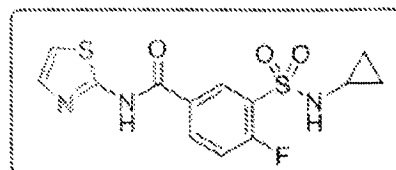
Compound II



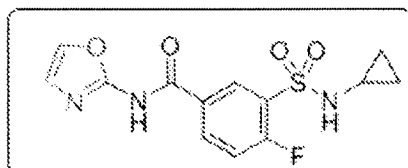
Compound JJ



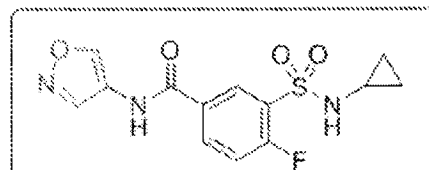
Compound KK



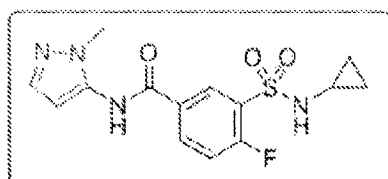
Compound LL



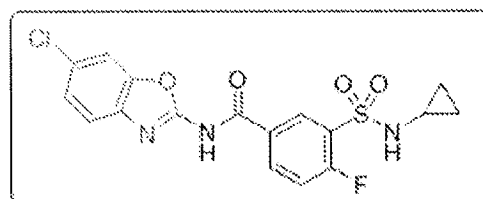
Compound MM



Compound NN



Compound OO



Compound PP

[0646] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(5-fluoropyridin-3-yl)benzamide (Compound AA), 100mg as white solid, MS: $M+H^+$ 354.

[0647] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(6-fluoropyridin-3-yl)benzamide (Compound BB), 100mg as off-white solid, $M+H^+$ 354.

[0648] 3-(N-cyclopropylsulfamoyl)-N-(5,6-dichloropyridin-3-yl)-4-fluorobenzamide (Compound CC), 100mg as off-white solid, $M+H^+$ 404.

[0649] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(2-fluoropyridin-4-yl)benzamide (Compound DD), 60mg as off-white solid, $M+H^+$ 354.

[0650] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(quinolin-3-yl)benzamide (Compound EE), 110mg as off-white solid, $M+H^+$ 386. ^1H NMR (CDCl_3 , Bruker Avance 400 MHz) δ : 0.41-0.48 (2H, m), 0.51-0.56 (2H, m), 2.25-2.32 (1H, m), 7.59-7.64 (1H, m), 7.68-7.72 (2H, m), 8.01 (1H, d, $J = 5.6$ Hz), 8.39-8.42 (2H, m), 8.91 (1H, d, $J = 3.6$ Hz), 8.83 (1H, s), 9.16 (1H, s), 10.99 (1H, brs).

[0651] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(pyridin-2-yl)benzamide (Compound FF), 100mg as off-white solid, $M+H^+$ 336.

[0652] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(quinolin-4-yl)benzamide (Compound GG), 100mg as off-white solid, $M+H^+$ 386. ^1H NMR (CDCl_3 , Bruker Avance 400 MHz) δ : 0.41-0.48 (2H, m), 0.51-0.60 (2H, m), 2.25-2.32 (1H, m), 7.63-7.67 (1H, m), 7.71 (1H, t, $J = 6.4$ Hz), 7.81 (1H, t, $J = 5.2$ Hz), 7.89 (1H, d, $J = 3.2$ Hz), 8.06 (1H, d, $J = 2.4$ Hz), 8.25 (1H, d, $J = 5.2$ Hz), 8.42-8.48 (2H, m), 8.51 (1H, d, $J = 4.4$ Hz), 8.91 (1H, d, $J = 3.6$ Hz), 10.95 (1H, brs).

[0653] N-(7-chloroquinolin-4-yl)-3-(N-cyclopropylsulfamoyl)-4-fluorobenzamide (Compound HH), 120mg as off-white solid, $M+H^+$ 420. ^1H NMR (CDCl_3 , Bruker Avance 400 MHz) δ : 0.35-0.41 (2H, m), 0.44-0.51 (2H, m), 2.25-2.30 (1H, m), 7.67-7.73 (2H, m), 7.91-7.93 (1H, m), 8.11 (1H, d, $J = 1.2$ Hz), 8.28-8.32 (1H, m), 8.42-8.47 (2H, m), 8.48-8.50 (1H, m), 8.93-8.96 (1H, m), 11.00 (1H, brs).

[0654] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(2-oxo-1,2-dihydropyridin-3-yl)benzamide (Compound II), 120mg as off-white solid, $M+H^+$ 352.

[0655] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(pyridin-3-ylmethyl)benzamide (Compound JJ), 60 mg as off-white solid, $M+H^+$ 350.

[0656] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(pyridin-4-ylmethyl)benzamide (Compound KK), 100mg as off-white solid, $M+H^+$ 350, ^1H NMR (CDCl_3 , Bruker Avance 400 MHz) δ : 0.35-0.41 (2H, m), 0.44-0.51 (2H, m), 2.25-2.30 (1H, m), 4.51 (2H, d, $J = 3.6$ Hz), 7.32 (2H, d, $J = 3.6$ Hz), 7.61 (1H, t, $J = 6.0$ Hz), 8.26 (1H, brs), 8.37-8.40 (2H, m), 8.49-8.53 (2H, m), 9.44 (1H, t, $J = 4.0$ Hz).

[0657] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(thiazol-2-yl)benzamide (Compound LL), 90mg as off-white solid, $M+H^+$ 342.

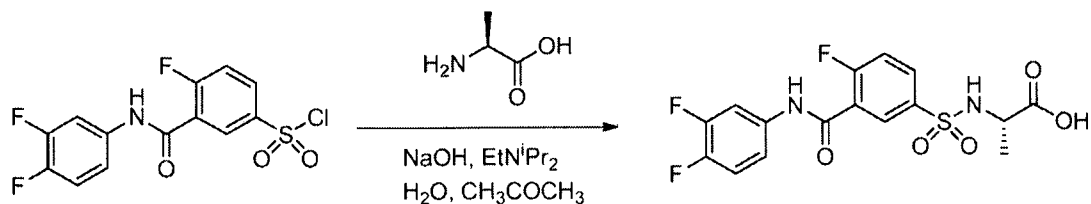
[0658] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(oxazol-2-yl)benzamide (Compound MM), 15mg as off-white solid, $M+H^+$ 326.

[0659] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(isoxazol-4-yl)benzamide (Compound NN), 10mg as off-white solid, $M+H^+$ 326.

[0660] 3-(N-cyclopropylsulfamoyl)-4-fluoro-N-(1-methyl-1H-pyrazol-5-yl)benzamide (Compound OO), 110mg as off-white solid, $M+H^+$ 339.

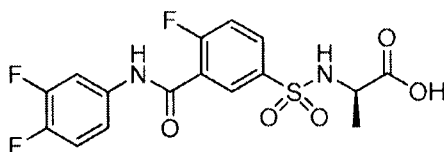
[0661] N-(6-chlorobenzo[d]oxazol-2-yl)-3-(N-cyclopropylsulfamoyl)-4-fluorobenzamide (Compound PP), 40mg as off-white solid, $M+H^+$ 410.

[0538] Example 14: General Procedure N:



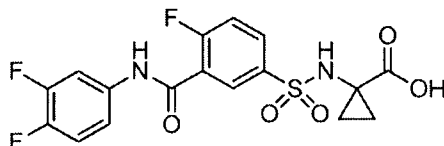
[0662] (S)-2-(3-((3,4-difluorophenyl)carbamoyl)-4-

fluorophenylsulfonamido)propanoic acid: To a vial (2 ml) was charged with L-alanine (25.5 mg, 0.28 mmol), NaOH (2M, 0.15 ml, 0.28 mmol). The mixture was cooled to 0°C, and treated with sulfonyl chloride (100 mg, 0.28 mmol), followed by EtNⁱPr₂ (0.055 ml, 0.31 mmol) and acetone (0.15 ml) to get a clear solution. The mixture was stirred at 0°C for 15 minutes and then at rt for 6 hours. Volatiles were removed in vacuo, the residue was diluted with water (1 ml), basicified with NaOH (2 M, 0.15 ml), extracted with diethyl ether. The aqueous phase was acidified with concentrated HCl to PH 1 and extracted with ethyl acetate. The organic phase was washed with brine and concentrated. The residue was dissolved in acetonitrile and purified on preparative HPLC with a gradient of acetonitrile in water from 20% to 100% in 15 minutes. A white solid was obtained after lyophilization (45 mg, 39%). ¹H NMR (300 MHz, CDCl₃): δ 8.62 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.40 (bd, *J* = 13.2 Hz, 1H), 8.10-8.00 (m, 1H), 7.77-7.66 (m, 1H), 7.33 (dd, *J* = 10.8, 8.5 Hz, 1H), 7.26-7.10 (m, 2H), 5.63 (bd, *J* = 8.2 Hz, 1H), 4.16-4.04 (m, 1H), 1.46 (d, *J* = 7.3 Hz, 3H); Calculated for C₁₆H₁₃F₃N₂O₅S, 402.05; observed MS (ESI) (*m/z*) 403.2 (*M* + 1)⁺.



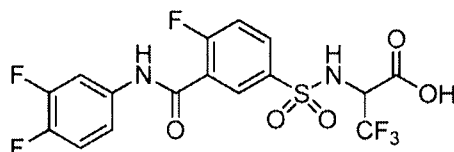
[0663] (R)-2-(3-((3,4-difluorophenyl)carbamoyl)-4-

fluorophenylsulfonamido)propanoic acid: Was prepared by a procedure analogous to that described for General Procedure N. ¹H NMR (300 MHz, MeOD): δ 8.20 (dd, *J* = 6.4, 2.3 Hz, 1H), 8.04 (ddd, *J* = 8.5, 4.7, 2.6 Hz, 1H), 7.81 (ddd, *J* = 13.0, 7.3, 2.3 Hz, 1H), 7.48-7.34 (m, 2H), 7.32-7.18 (m, 1H), 3.98 (q, *J* = 7.3 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H); Calculated for C₁₆H₁₃F₃N₂O₅S, 402.05; observed MS (ESI) (*m/z*) 403.2 (*M* + 1)⁺.



[0664] 1-(3-((3,4-difluorophenyl)carbamoyl)-4-

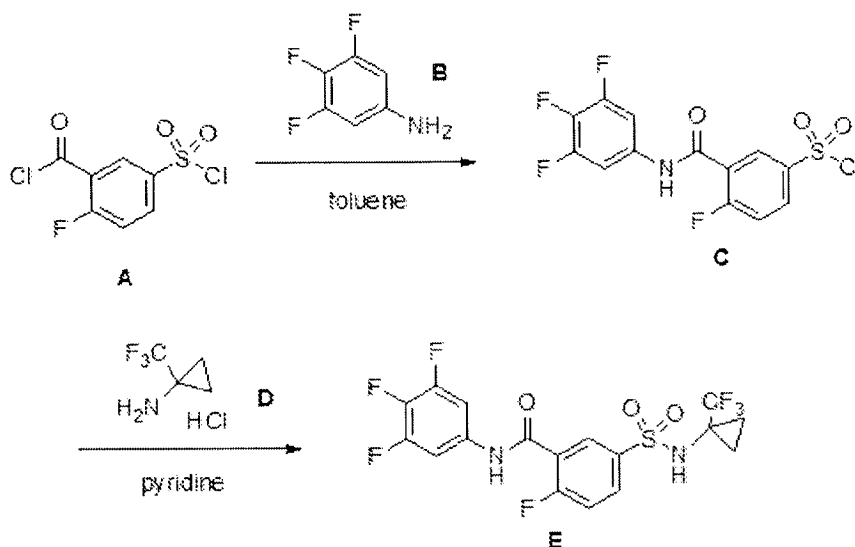
fluorophenylsulfonamido)cyclopropanecarboxylic acid: Was prepared by a procedure analogous to that described for General Procedure N. ^1H NMR (300 MHz, MeOD): δ 8.20 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.04 (ddd, $J = 8.5, 4.7, 2.6$ Hz, 1H), 7.82 (ddd, $J = 12.7, 7.6, 2.6$ Hz, 1H), 7.48-7.34 (m, 2H), 7.32-7.20 (m, 1H), 1.44-1.37 (m, 2H), 1.35-1.29 (m, 2H); Calculated for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_5\text{S}$, 414.05; observed MS (ESI) (m/z) 415.1 ($M + 1$) $^+$.



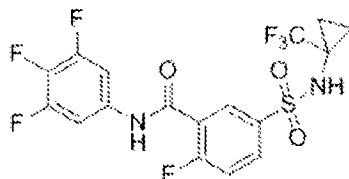
[0665] 2-(3-((3,4-difluorophenyl)carbamoyl)-4-fluorophenylsulfonamido)-3,3,3-

trifluoropropanoic acid: Was prepared by a procedure analogous to that described for General Procedure N. ^1H NMR (300 MHz, MeOD): δ 8.25 (dd, $J = 6.4, 2.6$ Hz, 1H), 8.08 (ddd, $J = 8.8, 4.7, 2.3$ Hz, 1H), 7.82 (ddd, $J = 12.7, 7.3, 2.6$ Hz, 1H), 7.49-7.37 (m, 2H), 7.32-7.20 (m, 1H), 4.79 (q, $J + 7.9$ Hz, 1H); Calculated for $\text{C}_{16}\text{H}_{10}\text{F}_6\text{N}_2\text{O}_5\text{S}$, 456.02; observed MS (ESI) (m/z) 457.2 ($M + 1$) $^+$.

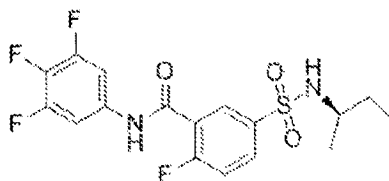
[0666] Example 15: General Procedure O



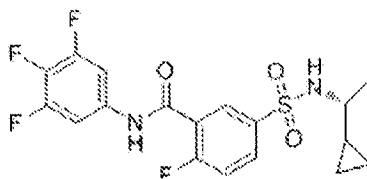
[0667] N-(3,4,5-Trifluorophenyl)-2-fluoro-5-(N-(1-(trifluoromethyl)cyclopropyl)sulfamoyl)benzamide: To a 0 °C solution of 3,4,5-trifluoroaniline (0.618 g, 0.0042 mol) in toluene (5mL) was added dropwise a solution of 5-chlorosulfonyl-2-fluorobenzoyl chloride (1.08 g, 0.0042 mol) (prepared as in the first step of General Procedure B) in 5 mL of toluene. The mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc/hexane) to give compound 3-(3,4,5-trifluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (1.14 g, 74 %). After drying overnight under vacuum, a mixture of 3-(3,4,5-trifluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (59 mg, 0.16 mmol), and 1-trifluoromethyl-cyclopropylamine · HCl (39 mg, 0.24 mmol) in pyridine (0.2 mL) was stirred at room temperature overnight. After which the reagent was evaporated, the residue was dissolved in EtOAc, washed with 1N HCl and then brine, dried and purified by chromatography (EtOAc/hexane) to give the desire product (58.2 mg, 80 %) as a white solid. ¹H NMR (300 MHz, d₄- MeOH): 8.20-8.18 (m, 1H), 8.06-8.01 (m, 1H), 7.58-7.43 (m, 3H), 1.22 (m, 4H); MS (ES) m/z: 457.2 (M+ H⁺), calculated 457.04.



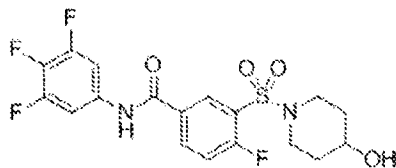
[0668] 2-Fluoro-5-(N-(1-(trifluoromethyl)cyclopropyl)sulfamoyl)-N-(3,4,5-trifluorophenyl) benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (58.2 mg, 80 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.20-8.18 (m, 1H), 8.06-8.01 (m, 1H), 7.58-7.43 (m, 3H), 1.22 (m, 4H); MS (ES) m/z : 457.2 ($\text{M} + \text{H}^+$), calculated 457.04.



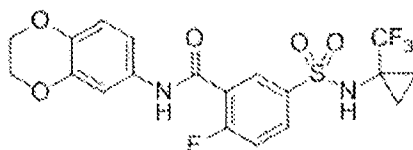
[0669] (R)-5-(N-(Sec-butyl)sulfamoyl)-2-fluoro-N-(3,4,5-trifluorophenyl)benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (29 mg, 42 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.22-8.19 (m, 1H), 8.08-8.03 (m, 1H), 7.58-7.43 (m, 3H), 3.24-3.18 (m, 1H), 1.42-1.35 (m, 2H), 1.01-0.98 (d, $J = 6.7$ Hz, 3H), 0.83-0.78 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 405.2 ($\text{M} + \text{H}^+$), calculated 405.08.



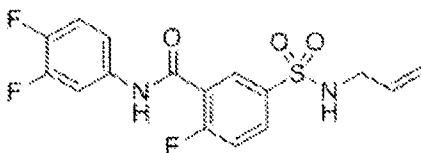
[0670] (R)-5-(N-(1-Cyclopropylethyl)sulfamoyl)-2-fluoro-N-(3,4,5-trifluorophenyl)benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (23.1 mg, 36 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.24-8.21 (m, 1H), 8.09-8.05 (m, 1H), 7.59-7.44 (m, 3H), 2.71-2.66 (m, 1H), 1.14-1.12 (d, $J = 6.7$ Hz, 3H), 0.82-0.76 (m, 1H), 0.48-0.40 (m, 1H), 0.35-0.29 (m, 1H), 0.19-0.14 (m, 1H), 0.06-0.03 (m, 1H); MS (ES) m/z : 417.2 ($\text{M} + \text{H}^+$), calculated 417.08.



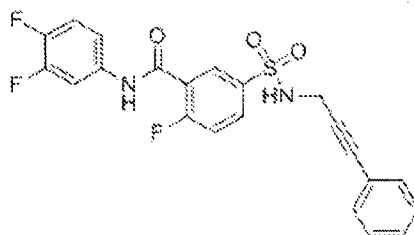
[0671] 4-Fluoro-3-((4-hydroxypiperidin-1-yl)sulfonyl)-N-(3,4,5-trifluorophenyl)benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (53 mg, 77 %). ¹H NMR (300 MHz, d₄- MeOH): 8.42-8.39 (m, 1H), 8.27-8.22 (m, 1H), 7.62-7.47 (m, 3H), 3.75-3.70 (m, 1H), 3.54-3.52 (m, 2H), 3.08-3.01 (m, 2H), 1.92-1.86 (m, 2H), 1.62-1.52 (m, 2H); MS (ES) m/z: 433.2 (M+ H⁺), calculated 433.08.



[0672] N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-fluoro-5-(N-(1-(trifluoromethyl)cyclopropyl)sulfamoyl)benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (73 mg, 69.2 %). ¹H NMR (300 MHz, d₄- MeOH): 8.19-8.16 (m, 1H), 8.03-7.99 (m, 1H), 7.47-7.41 (t, *J* = 9.2 Hz, 1H), 7.30 (s, 1H), 7.07-7.04 (m, 1H), 6.83-6.80 (d, *J* = 8.7 Hz, 1H), 4.24 (s, 4H), 1.24 (s, 4H); MS (ES) m/z: 461.2 (M+ H⁺), calculated 461.07.

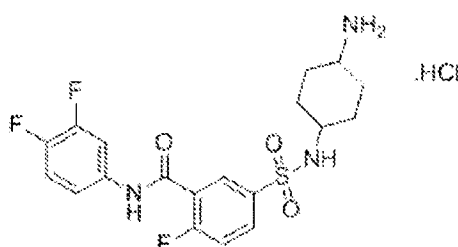


[0673] 5-(N-Allylsulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (6.4 mg, 12 %). ¹H NMR (300 MHz, d₄- MeOH): 8.20-8.17 (m, 1H), 8.06-8.01 (m, 1H), 7.86-7.78 (m, 1H), 7.49-7.36 (m, 2H), 7.31-7.22 (m, 1H), 5.80-5.67 (m, 1H), 5.21-5.14 (m, 1H), 5.08-5.03 (m, 1H), 4.87-4.84 (m, 2H); MS (ES) m/z: 371.2 (M+ H⁺), calculated 371.06.

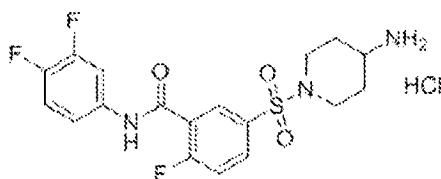


[0674] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(3-phenylprop-2-yn-1-yl)sulfamoyl)benzamide: In a similar procedure as General Procedure O, final compound was obtained as a white solid (58.8 mg, 65.2 %). ^1H NMR (300 MHz, $\text{d}_4\text{-MeOH}$): 8.33-8.30 (m, 1H), 8.12-8.07 (m, 1H), 7.81-7.75 (m, 1H), 7.41-7.19 (m, 8H), 4.07 (s, 2H); MS (ES) m/z : 445.2 ($\text{M} + \text{H}^+$), calculated 445.08.

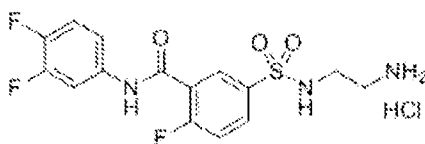
[0675] Example 16: General Procedure P



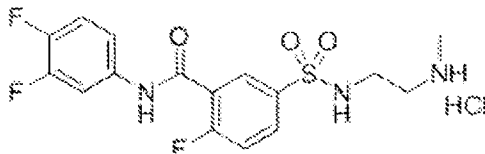
5-(N-(4-Aminocyclohexyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide hydrochloride: *tert*-Butyl (4-(3-((3,4-difluorophenyl)carbamoyl)-4-fluorophenylsulfonamido)cyclohexyl) carbamate (25 mg, 0.047 mmol) was treated with 4N HCl in dioxane (0.5 mL). The mixture was stirred at room temperature overnight. The white solid was filtered and washed with ether gave the desired product as an HCl salt (25 mg, 100%). ^1H NMR (300 MHz, CD_3OD): 8.24-8.21 (m, 1H), 8.10-8.05 (m, 1H), 7.87-7.79 (m, 1H), 7.51-7.48 (m, 1H), 7.45-7.35 (m, 1H), 7.31-7.22 (m, 1H), 3.28-3.25 (m, 1H), 3.15-3.09 (m, 1H), 1.87-1.56 (m, 8H); MS (ES) m/z : 428.2 ($\text{M} + \text{H}^+$), calculated 428.12.



[0676] 5-((4-Aminopiperidin-1-yl)sulfonyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide hydrochloride: In a similar procedure as General Procedure P, the final product was obtained as an HCl salt (49 mg, 100 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.14-8.11 (m, 1H), 8.03-7.98 (m, 1H), 7.87-7.79 (m, 1H), 7.56-7.50 (m, 1H), 7.40-7.36 (m, 1H), 7.32-7.23 (m, 1H), 3.92-3.88 (m, 2H), 3.15-3.07 (m, 1H), 2.56-2.47 (m, 2H), 2.08-2.05 (m, 2H), 1.73-1.63 (m, 2H); MS (ES) m/z : 414.2 ($\text{M} + \text{H}^+$), calculated 414.10.

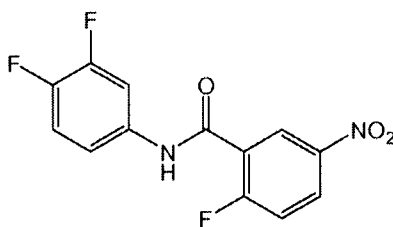


[0677] 5-(N-(2-Aminoethyl)sulfamoyl)-N-(3,4-difluorophenyl)-2-fluorobenzamide hydrochloride: In a similar procedure as General Procedure P, the final product was obtained as an HCl salt (8.3 mg, 37 %). ^1H NMR (300 MHz, d_4 - MeOH): 8.24-8.22 (m, 1H), 8.10-8.05 (m, 1H), 7.87-7.79 (m, 1H), 7.55-7.49 (m, 1H), 7.40-7.36 (m, 1H), 7.32-7.23 (m, 1H), 3.16-3.05 (m, 4H); MS (ES) m/z : 374.2 ($\text{M} + \text{H}^+$), calculated 374.07.

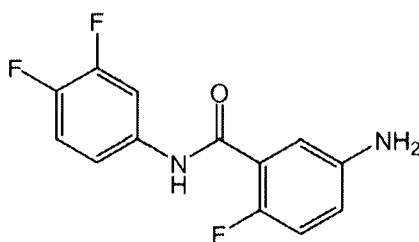


[0678] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(2-(methylamino)ethyl)sulfamoyl)benzamide hydrochloride: In a similar procedure as General Procedure P, the final product was obtained as an HCl salt (20 mg, 56%). MS (ES) m/z : 388.2 ($\text{M} + \text{H}^+$), calculated 388.09.

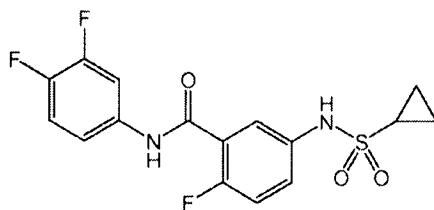
[0679] Example 17: Other Syntheses



[0680] ***N*-(3,4-Difluorophenyl)-2-fluoro-5-nitrobenzamide**: To a solution of 3,4-difluoroaniline (0.64 g, 4.92 mmol) and NEt_3 (0.82 g, 8.22 mmol) in CH_2Cl_2 (18 mL) was added dropwise a solution of 2-fluoro-5-nitro-benzoyl chloride (1.00 g, 4.92 mmol) in CH_2Cl_2 (18 mL). The reaction was stirred for 14 days, then was concentrated. The residue was partitioned between EtOAc (50 mL) and dilute NaHCO_3 (20 mL). The organic layer was washed with and d5 mL), dilute NaHCO_3 (10 mL), water (10 mL), 2 N HCl (2 x 15 mL), and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by silica column (10 -20% EtOAc/ Hexane) to give the desired product (0.91 g, 62%) as a pale yellow solid. MS: $\text{M}+\text{H}^+$ 273. ^1H NMR (300 MHz, CDCl_3): 8.62 (dd, $J = 2.9, 6.7$ Hz, 1H), 8.46-8.41 (m, 1H), 8.35 (d, $J = 14.1$ Hz, 1H), 7.80-7.73 (m, 1H), 7.41 (dd, $J = 1.5, 9.1$ Hz, 1H), 7.26-7.14 (m, 3H).

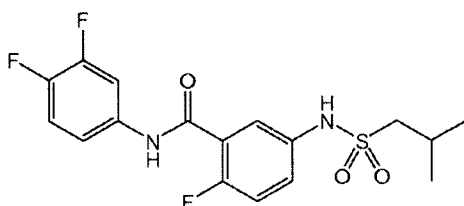


[0681] **5-amino-*N*-(3,4-Difluorophenyl)-2-fluorobenzamide**: A mixture of *N*-(3,4-difluorophenyl)-2-fluoro-5-nitrobenzene (0.50 g, 1.69 mmol) and 10% Pd/C (30 mg) in methanol (8 mL) was evacuated and then purged with hydrogen three times. The reaction was stirred under a hydrogen atmosphere for 16 hours. The reaction was filtered through Celite, and the filtrate was concentrated to give the desired product (0.43 g, 96%) as a pale yellow solid. MS: $\text{M}+\text{H}^+$ 267. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): 10.46 (s, 1H), 7.89-7.82 (m, 1H), 7.47-7.35 (m, 2H), 6.98 (dd, $J = 1.2, 8.8$ Hz, 1H), 6.77-6.65 (m, 2H), 5.20 (s, 2H).

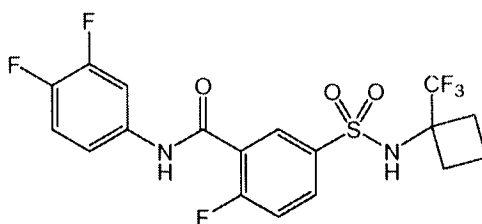


[0682] **5-(cyclopropanesulfonamido)-*N*-(3,4-Difluorophenyl)-2-fluorobenzamide**: To a 0°C solution of 5-amino-(*N*-3,4-difluorophenyl)-2-fluorobenzamide (40 mg, 0.15 mmol) in THF (1 mL) was added and NEt_3 (30 mg, 0.30 mmol) and cyclopropyl-sulfonyl chloride (24 mg, 0.17 mmol).

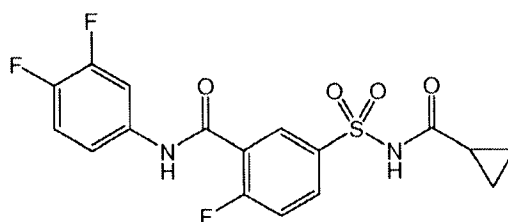
The reaction was warmed to 20°C, and was stirred for 3 hours. The reaction was cooled to 0 °C and further NEt₃ (19 mg, 0.19 mmol) in THF (1 mL) was added cyclopropyl -sulfonyl chloride (24 mg, 0.17 mmol) were added. The reaction was warmed to 20 °C, and was stirred for 60 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (44 mg, 79%) as an off-white solid. MS: M+H⁺ 371. ¹H NMR (300 MHz, DMSO-d₆): 10.64 (s, 1H), 9.9 (s, 1H), 7.90-7.81 (m, 1H), 7.47-7.41 (m, 5H), 2.66-2.60 (m, 1H), 1.00-0.91 (m, 4H).



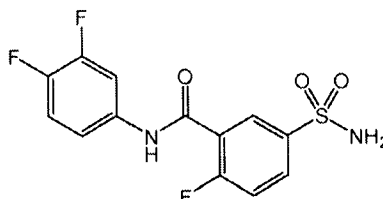
[0683] N-(3,4-Difluorophenyl)-2-fluoro-5-(2-methylpropylsulfonamido)benzamide: A mixture of 5-amino-(N-3,4-difluorophenyl)-2-fluorobenzamide (25 mg, 0.094 mmol) and DMAP (10 mg) in pyridine (1 mL) was treated with isobutane-sulfonyl chloride (16 mg, 0.11 mmol). The reaction was heated at 110°C for 16 hours. Further DMAP (10 mg) and isobutane-sulfonyl chloride (32 mg, 0.22 mmol) were added, and the reaction was heated at 110°C for 3 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (15 mg, 41%) as an off-white solid. MS: M+H⁺ 387. ¹H NMR (300 MHz, DMSO-d₆): 10.64 (s, 1H), 9.97 (s, 1H), 7.89-7.82 (m, 1H), 7.45-7.34 (m, 5H), 2.99 (d, *J* = 6.5 Hz, 1H), 2.16-2.07 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 1H).



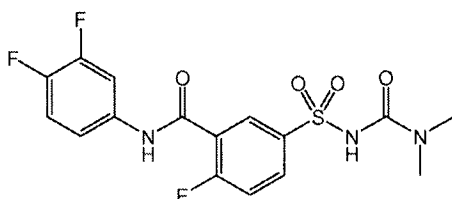
[0684] *N*-(3,4-Difluorophenyl)-2-fluoro-5-(*N*-(1-(trifluoromethyl)cyclobutyl)sulfamoyl)benzamide: A mixture of 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (30 mg, 0.086 mmol) and DMAP (10 mg) in pyridine (1 mL) was treated with 1-trifluoromethyl-cyclobutane (36 mg, 0.26 mmol). The reaction was heated at 95°C for 4 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (10 -50% EtOAc/ Hexane) to give the desired product (2 mg, 5%) as a clear gum. MS: M+H⁺ 453. ¹H NMR (300 MHz, DMSO-d₆): 8.22-8.20 (m, 1H), 8.10-8.06 (m, 1H), 7.82-7.76 (m, 1H), 7.49 (d, *J* = 9.4 Hz, 1H), 7.32-7.23 (m, 3H), 2.47-2.41 (m, 4H), 1.92-1.83 (m, 2H).



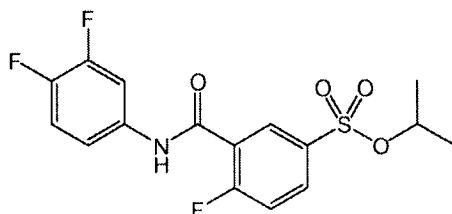
[0685] 5-(*N*-(Cyclopropanecarbonyl)sulfamoyl)-*N*-(3,4-difluorophenyl)-2-fluorobenzamide. To a 0°C solution of cyclopropanecarboxamide (29 mg, 0.28 mmol) in THF (1 mL) was added a 60% dispersion of NaH in mineral oil (11 mg, 0.28 mmol). The reaction was warmed to 20°C, and was stirred for 30 minutes. The mixture was cooled to 0°C, then 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol) was added. The reaction was warmed to 20°C, and was stirred for 16 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and dilute NaHCO₃ (5 mL). The organic layer was washed with water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (20 -100% EtOAc/ Hexane), followed by prep-TLC (70% EtOAc/ Hexane) to give the desired product (3 mg, 5%) as a clear gum. MS: M+H⁺ 399.



[0686] N-(3,4-Difluorophenyl)-2-fluoro-5-sulfamoylbenzamide. To a solution of 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (0.50 g, 1.43 mmol) in THF (4 mL) was added dropwise 28-30% ammonia in water (1 mL). The reaction was stirred for 60 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by silica column (20 -100% EtOAc/Hexane) to give the desired product (410 mg, 87%) as a white solid. MS: $\text{M}+\text{H}^+$ 331.

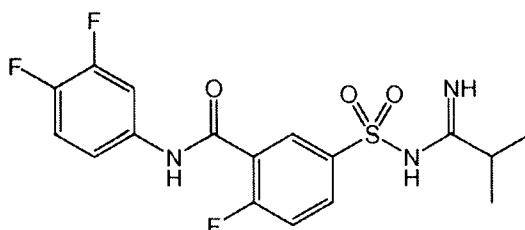


N-(3,4-Difluorophenyl)-5-(N-(dimethylcarbamoyl)sulfamoyl)-2-fluorobenzamide. A mixture of N-(3,4-difluorophenyl)-2-fluoro-5-sulfamoylbenzamide (50 mg, 0.15 mmol) and DMAP (10 mg) in pyridine (0.1 mL) was treated with dimethyl carbamoyl chloride (48 mg, 0.45 mmol). The reaction was heated at 90°C for 2 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by silica column (1 -10% MeOH/ CH_2Cl_2) to give the desired product (12 mg, 20%) as a white solid. MS: $\text{M}+\text{H}^+$ 402.

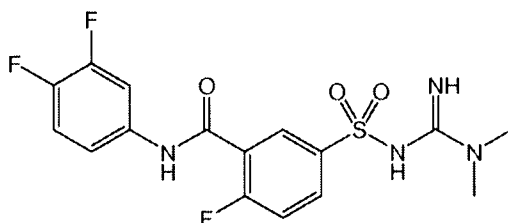


Isopropyl 3-((3,4-difluorophenyl)carbamoyl)-4-fluorobenzenesulfonate. To a 0 °C solution of isopropanol (0.1 mL) and pyridine (0.1 mL) was added portionwise of 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol). The reaction was warmed to 20°C, and was stirred for 16 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2

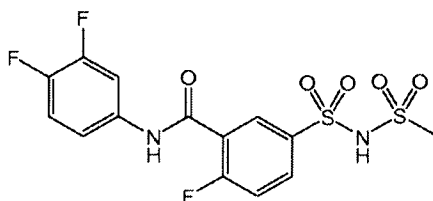
N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated to give the desired product (22 mg, 42%) as a white solid. MS: $\text{M}+\text{H}^+$ 374.



[0687] N-(3,4-Difluorophenyl)-2-fluoro-5-(N-(1-imino-2-methylpropyl)sulfamoyl)benzamide. To a mixture of 2-methyl-propanimidamide.HCl (35 mg, 0.28 mmol) in THF (0.2 mL) was added a 10 N solution of NaOH (4 drops), followed by a solution of 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol) in THF (0.2 mL). The reaction was stirred for 16 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and dilute NaHCO_3 (5 mL). The organic layer was washed with water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by preparative-HPLC to give the desired product (2 mg, 5%) as an off-white solid. MS: $\text{M}+\text{H}^+$ 400.

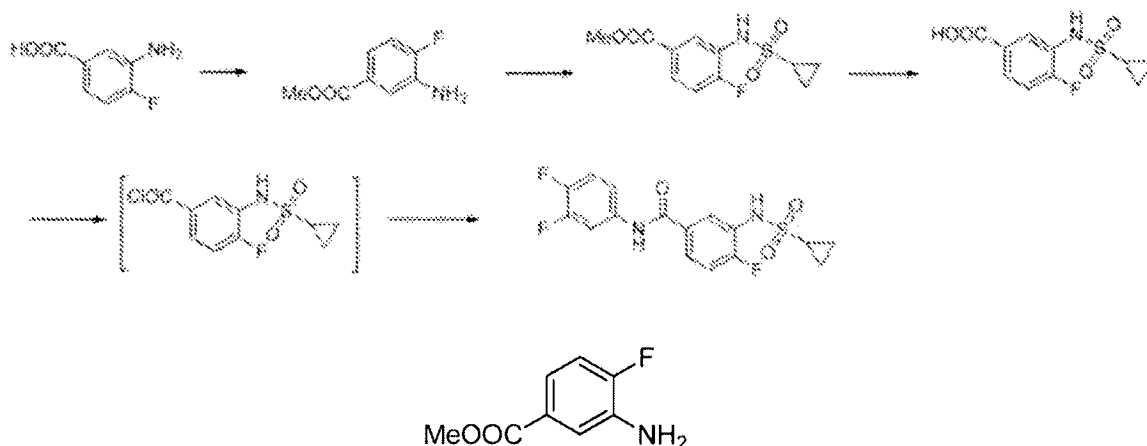


N-(3,4-Difluorophenyl)-5-(N-(N,N-dimethylcarbamimidoyl)sulfamoyl)-2-fluorobenzamide. A mixture of 1,1-dimethylguanidine sulfate (76 mg, 0.28 mmol) and 10 N aqueous NaOH solution (9 drops) was heated at 40°C for 10 minutes. To this mixture was added THF (0.3 mL), and the mixture was cooled to 0°C. To the cooled solution was added 3-(3,4-difluorophenylcarbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol). The reaction was warmed to 20°C, and was stirred for 16 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and dilute NaHCO_3 (5 mL). The organic layer was washed with water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated to give the desired product (33 mg, 59%) as a pale yellow solid. MS: $\text{M}+\text{H}^+$ 401.

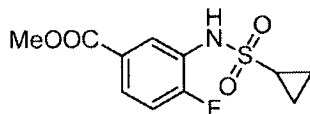


[0688] N-(3,4-difluorophenyl)-2-fluoro-5-(N-(methanesulfonyl)sulfamoyl)benzamide: To a solution of methanesulfonamide (38 mg, 0.14 mmol) and NEt_3 (40 mg, 40 mmol) in acetonitrile (1 mL) was added 3-(3,4-difluorophenyl-carbamoyl)-4-fluorobenzene-1-sulfonyl chloride (50 mg, 0.14 mmol). The reaction was heated at reflux for 2 hours. The mixture was concentrated, then the residue was partitioned between EtOAc (20 mL) and 1 N HCl (5 mL). The organic layer was washed with 2 N HCl (5 mL), water (5 mL), and brine (1 mL), dried (Na_2SO_4), and concentrated to give the desired product (33 mg, 60%) as a pale brown solid. MS: $\text{M}+\text{H}^+$ 409.

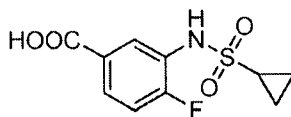
[0689] Synthesis of 3-(cyclopropanesulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide



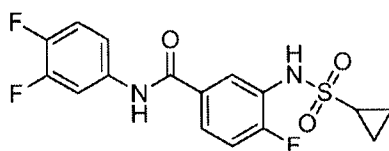
[0690] Methyl 3-amino-4-fluorobenzoate: 3-amino-4-fluorobenzoic acid (0.5g) was dissolved in methanol (10ml), then concentrated sulfuric acid (1ml) was added. The reaction solution was heated to reflux until the reaction is complete. Then the reaction mixture was cooled down and poured into water, the pH of the resultant solution was adjusted to 8 by 2N NaOH solution. The product was extracted to EtOAc layer and the solvent was stripped off. 290mg of methyl 3-amino-4-fluorobenzoate was obtained.



[0691] Methyl 3-(cyclopropanesulfonamido)-4-fluorobenzoate: Methyl 3-amino-4-fluorobenzoate (275mg) and DMAP (100mg) were dissolved in pyridine (10ml). Then cyclopropanesulfonyl chloride (330mg) was added into the solution. The reaction mixture was heated to 110°C and stirred for 12 hours until the reaction is complete. The solvent was stripped off, the solid was dissolved in CH₂Cl₂ (50ml) followed by 1N HCl solution (50ml). The bottom aqueous layer was split off and the organic layer was washed with water and dried by anhydrous Na₂SO₄. The CH₂Cl₂ was stripped off and 270mg of methyl 3-(cyclopropanesulfonamido)-4-fluorobenzoate was used for the next step directly.



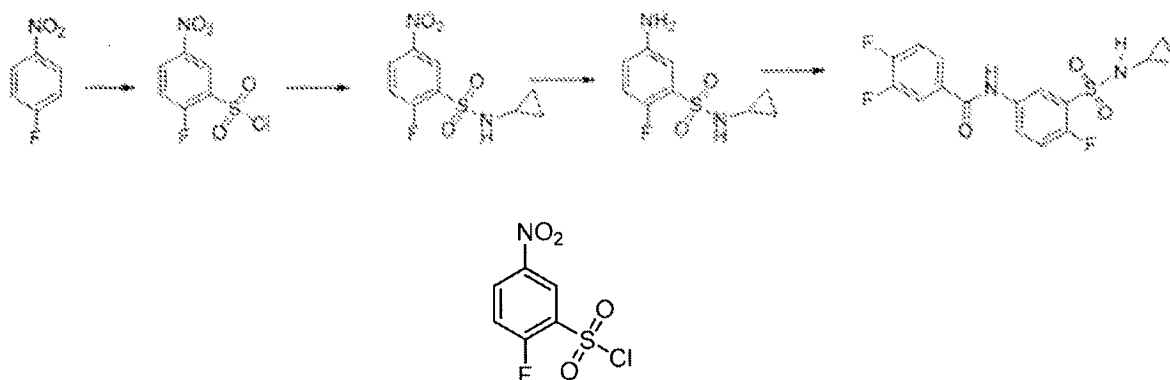
[0692] 3-(Cyclopropanesulfonamido)-4-fluorobenzoic acid: Crude methyl 3-(cyclopropanesulfonamido)-4-fluorobenzoate (270mg) was dissolved in MeOH (15ml) and 10% LiOH solution (15ml) was added. The reaction mixture was stirred at ambient temperature overnight until the reaction is complete. The solvent was stripped off and the pH of the resultant aqueous solution was adjusted to 1.0 by 1N HCl solution. The product was extracted with EtOAc and the EtOAc layer was dried with anhydrous Na₂SO₄. The solvent was stripped off and the resultant 3-(cyclopropanesulfonamido)-4-fluorobenzoic acid (250mg) was used directly for the next step.



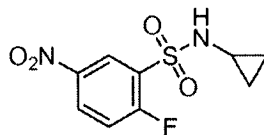
[0693] 3-(cyclopropanesulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide: 3-(cyclopropanesulfonamido)-4-fluorobenzoic acid (250mg) was dissolved in SOCl₂ (5ml) and the solution was heated to reflux and kept for 1 hours until the reaction is complete. The solvent was stripped off, then CH₂Cl₂(10ml) was added in. The resultant solution was cooled to 0°C, then Et₃N (1ml) and 3,4-difluoroaniline (0.25g) were added. The resultant solution was stirred at ambient temperature overnight until the reaction is complete. The reaction mixture was poured into water

(10ml) and the bottom aqueous layer was split off. The organic layer was washed with 1N HCl solution, followed by brine solution and then dried with anhydrous Na_2SO_4 . The solvent was stripped off and the crude product was purified by silica column twice. 35mg of 3-(cyclopropanesulfonamido)-N-(3,4-difluorophenyl)-4-fluorobenzamide was obtained. HPLC purity: 96%. LC-MS: Calcd: 370.3; Measured: $[M+1]=371.3$.

[0694] Synthesis of N-(3-(N-cyclopropylsulfamoyl)-4-fluorophenyl)-3,4-difluorobenzamide:

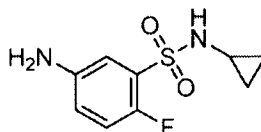


[0695] 2-Fluoro-5-nitrobenzene-1-sulfonyl chloride: 1-fluoro-4-nitrobenzene (20g) was dissolved in chlorosulfonic acid (35ml), the reaction mixture was heated to 115°C and stirred for 9 h until the reaction is complete. Then the reaction was cooled to ambient temperature and poured into ice water (300g), the compound was extracted into EtOAc. The aqueous layer was split off. The EtOAc layer was washed by water, then brine solution and dried with anhydrous Na_2SO_4 . The solvent was stripped off the crude product was purified by silica column (petroleum ether/EtOAc=10:1). 15g of 2-fluoro-5-nitrobenzene-1-sulfonyl chloride was obtained.

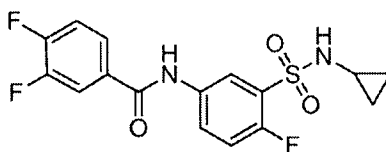


[0696] N-cyclopropyl-2-fluoro-5-nitrobenzenesulfonamide: To the mixture of cyclopropylamine (7.92g) and N,N-Diisopropylethylamine (11g) and CH_2Cl_2 (60 ml) at 0°C, the solution of 2-fluoro-5-nitrobenzene-1-sulfonyl chloride (7.2g) dissolved in CH_2Cl_2 (50 ml) was added

in dropwise, the reaction mixture was stirred for 2 hours at 0°C until the reaction is complete. The solvent was stripped off and the crude product was dissolved in CH₂Cl₂ and washed by water twice. The crude product was purified by silica column (Petroleum ether/EtOAc=3:1) and 4.3g of N-cyclopropyl-2-fluoro-5-nitrobenzenesulfonamide was obtained, yield: 67%.

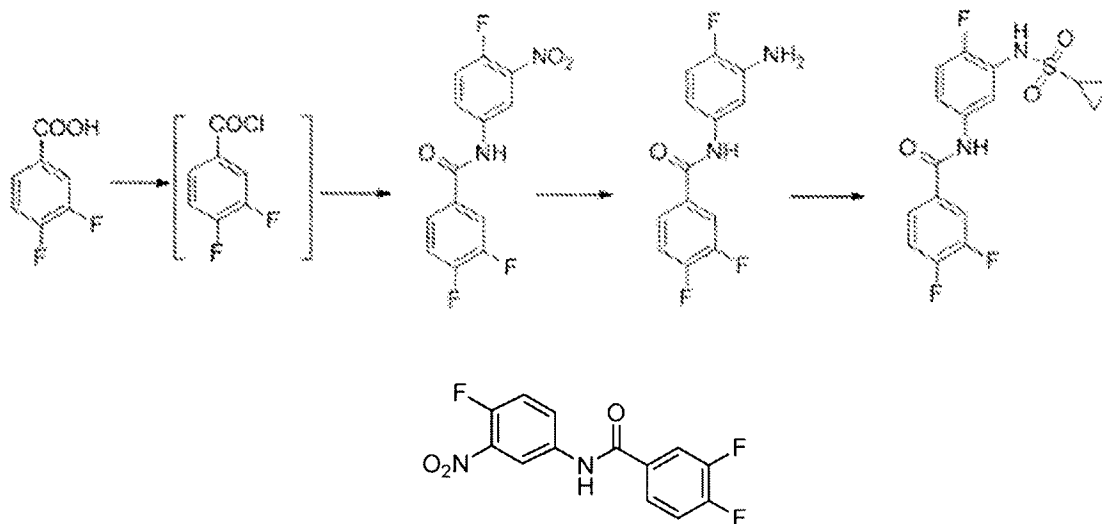


[0697] 5-Amino-N-cyclopropyl-2-fluorobenzenesulfonamide: N-cyclopropyl-2-fluoro-5-nitrobenzenesulfonamide (2.2g) was dissolved in 1,4-dioxane (44ml), then 6N HCl (4.4ml) and SnCl₂ (7.7g) were added into the reaction mixture. The resultant mixture was stirred for 2h at ambient temperature until the reaction is complete. The reaction mixture was poured into the mixture of EtOAc (100ml) and water (50ml) and the pH of the resultant mixture was adjusted to 11 by 2N NaOH. The bottom aqueous layer was split off and the organic layer was washed with water and dried with anhydrous Na₂SO₄. The solvent was stripped off by rotovap and 2g of 5-amino-N-cyclopropyl-2-fluorobenzenesulfonamide was obtained as brown oil.

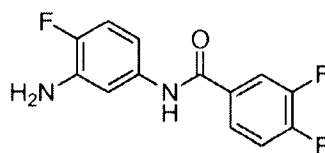


[0698] N-(3-(N-cyclopropylsulfamoyl)-4-fluorophenyl)-3,4-difluorobenzamide: To the mixture of 5-amino-N-cyclopropyl-2-fluorobenzenesulfonamide (2g), CH₂Cl₂ (50ml) and Et₃N (1.8g), 3,4-Difluorobenzoyl chloride (1.5g) was added dropwise. The resultant reaction mixture was stirred at ambient temperature for 2 hours until the reaction is complete. The product was filtered and washed with CH₂Cl₂ twice and dried in a vacuum oven at 50°C. 1.3g as a white solid. Yield 62%. HPLC purity: 96%. LC-MS, Calcd: 370.0, Measured: [M+1] = 371.0. ¹HNMR (DMSO-d₆, Bruker Avance 400 MHz) δ: 0.42 (2H, m), 0.49 (2H, m), 2.25-2.36 (1H, m), 7.45-7.48 (1H, t), 7.62-7.67 (1H, dd), 7.89 (1H, brs.), 8.05-8.11 (2H, m), 8.20-8.32 (2H, m), 10.62 (1H, s)

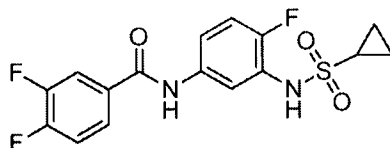
[0699] Synthesis of N-(3-(cyclopropanesulfonamido)-4-fluorophenyl)-3,4-difluorobenzamide:



[0700] 3,4-Difluoro-N-(4-fluoro-3-nitrophenyl)benzamide: 3,4-difluorobenzoic acid (1g) was dissolved in CH_2Cl_2 (10ml). To the solution, oxalyl chloride (1ml) was added. The reaction mixture was stirred at ambient temperature for 30 minutes until the reaction is complete. The solvent was stripped off and CH_2Cl_2 (20ml) was added, the resultant solution was cooled to -5°C and then Et_3N (2ml) was added, followed by addition of 3-nitro-4-fluoroaniline (1g). The reaction mixture was stirred at ambient temperature for 30 minutes until the reaction is complete. The solvent was stripped off and 3g of 3,4-difluoro-N-(4-fluoro-3-nitrophenyl)benzamide was obtained as solid.



[0701] N-(3-amino-4-fluorophenyl)-3,4-difluorobenzamide: 3,4-difluoro-N-(4-fluoro-3-nitrophenyl)benzamide (2g) was dissolved in 1,4-dioxane (40 ml), then 6N HCl (6ml) and SnCl_2 (8g) were added. The reaction mixture was stirred at ambient temperature for 4 hours until the reaction is complete. The reaction mixture was poured into 1N NaOH solution and extracted with EtOAc twice. The organic layer was washed with brine solution and the solvent was stripped off by rotovap and 1.24g of N-(3-amino-4-fluorophenyl)-3,4-difluorobenzamide was obtained as oil. The crude product was used without further purification.



[0702] N-(3-(cyclopropanesulfonamido)-4-fluorophenyl)-3,4-difluorobenzamide: N-(3-amino-4-fluorophenyl)-3,4-difluorobenzamide (12.4g) was dissolved in pyridine (15ml), then DMAP (100mg) and cyclopropanesulfonyl chloride (0.65g) were added. The reaction mixture was stirred at ambient temperature overnight until the reaction is complete. The reaction mixture was poured into water (100ml) and extracted with EtOAc twice. The organic layer was washed with water and dried with anhydrous Na₂SO₄. The solvent was stripped off by rotovap and the solid product was purified by slurried in MTBE(20ml). 800 mg of N-(3-(cyclopropanesulfonamido)-4-fluorophenyl)-3,4-difluorobenzamide was obtained as off white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.8-7.10 (m, 6H), 6.6 (bs, 1H), 2.58 (m, 1H), 1.21 (m, 2 H), 1.0 (m, 2 H). MS (ESI) (m/z) observed (M+1) = 371. HPLC purity: 98%. LC-MS: Calcd: 370.0; Measured: [M+1] = 371.0

PROCEDURES

[0703] The following procedures can be utilized in evaluating and selecting compounds as inhibitors of HBV infection.

[0704] The HBV replication inhibitors of the present invention are capable of treating and preventing diseases associated with HBV infection. The results presented in **Tables 21 to 39** demonstrated that compounds of the present invention inhibit HBV replication in an immortalized murine hepatocyte (AML12)-derived stable cell line (AML12HBV10) that supports robust HBV replication in a tetracycline inducible manner without measurable cytotoxicity up to 50 μM by using the standard MTT assay (Promega).

[0705] The antiviral efficacy of the compounds of the disclosure, as presented in **Tables 21 through 39** were determined in AML12HBV10 cells. AML12HBV10 is an immortalized murine hepatocyte (AML12)-derived stable cell line that supports robust HBV replication in a tetracycline inducible manner (Xu et al.). The cells were seeded into 96 well plates at a density of 2 x 10⁴ cells per well and cultured in DMEM/F12 media with 10% fetal bovine serum in the absence of tetracycline to allow pgRNA transcription and HBV DNA replication. One day after seeding, cells were left untreated or treated with a serial dilution of testing compounds, ranging from 50 μM to 0.39 μM, for

48 hours. Cells were then lysed by adding into each well of 100 μ l lysis buffer containing 10 mM Tris-HCl (pH 7.6), 1 mM EDTA, 100 mM NaCl and 1% NP-40 and incubated at 37 °C for 30 minutes. Half amount (50 μ l) of cell lysate from each well was combined with equal volume of denaturing solution containing 0.5N NaOH and 1.5M NaCl. After 5 minute incubation, 100 μ l of neutralization solution (1M Tris-HCl, pH 7.4, 1.5M NaCl) was added into each well. The denatured cell lysates (totally 200 μ l) were applied onto Nylon membrane using 96-well dot-blot manifold (Biorad). HBV DNA in the cell lysates were determined by dot-blot hybridization with alpha-³²P-UTP-labelled riboprobe specific for HBV minus strand DNA. The antiviral efficacy of a compound of the disclosure was expressed as the concentration that reduces the amount of HBV DNA by 50% (EC₅₀).

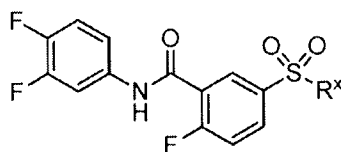
[0706] Determination of cytotoxicity of compounds of the disclosure in AML12HBV10 cells: To determine the cytotoxicity of the compounds, AML12HBV10 cells were seeded into 96-well plates at a density of 2×10^4 cells per well and cultured in DMEM/F12 media with 10% fetal bovine serum in the absence of tetracycline to allow pgRNA transcription and HBV DNA replication. One day after seeding, cells were left untreated or treated with a serial dilution of testing compounds, ranging from 50 μ M to 0.39 μ M, for 48 hours. The cell viability was measured by a MTT assay, following procedure provided by the manufacturer (Promega). The cytotoxicity of a compound was expressed as the concentration of compound that reduces the viability of the cells by 50% (CC₅₀).

[0707] Determination of antiviral activity of compounds of the disclosure, as presented in **Tables 21 through 39**, in human hepatoma-derived cell lines: To further confirm the antiviral activity of the compounds of the disclosure against HBV in human hepatocyte-derived cells, HepDES19 cells, a human hepatoma cell line supporting HBV replication in a tetracycline inducible manner (Guo et al., 2007), seeded into 12-well plates at a density of 5×10^5 cells per well and cultured in DMEM/F12 media with 10% fetal bovine serum and 1 μ g/ml tetracycline. Two days after seeding, the cells were mock-treated or treated with a serial dilution of compounds of the disclosure, ranging from 10 μ M to 0.018 μ M, for 6 days in the absence of tetracycline. Upon the completion of treatment, cells were lysed by adding into each well of the 12-well plates 0.5 ml of lysis buffer containing 10 mM Tris-HCl (pH 8.0), 1 mM EDTA, 1% NP40 and 2% sucrose and incubating at 37°C for 10 minutes. Cell debris and nuclei were removed by centrifugation and the supernatant was mixed with 130 μ l of 35% polyethylene glycol (PEG) 8000 containing 1.5 M NaCl. After 1 hour incubation in ice, viral

nucleocapsids were pelleted by centrifugation at 6,000 X g for 5 min at 4°C, followed by 1 hour digestion at 37°C in 400 µl of digestion buffer containing 0.5 mg/ml pronase (Calbiochem), 0.5% SDS, 150 mM NaCl, 25 mM Tris-HCl (pH 8.0) and 10 mM EDTA. The digestion mixture was extracted twice with phenol and DNA was precipitated with ethanol, dissolved in TE buffer (10 mM Tris-HCl, pH 8.0; 0.1 mM EDTA). One half of the DNA sample from each well was resolved by electrophoresis into a 1.5% agarose gel. The gel was then subjected to denaturation in a solution containing 0.5 M NaOH and 1.5 M NaCl, followed by neutralization in a buffer containing 1 M Tris-HCl (pH7.4) and 1.5 M NaCl. DNA was then blotted onto Hybond-XL membrane (GE Health care) in 20X SSC buffer. The amounts of cytoplasmic HBV core-associated HBV DNA were determined by Southern blot hybridization and the antiviral efficacy of a compound was expressed as its concentration that reduce the amount of HBV DNA by 50% (EC₅₀) or 90% (EC₉₀).

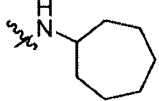
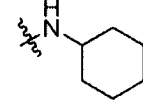
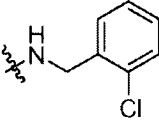
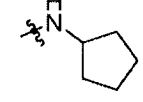
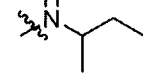
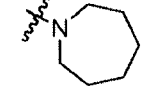
[0708] Determination of cytotoxicity of compounds of the disclosure in human hepatoma-derived cell lines, HepDES19 cells were seeded into 96-well plates at a density of 6×10^4 cells per well and cultured in DMEM/F12 media with 10% fetal bovine serum in the absence of tetracycline. One day after seeding, cells were left untreated or treated with a serial dilution of testing compounds, ranging from 50 µM to 0.39 µM, for 6 days. The cell viability was measured by a MTT assay, following procedure provided by the manufacturer (Promega). The cytotoxicity of a compound was expressed as the concentration of compound that reduces the viability of the cells by 50% (CC₅₀).

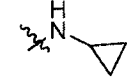
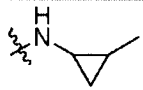
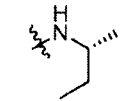
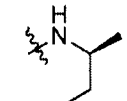
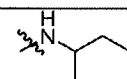
[0709] Table 21: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 µM; 1 = 5-10 µM; 2 = 1-5 µM; 3 = <1 µM.

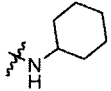
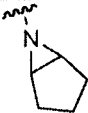
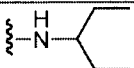
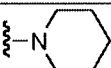
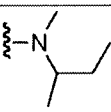
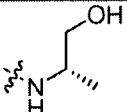
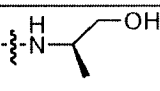
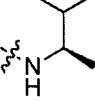


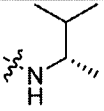
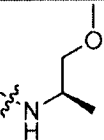
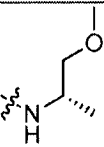
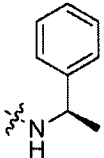
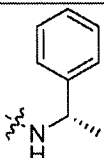
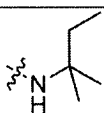
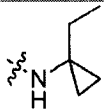
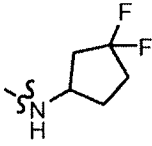
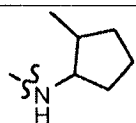
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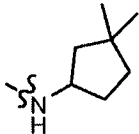
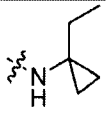
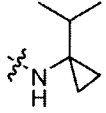
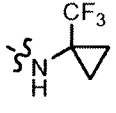
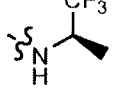
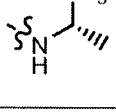
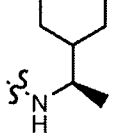
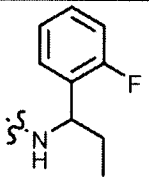
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀

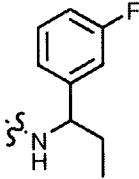
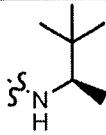
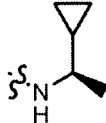
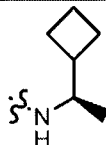
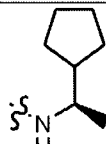
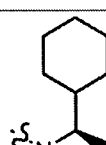
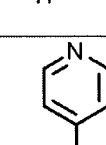
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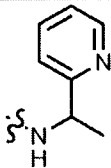
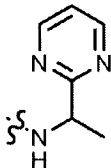
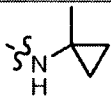
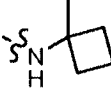
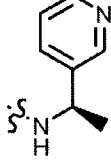
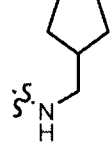
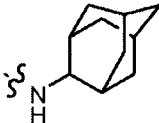
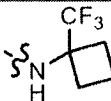
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	1	-
	2	-
	3	3
	3	3
	3	-

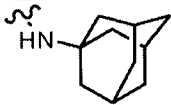
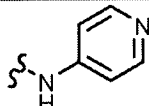
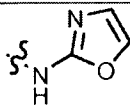
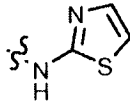
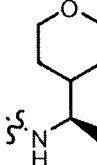
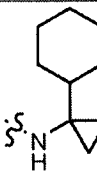
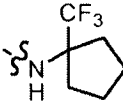
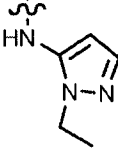
	3	3
	1	-
	3	3
	0	-
	2	-
	1	-
	0	-
	3	2
	3	-
	2	-
	1	-
	3	3
	3	3

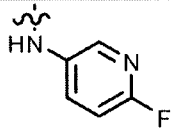
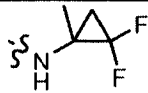
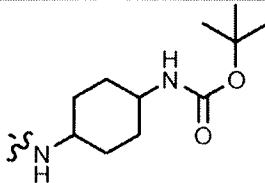
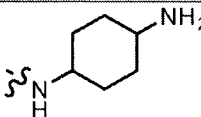
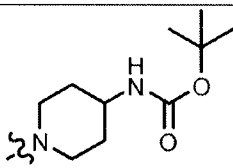
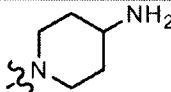
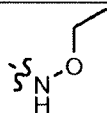
	2	2
	3	3
	2	-
	3	3
	2	-
	3	3
	3	3
	3	-
	3	-

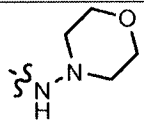
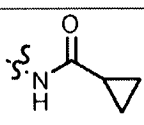
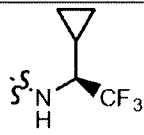
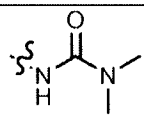
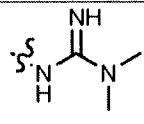
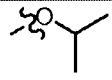
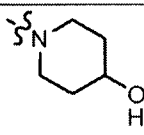
	3	-
	3	3
	3	-
	3	3
	3	-
	3	-
	3	-
	3	-

	3	-
	3	-
	3	3
	3	3
	3	3
	3	3
	3	3

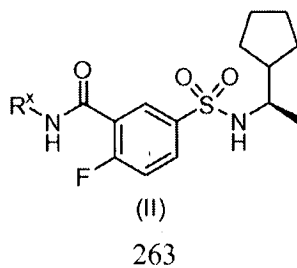
	3	-
	2	-
	3	3
	3	3
	3	3
	3	3
	3	2
	3	3

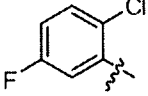
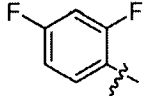
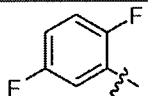
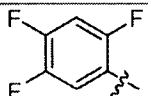
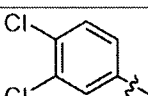
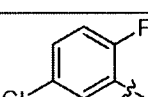
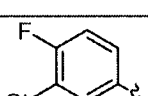
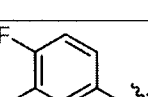
	2	-
	0	-
	0	-
	0	-
	1	-
	3	3
	3	-
	0	-

	0	-
	2	-
	3	-
	0	-
	0	-
	0	-
	3	-
	2	-

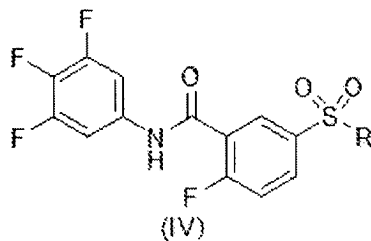
	0	-
	0	-
	2	-
	3	-
	0	-
	0	-
	0	-
	0	-

[0710] Table 22: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.



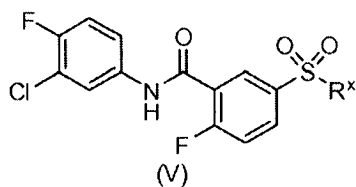
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	0	-
	1	-
	2	-
	2	-
	2	-
	1	-
	3	-
	0	-

[0711] Table 23: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

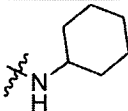
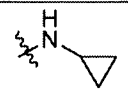
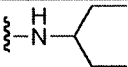
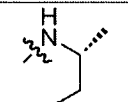


R	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	3	-
	3	-
	3	-

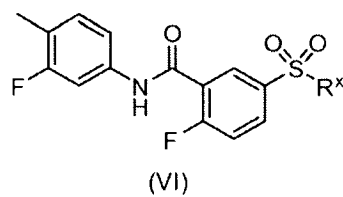
[0712] Table 24: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μM; 1 = 5-10 μM; 2 = 1-5 μM; 3 = <1 μM.

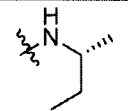
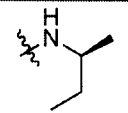
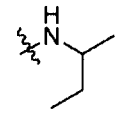


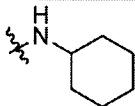
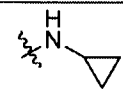
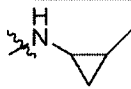
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	2

	2	-
	1	-
	3	3
	3	-

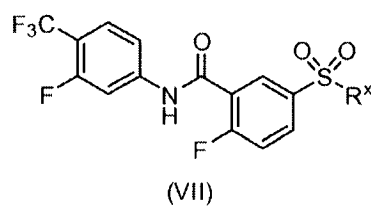
[0713] Table 25: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC_{50} key: 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$.

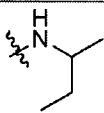


R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	1	-
	0	-
	0	-

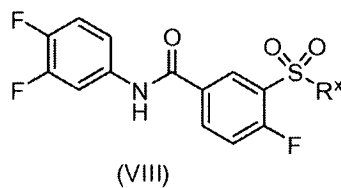
	0	-
	0	-
	0	-

[0714] **Table 26:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀ key:** 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

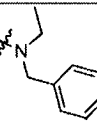
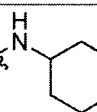
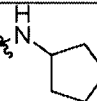
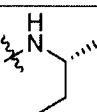
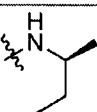


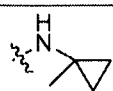
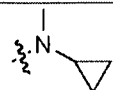
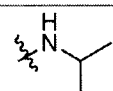
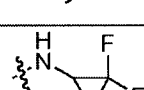
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	0	-

[0715] **Table 27:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀ key:** 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

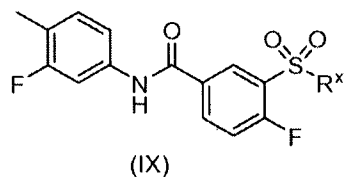


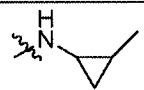
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀

	3	2
	3	2
	3	2
	3	3
	3	3
	2	3
	3	-
	2	-
	3	-
	3	-
	3	3
	2	-

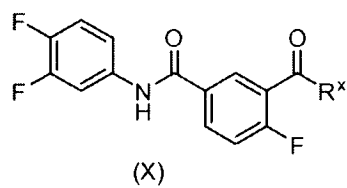
	0	-
	3	-
	3	2
	2	-
	0	-
	2	-

[0716] **Table 28:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC_{50} key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.



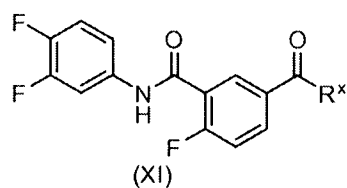
R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	0	-

[0717] **Table 29:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC_{50} key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.



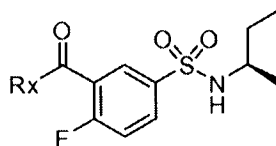
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	-

[0718] Table 30: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μM; 1 = 5-10 μM; 2 = 1-5 μM; 3 = <1 μM.



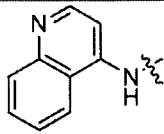
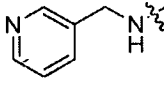
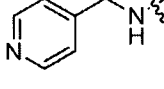
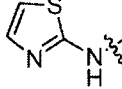
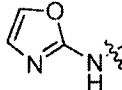
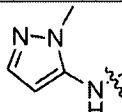
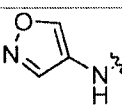
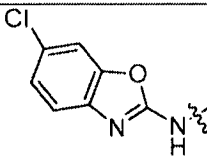
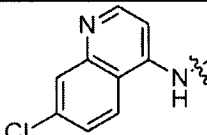
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	-
	0	-
	0	-
	0	-

[0719] Table 31: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

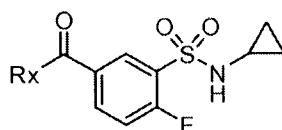


(XII)

Rx	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	-
	2	-
	0	-
	0	-
	0	-
	0	-
	0	-

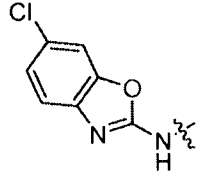
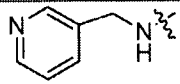
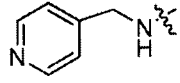
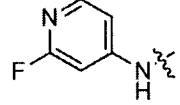
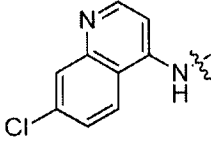
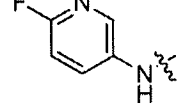
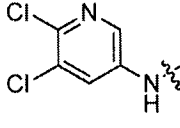
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-

[0720] Table 32: Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀ key:** 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

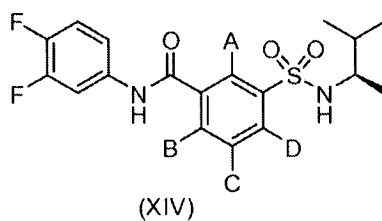


(XIII)

Rx	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-

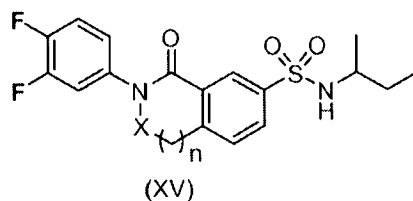
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-

[0721] **Table 33:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC_{50} key: 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$.



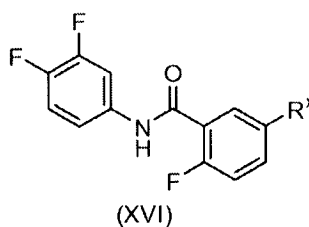
A	B	C	D	AML12HBV10	HepDES19
				EC ₅₀	EC ₅₀
H	Cl	H	H	3	-
H	OMe	H	H	3	3
H	F	H	F	2	-
H	Me	H	H	3	3

[0722] **Table 34:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

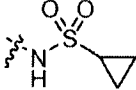
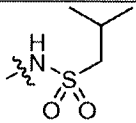


X	n	AML12HBV10	HepDES19
		EC ₅₀	EC ₅₀
CH ₂	1	0	-

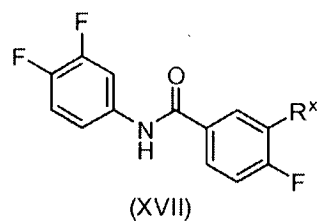
[0723] **Table 35:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.

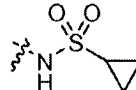
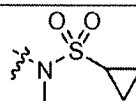


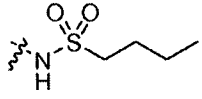
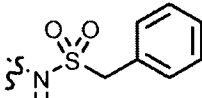
R _x	AML12HBV10	HepDES19
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	EC50	EC50
-NO ₂	1	-
-NH ₂	1	-
	2	0
	2	-

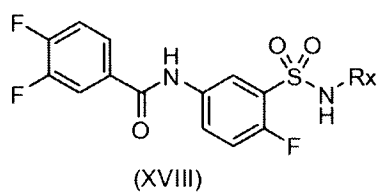
[0724] **Table 36:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, EC₅₀ key: 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.



R _x	AML12HBV10 EC50	HepDES19 EC50
-NO ₂	0	-
-NH ₂	0	-
	3	2
	0	0

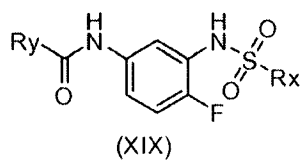
	0	0
	0	0

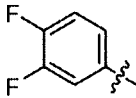
[0725] **Table 37:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀** key: **0** = >10 μM ; **1** = 5-10 μM ; **2** = 1-5 μM ; **3** = <1 μM .



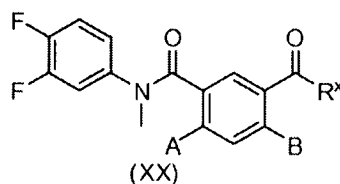
Rx	AML12HBV10 EC50	HepDES19 EC50
	0	-

[0726] **Table 38:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀** key: **0** = >10 μM ; **1** = 5-10 μM ; **2** = 1-5 μM ; **3** = <1 μM .



Rx	Ry	AML12HBV10 EC50	HepDES19 EC50
		0	-

[0727] **Table 39:** Antiviral activity of exemplary compounds in AML12HBV10 and HepDES19 cells. In the Table, **EC₅₀ key:** 0 = >10 μ M; 1 = 5-10 μ M; 2 = 1-5 μ M; 3 = <1 μ M.



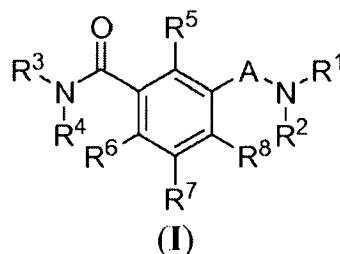
R ^x	A	B	AML12HBV10	HepDES19
			EC ₅₀	EC ₅₀
	F	H	2	-
	H	F	0	-

[0728] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description and the examples that follow are intended to illustrate and not limit the scope of the invention. It will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the invention, and further that other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. In addition to the embodiments described herein, the present invention contemplates and claims those inventions resulting from the combination of features of the invention cited herein and those of the cited prior art references which complement the features of the present invention. Similarly, it will be appreciated that any described material, feature, or article may be used in combination with any other material, feature, or article, and such combinations are considered within the scope of this invention.

[0729] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, each in its entirety, for all purposes.

WHAT IS CLAIMED

1. A compound comprising a structure of Formula (I), or an enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate thereof:



including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein:

A is selected from a group consisting of SO₂ and CO;

R¹ is selected from a group consisting of optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted aryl, and optionally substituted benzyl, optionally substituted 3-7 membered cycloheteroalkyl, optionally substituted C₂₋₈ alkenyl, optionally substituted C₂₋₈ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted amine, optionally substituted amidine, optionally substituted carboxyamine, optionally substituted carboxy-C₁₋₆-alkoxide, -SO₂-C₁₋₆alkyl, optionally substituted heterocyclic, or optionally substituted heteroaryl;

R² is selected from a group consisting of hydrogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₃₋₇ cycloalkyl, and optionally substituted heterocyclic; or

R¹ and R² are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 3 to 10 atoms; and

R³ is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, optionally substituted alkylheteroaryl, and optionally substituted C₁₋₆ linear alkyl;

R⁴ is selected from a group consisting of hydrogen and optionally substituted C₁₋₆ linear alkyl;

R⁵ is selected from a group consisting of hydrogen, halogen, optionally substituted C₁₋₆ linear alkyl, optionally substituted C₁₋₆ branched alkyl, optionally substituted C₁₋₆ haloalkyl, OR⁹, cyano and N(R⁹)₂;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls; and

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, OR^9 , cyano and $N(R^9)_2$; or

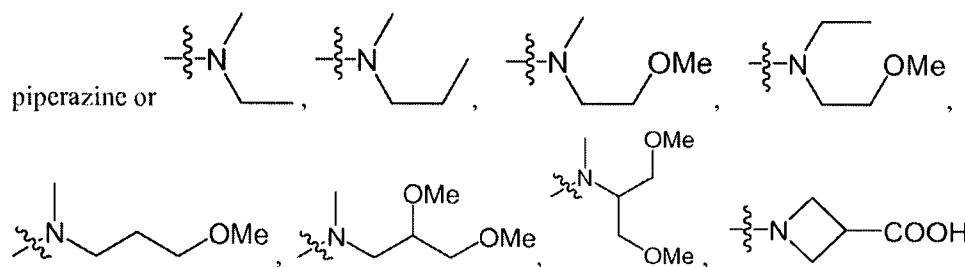
R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, OR^9 , cyano and $N(R^9)_2$; or

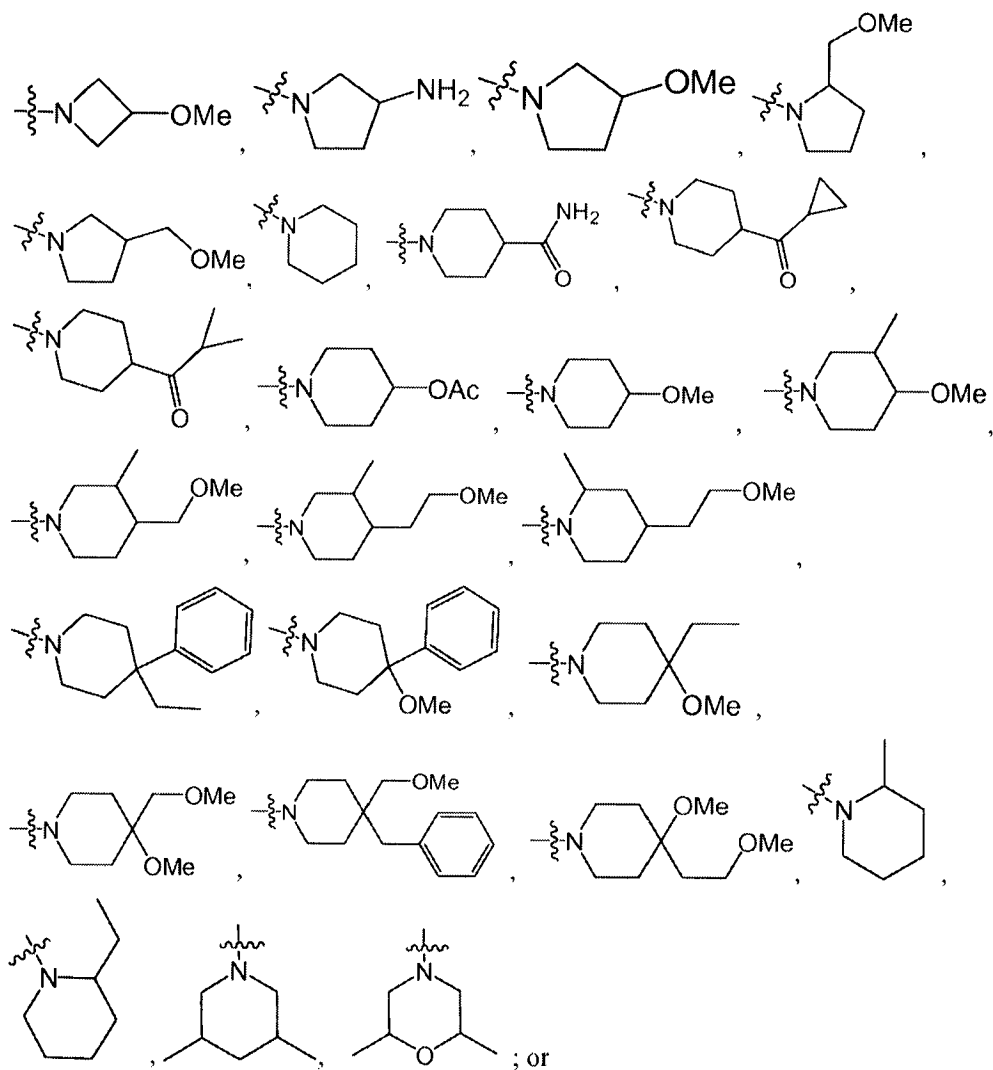
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms; and

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl;

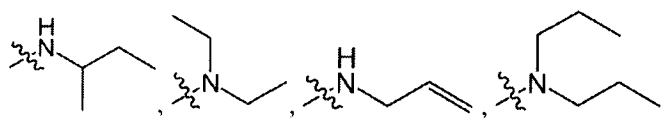
[0730] provided that when A is SO_2 ; R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring, then none of the following (a) through (d) apply:

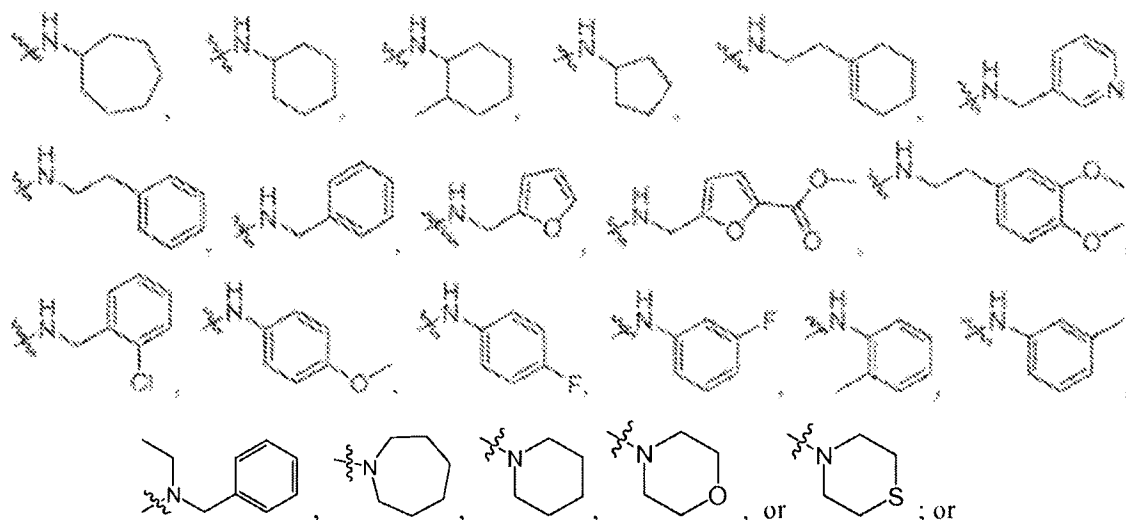
- (a) R^3 is an optionally substituted phenyl and R^1 or R^2 , either individually or when taken together, contain a hydroxyl group; or
- (b) R^3 is an optionally substituted alkyl or phenyl, and $N(R^1)(R^2)$ is an optionally substituted





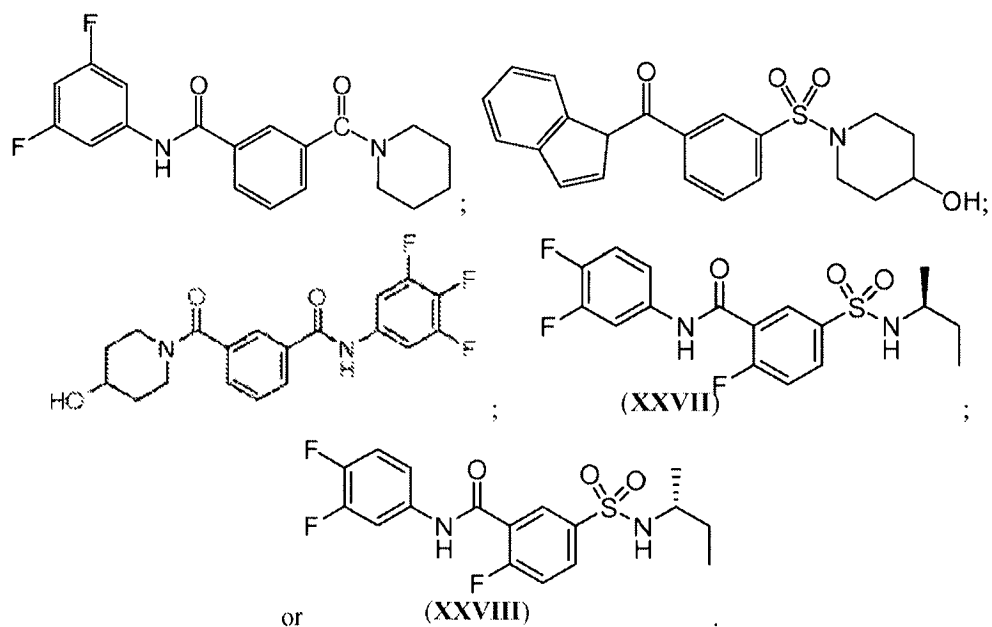
(c) R^3 is optionally substituted alkyl, aryl, or alkaryl and $N(R^1)(R^2)$ is





- (d) either R^3 or R^4 is an unsubstituted or monosubstituted aryl, or an unsubstituted or monosubstituted alkyl, or unsubstituted or monosubstituted heteroaryl and R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocyclic ring structure with 6 to 12 atoms; or

[0731] provided that the compound is not 3-(((dicyclopropylmethyl)amino)sulfonyl)-N-(4-isopropoxyphenyl)benzamide; or 3-([2-(1H-benzimidazol-2-yl)propyl]amino)sulfonyl)-N-(4-isopropoxyphenyl)benzamide; or 3-[(cyclohexylamino)sulfonyl]-N-(4-isopropylphenyl)benzamide; or 3-(anilinosulfonyl)-N-(4-isopropylphenyl)benzamide; or 5-{[(3-[(4-methoxyphenyl)amino]carbonyl]phenyl)sulfonyl]amino}pentanoic acid; or 3-[(*tert*-butylamino)sulfonyl]-N-(4-methoxyphenyl)benzamide; or (3S)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or (3R)-1-[(3-[(5-isopropoxypyridin-2-yl)amino]carbonyl]phenyl)sulfonyl]piperidine-3-carboxamide; or 3-(piperidin-1-ylsulfonyl)-N-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide; or N-(5-bromo-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenylpyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-phenoxy-pyridin-2-yl)-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-[3-methoxy-5-(phenylthio)pyridin-2-yl]-3-(pyrrolidin-1-ylsulfonyl)benzamide; or N-(5-ethyl-3-methoxypyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or N-(3-methoxy-5-vinylpyridin-2-yl)-3-(piperidin-1-ylsulfonyl)benzamide; or

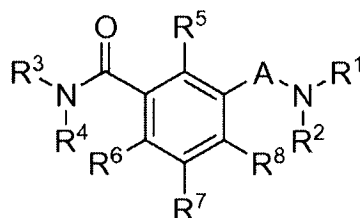


2. The compound of formula (I) wherein:

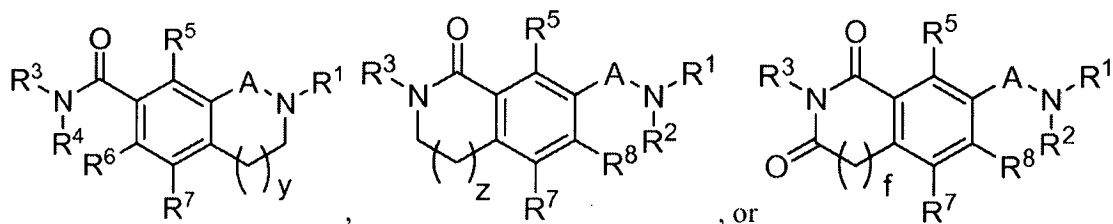
R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring;

thereby providing compounds having formula:



3. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, the compound comprising one of the following structures:



wherein, as appropriate:

R^4 and R^6 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

R^2 and R^8 taken together with the atoms to which they are bound do not to form an optionally substituted ring; and

wherein z and f are independently is 0 or 1, and y is independently 0, 1, or 2.

4. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein A is SO_2 .

5. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein A is CO .

6. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein

R^3 is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl; and

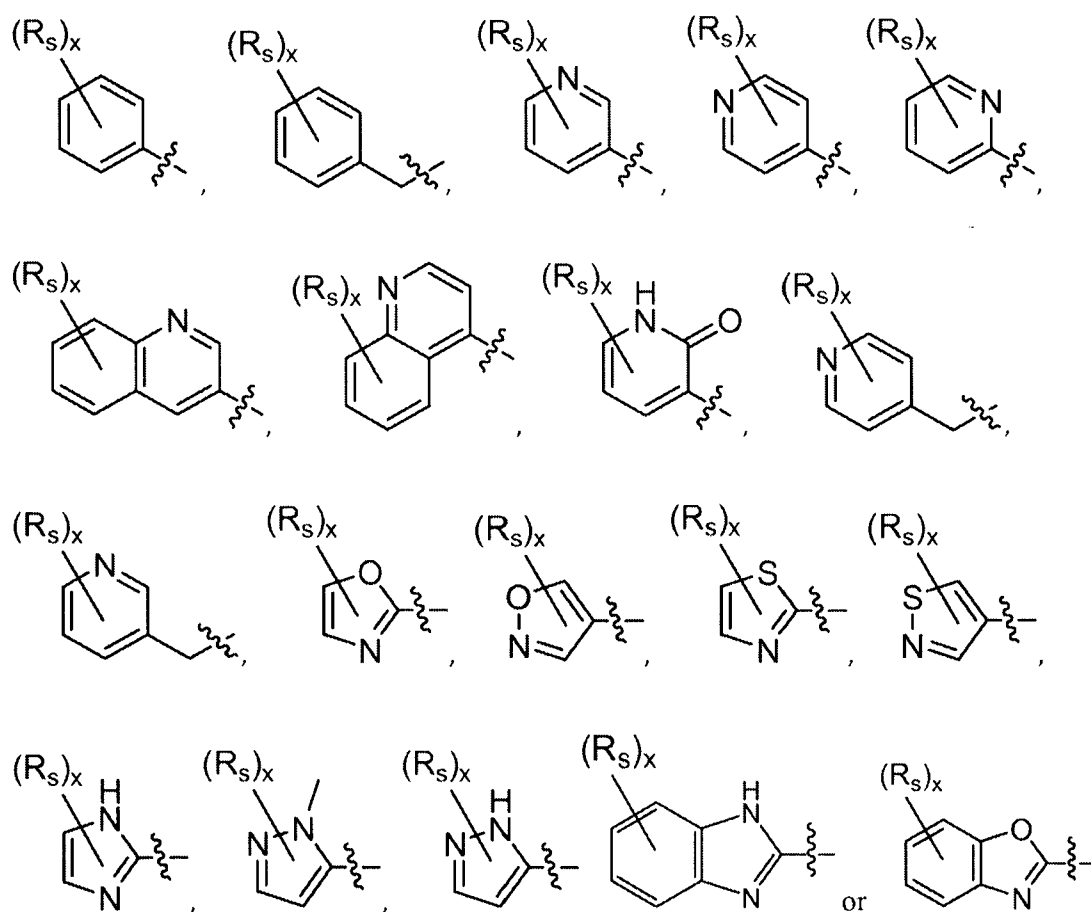
where present, R^4 is hydrogen.

7. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 6, wherein

R^3 is selected from a group consisting of optionally substituted phenyl, optionally substituted benzyl, optionally substituted benzoisoxazolyl, optionally substituted

benzooxazolyl, optionally substituted furyl, optionally substituted imidazolyl, optionally substituted indoyl, optionally substituted isoxazolyl, optionally substituted isothiazolyl, optionally substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted pyridin-2-on-yl, optionally substituted pyridyl, optionally substituted pyrrolyl, optionally substituted quinolinyl, optionally substituted thiazolyl optionally substituted thienyl, and optionally substituted methylpyridyl.

8. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 7, wherein R^3 is



wherein

R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl, $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

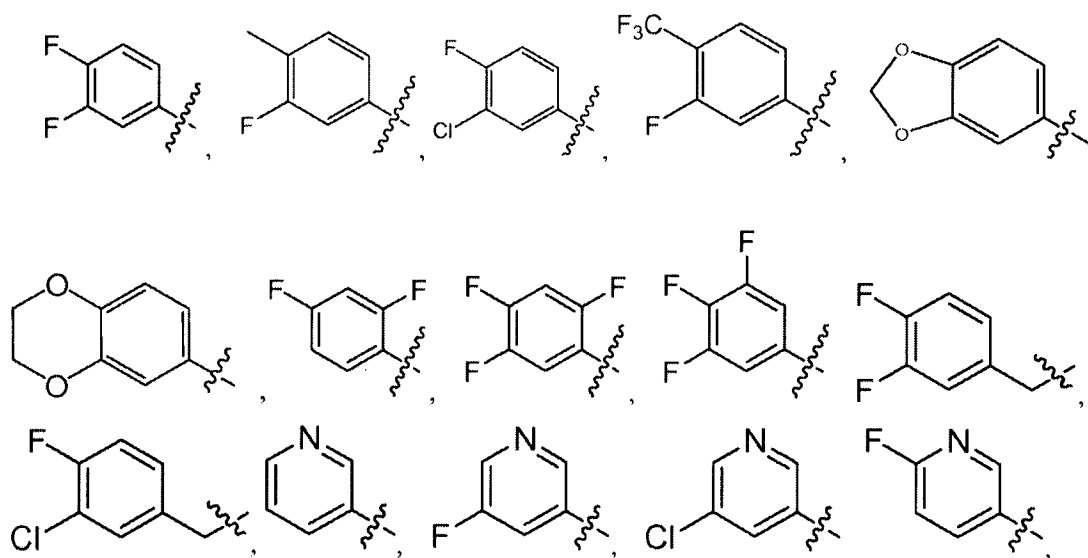
x is 0, 1, 2, or 3; and

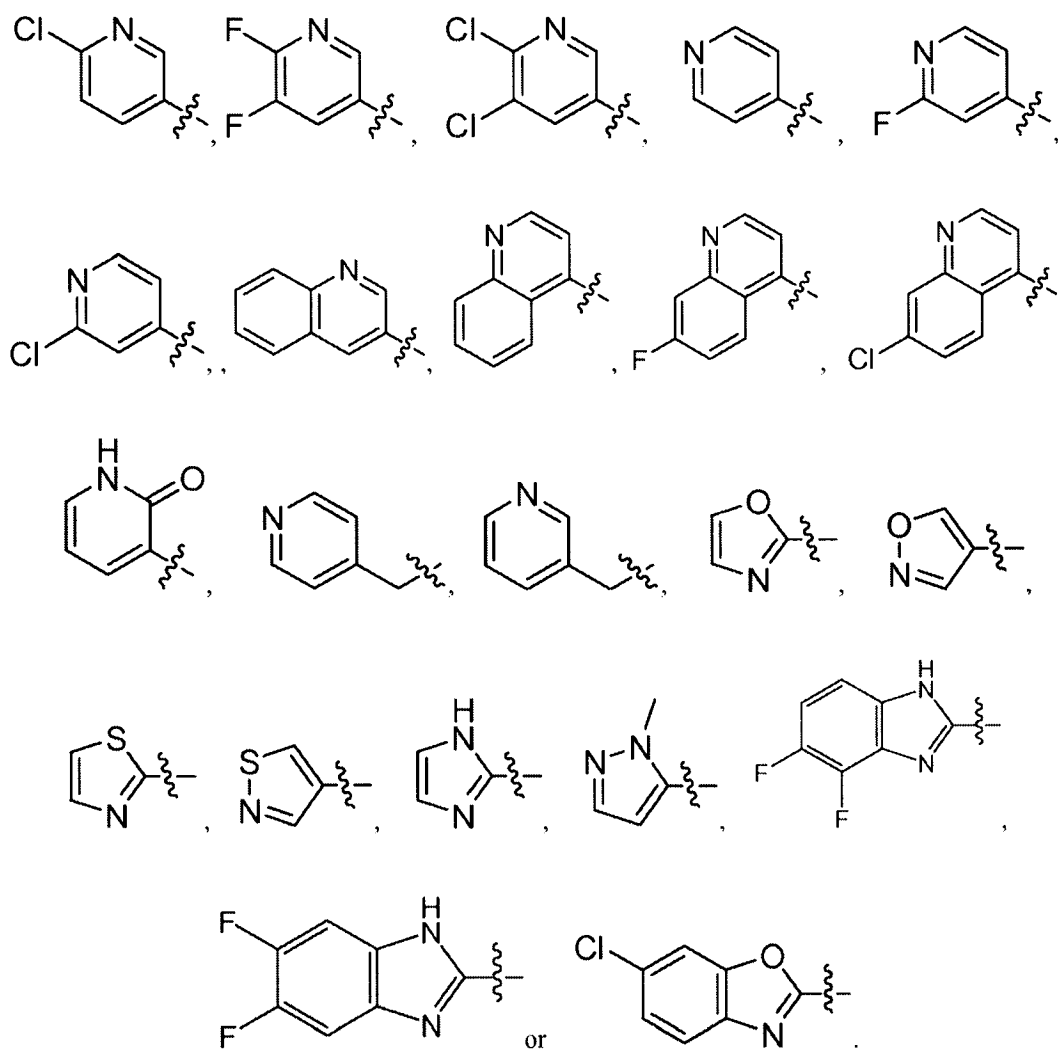
where present, R^4 is hydrogen.

9. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 7, wherein the optional substitution of R^3 comprises at least one halo or C_{1-6} alkyl.

10. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 9, wherein the optional substitution of R^3 comprises at least one halo.

11. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, wherein R^3 is



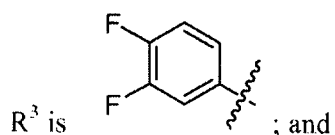


12. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein

R^5 , and R^7 are each independently at each occurrence H or F; and

R^6 and R^8 are each independently at each occurrence hydrogen, chloro, fluoro, or C_{1-3} alkyl, or C_{1-3} alkoxy..

13. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, wherein



where present, R^4 is hydrogen.

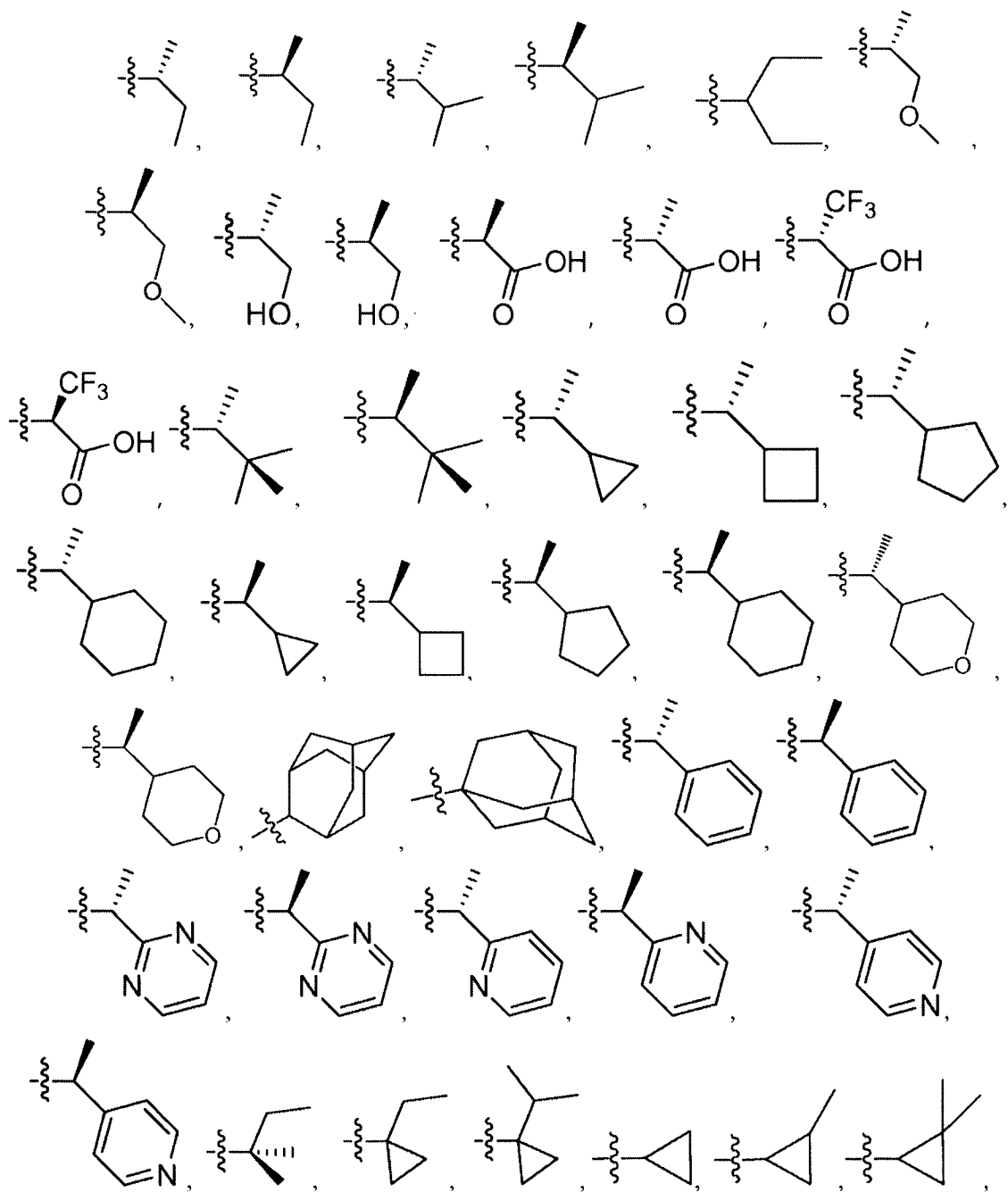
14. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein

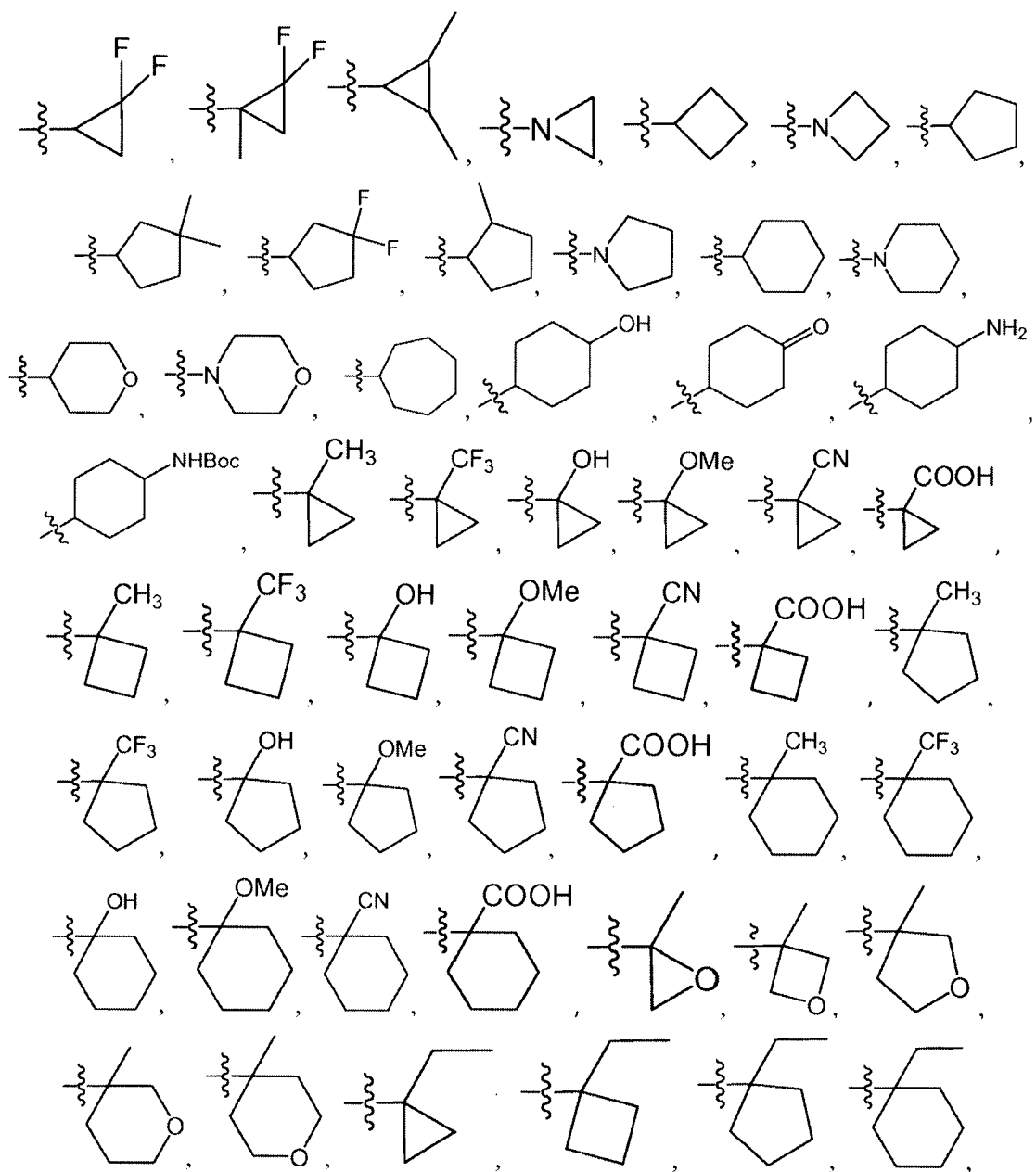
R^5 , R^7 , and R^8 are each H; and

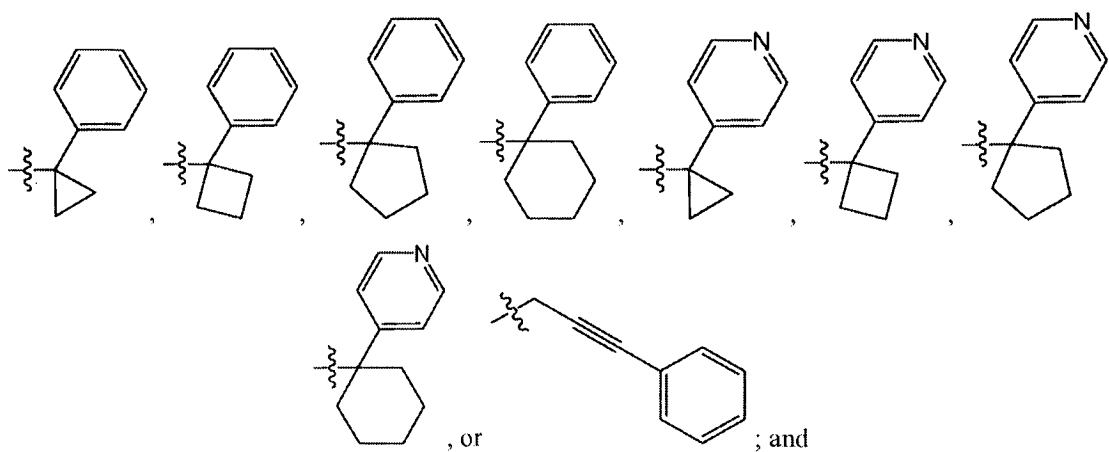
R^6 is hydrogen, chloro, fluoro, or methoxy.

15. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein,

R^1 is methyl, methoxy, ethyl, ethoxy, n-propyl, n-propoxy, isopropyl, isopropoxy, n-butyl, n-butoxy, sec-butyl, sec-butoxy, tert-butyl, tert-butoxy, optionally substituted phenyl, optionally substituted benzyl, optionally substituted benzoisoxazolyl, optionally substituted benzooxazolyl, optionally substituted furyl, optionally substituted imidazolyl, optionally substituted indoyl, optionally substituted isoxazolyl, optionally substituted isothiazolyl, optionally substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted pyridin-2-on-yl, optionally substituted pyridyl, optionally substituted pyrrolyl, optionally substituted quinolinyl, optionally substituted thiazolyl optionally substituted thienyl, and optionally substituted methylpyridyl,

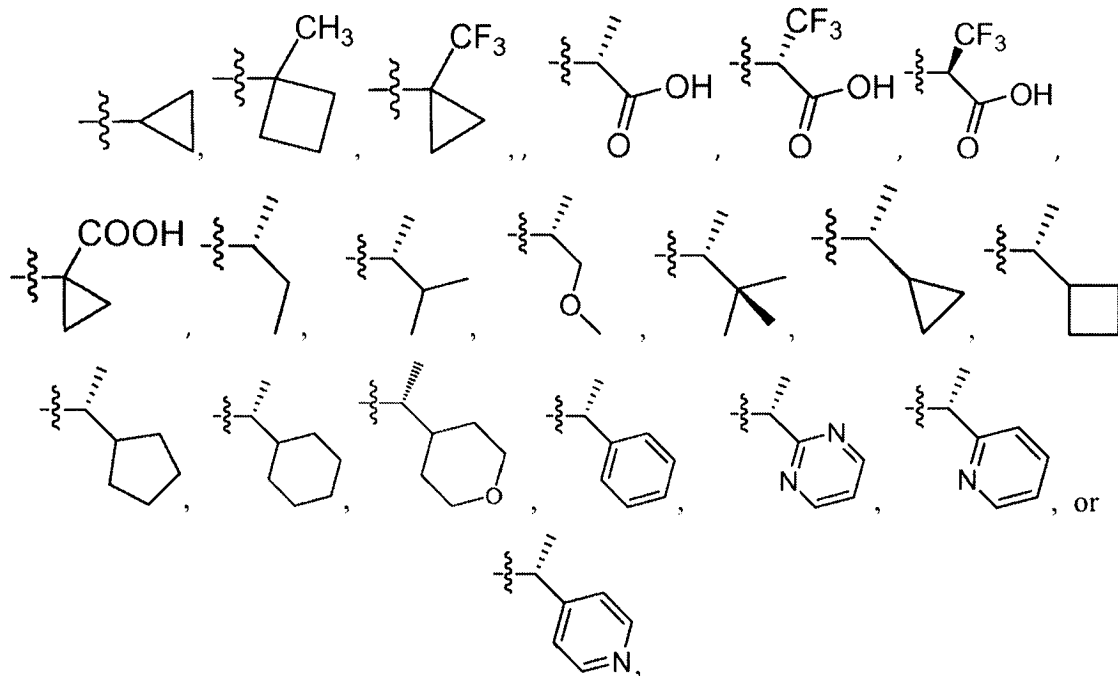






where present, R^2 is H.

16. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, salt, or hydrate of claim 15, wherein R^1 is isopropyl, t-butyl,

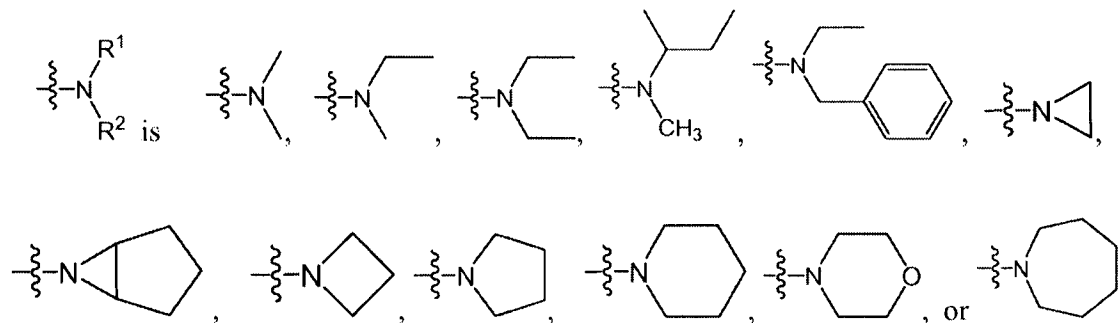


and, where present, R^2 is H.

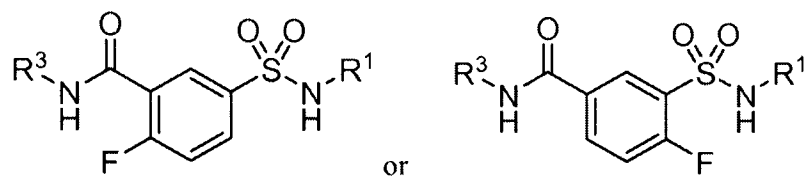
17. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, with the proviso that the $-N(R^1)(R^2)$ moiety does not contain hydroxyl.

18. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, with the proviso that R^1 is not cyclopentane

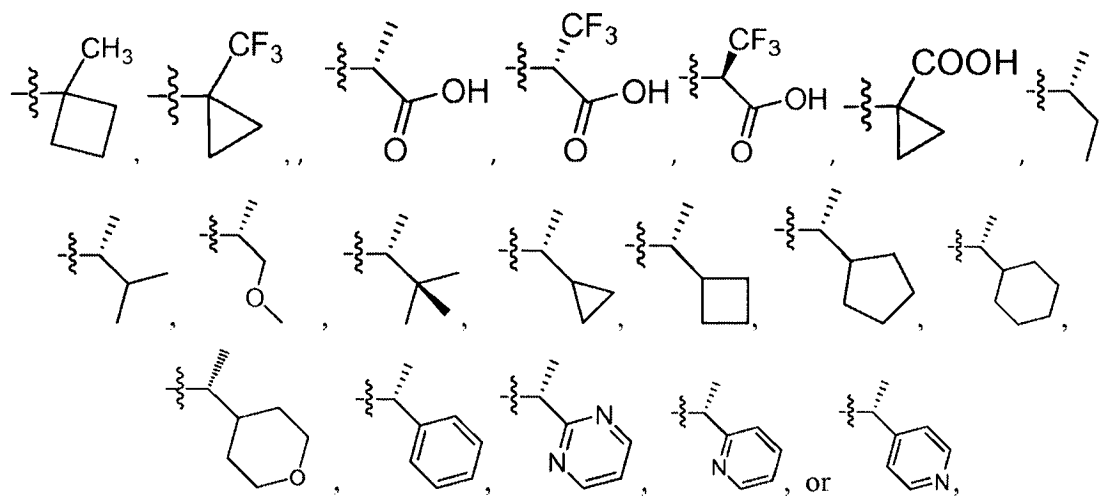
19. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, wherein



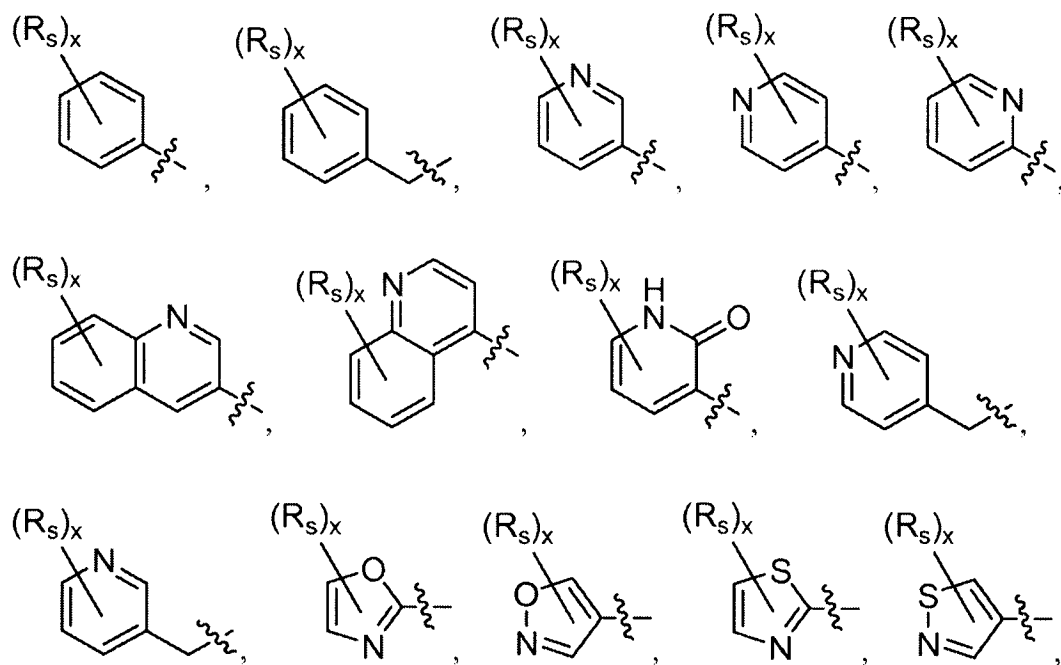
20. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, comprising a structure

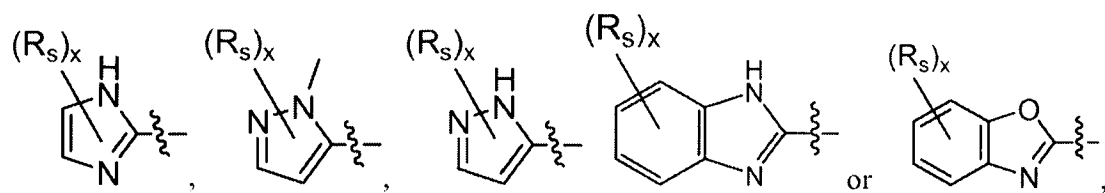


wherein R^1 is



and R^3 is



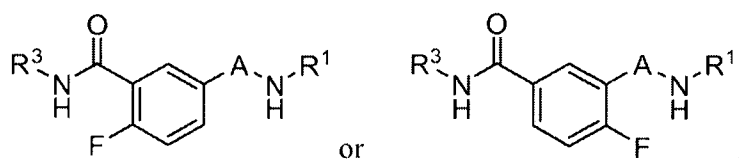


wherein

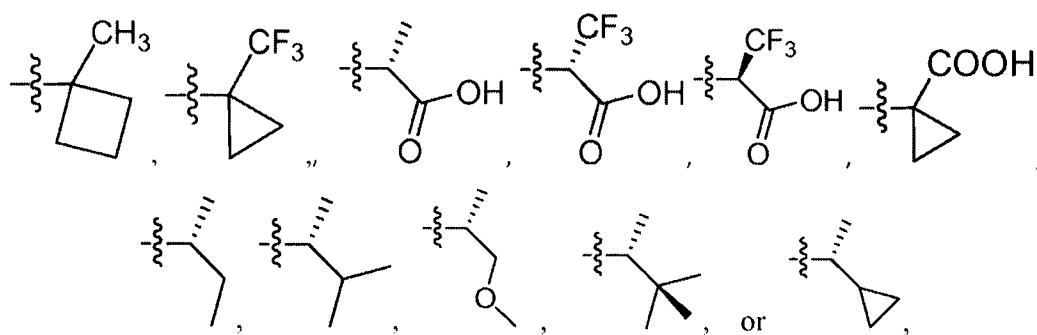
R_S is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl, $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

x is 0, 1, 2, or 3.

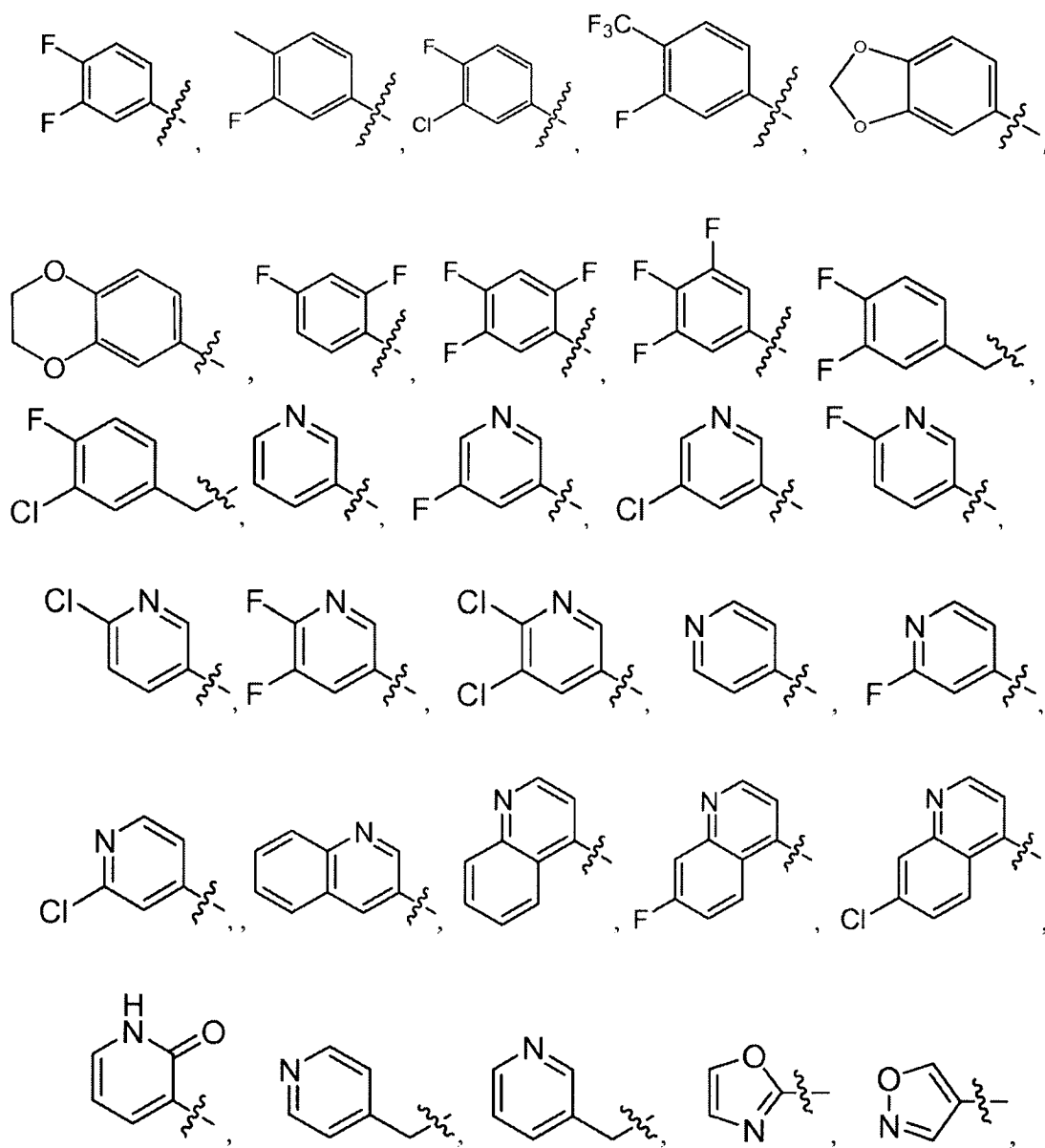
21. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 20, comprising a structure

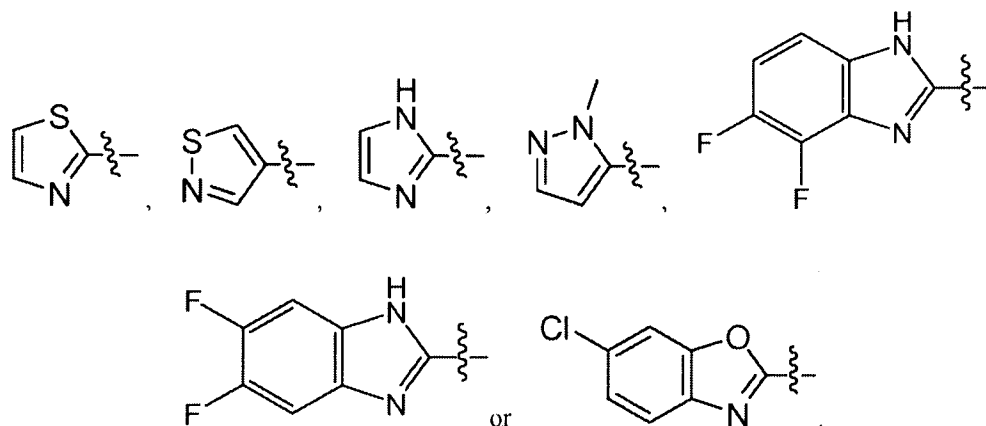


wherein R^1 is

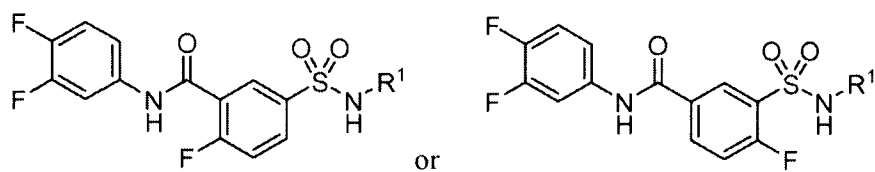


and R^3 is

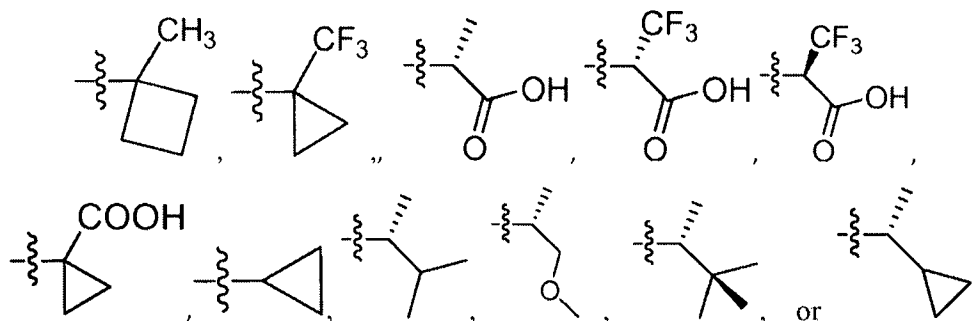




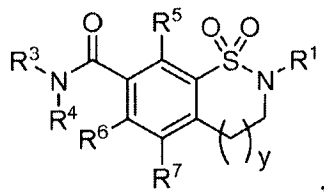
22. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, comprising a structure



wherein R^1 is isopropyl, t-butyl,



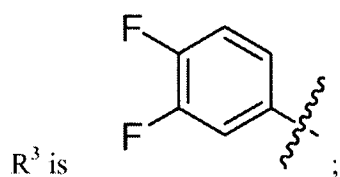
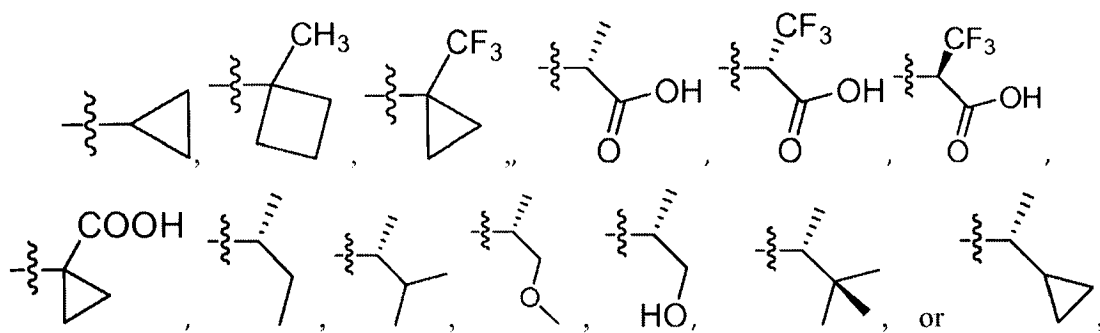
23. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 3, the compound comprising a structure:



wherein y is 0, 1, or 2.

24. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 23, wherein

R^1 is isopropyl, t-butyl,

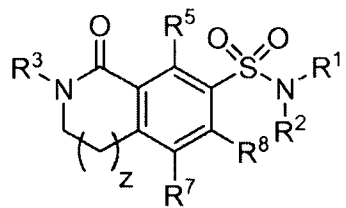


R^3 is

R^4 , R^5 , and R^7 are H; and

R^6 is H or F.

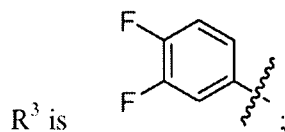
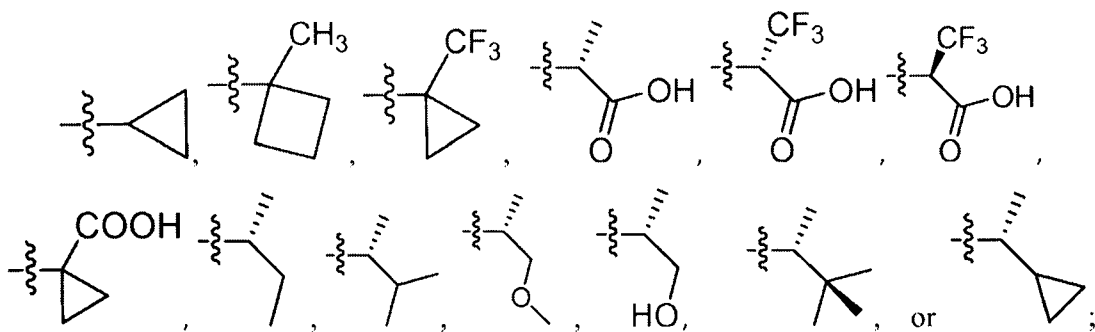
25. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 3, the compound comprising a structure:



wherein z is 0 or 1.

26. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 25, wherein

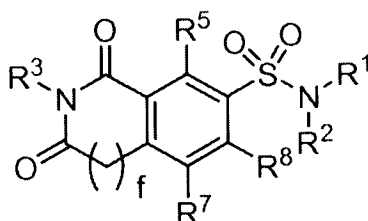
R^1 is isopropyl, tert-butyl,



R^5 , and R^7 are H; and

R^8 is H or F.

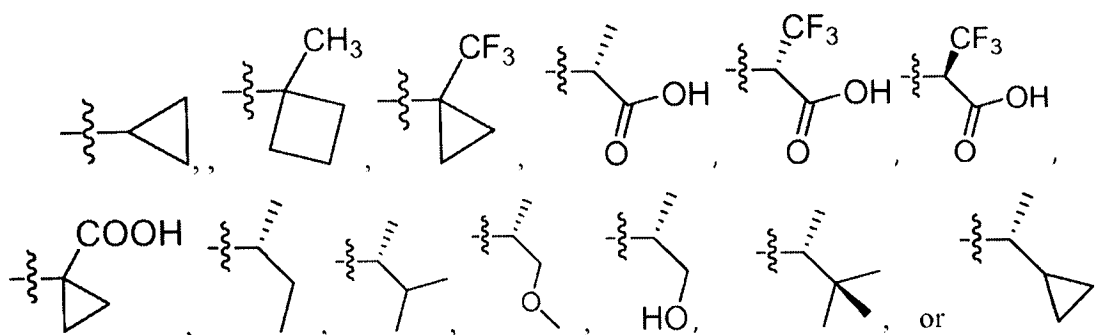
27. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 3, the compound comprising a structure:



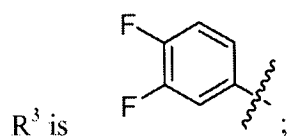
wherein f is 0 or 1.

28. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 27, wherein

R^1 is isopropyl, tert butyl,



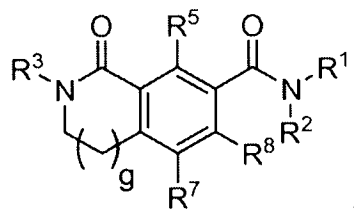
R^2 is H;



R^5 , and R^7 are H; and

R^8 is H or F.

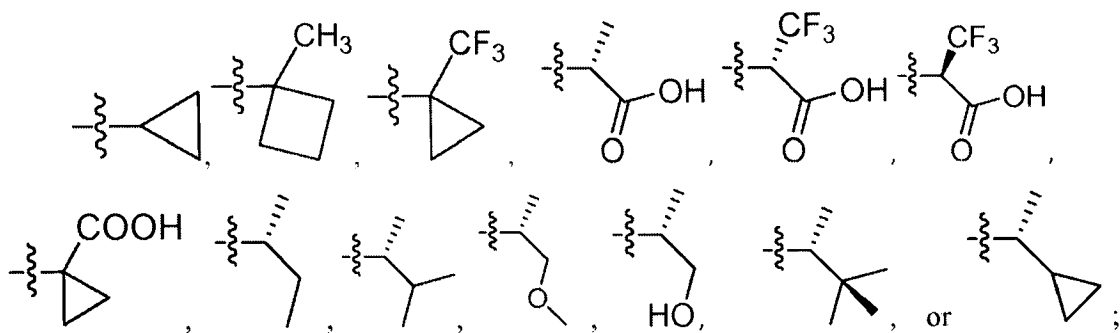
29. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 3, the compound comprising a structure:



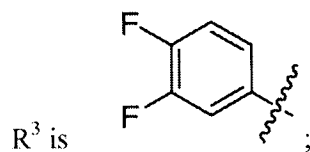
wherein g is 0 or 1.

30. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 29, wherein

R^1 is isopropyl, tert-butyl,



R^2 is H;

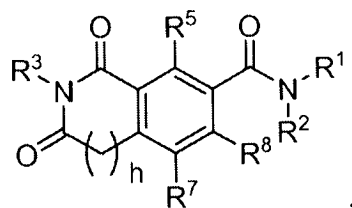


R^3 is

R^5 , and R^7 are H; and

R^8 is H or F.

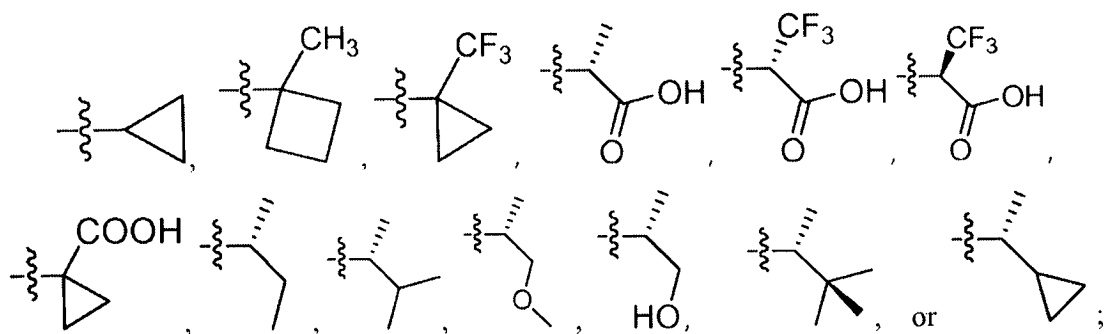
31. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 3, the compound comprising a structure:



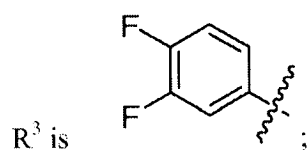
wherein h is 0 or 1.

32. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 31, wherein

R¹ is isopropyl, *tert*-butyl,



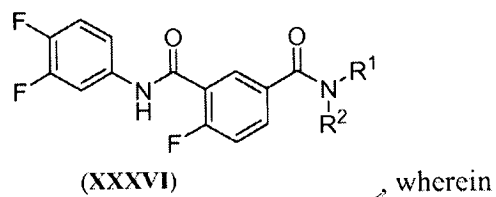
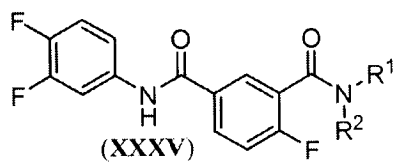
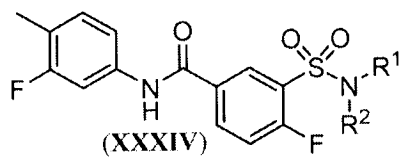
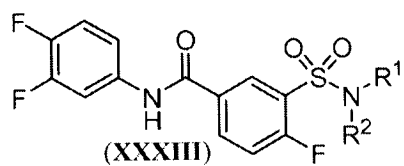
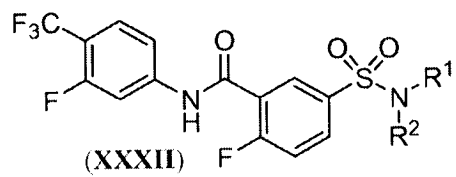
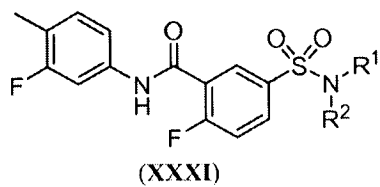
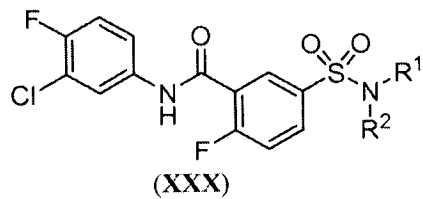
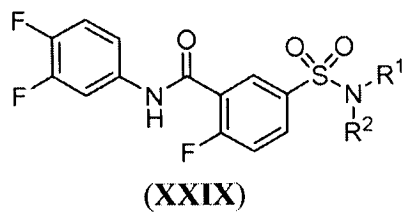
R² is H;



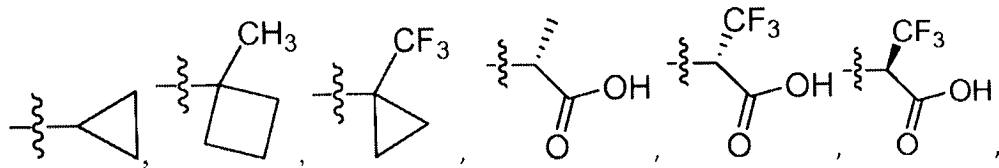
R⁵, and R⁷ are H; and

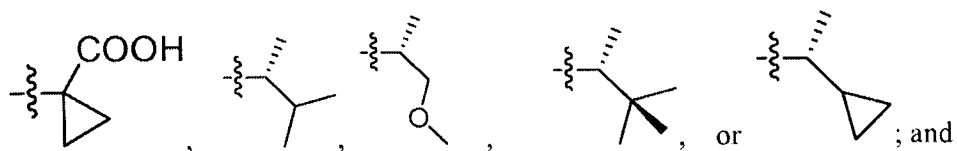
R⁸ is H or F.

33. The compound, enantiomer, diastereomer or pharmaceutically accepted salt, hydrate, or solvate of claim 1, the compound comprising a structure of any one of:



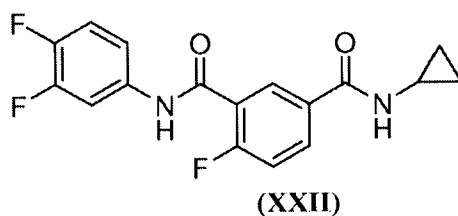
, wherein

R¹ is isopropyl, t-butyl,

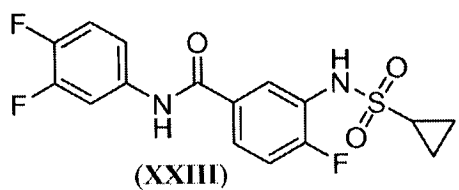


R² is H.

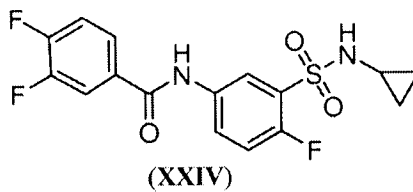
34. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, the compound comprising a structure of Formula (XXII):



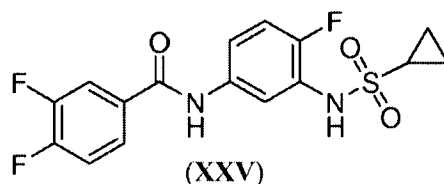
35. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, the compound comprising a structure of Formula (XXIII):



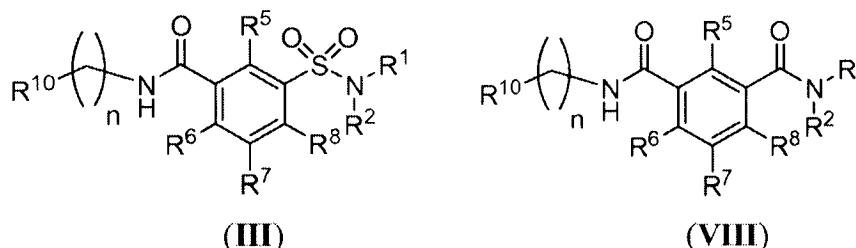
36. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, the compound comprising a structure of Formula (XXIV):



37. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1, the compound comprising a structure of Formula (XXV):



38. A compound comprising a structure of Formula (III) or Formula (VIII), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R^2 is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{3-7} cycloalkyl, and optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 3 to 10 atoms; and

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$; or

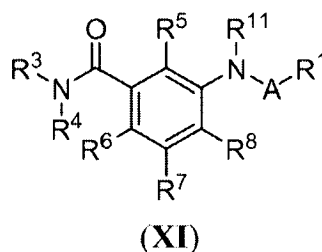
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted ring with 5 to 6 atoms; and

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl;

R^{10} is selected from a group consisting of optionally substituted aryl and optionally substituted heteroaryl; and

n is 0 or 1.

39. A compound comprising a structure of Formula (XI), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R^3 is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, optionally substituted alkylheteroaryl; and optionally substituted C_{1-6} linear alkyl;

R^4 is selected from a group consisting of hydrogen and optionally substituted C_{1-6} linear alkyl;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$; or

R^4 and R^6 are taken together with the atoms to which they are bound to form an optionally substituted carbocyclic or heterocyclic ring with 5 to 6 atoms, optionally containing a carbonyl, optionally containing two carbonyls;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

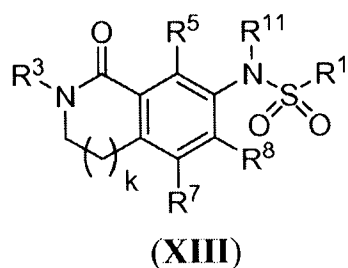
R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl; and

R^{11} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl.

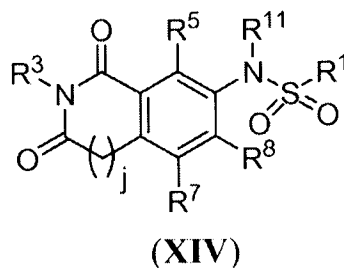
40. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, wherein A is SO₂.

41. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of Formula (XIII):



wherein k is 0 or 1.

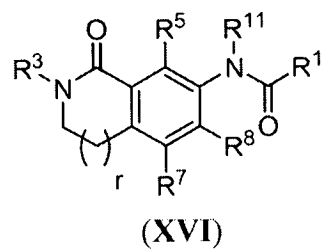
42. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of Formula (XIV),



where j is 0 or 1.

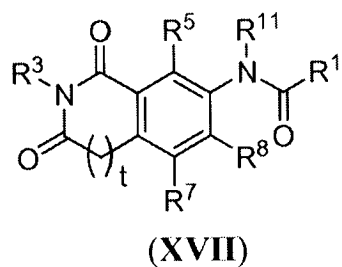
43. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, wherein A is carbonyl, CO.

44. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of Formula (XVI):



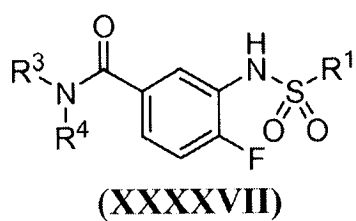
wherein r is 0 or 1.

45. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of Formula (XVII),

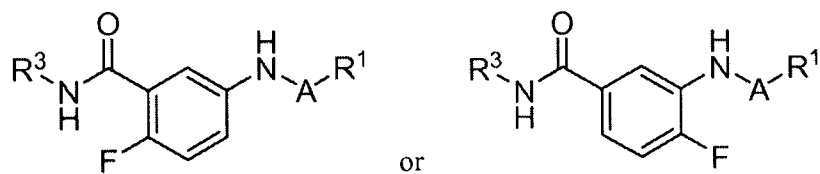


wherein t is 0 or 1.

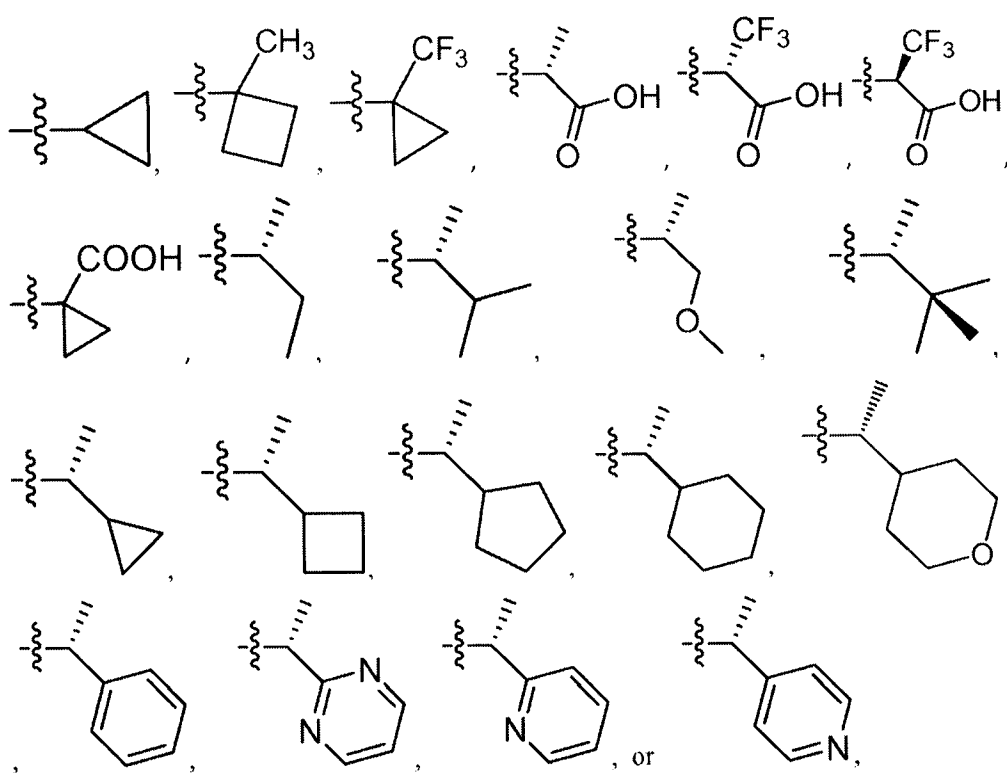
46. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of Formulae XXXXVII:



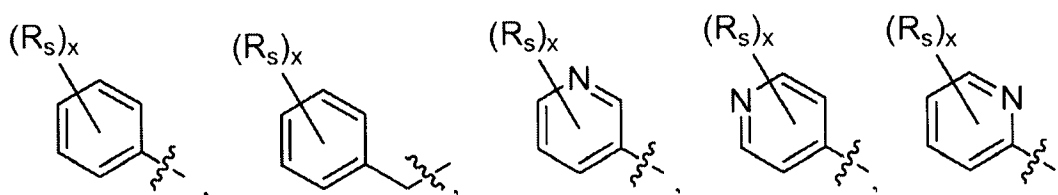
47. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 39, the compound comprising a structure of

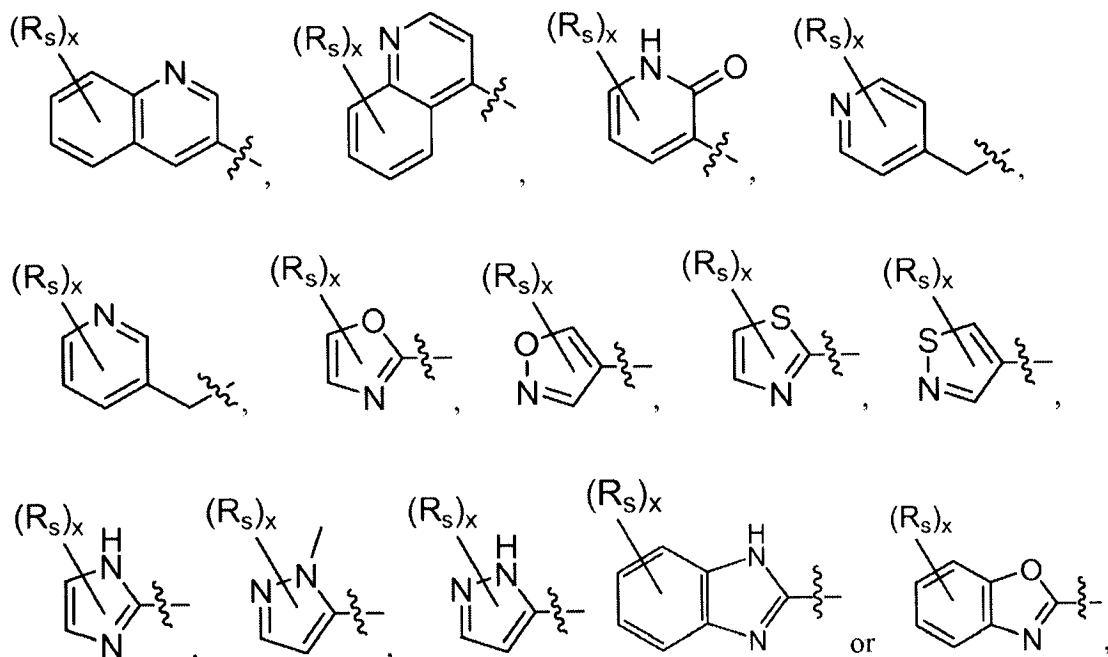


wherein R^1 is isopropyl, t-butyl,



R^3 is

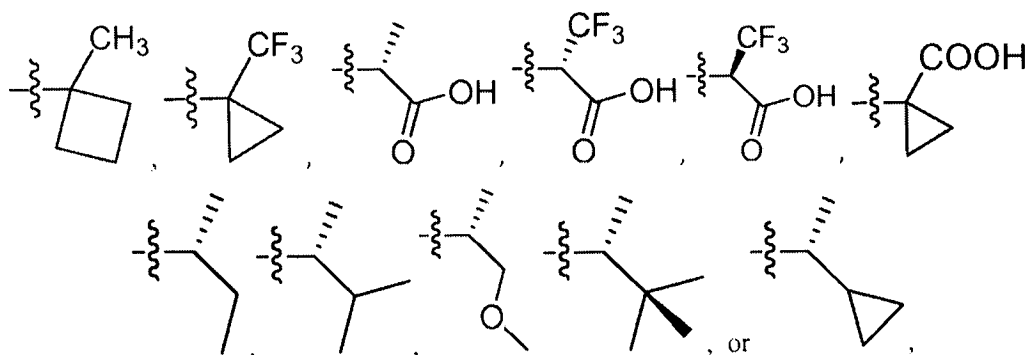




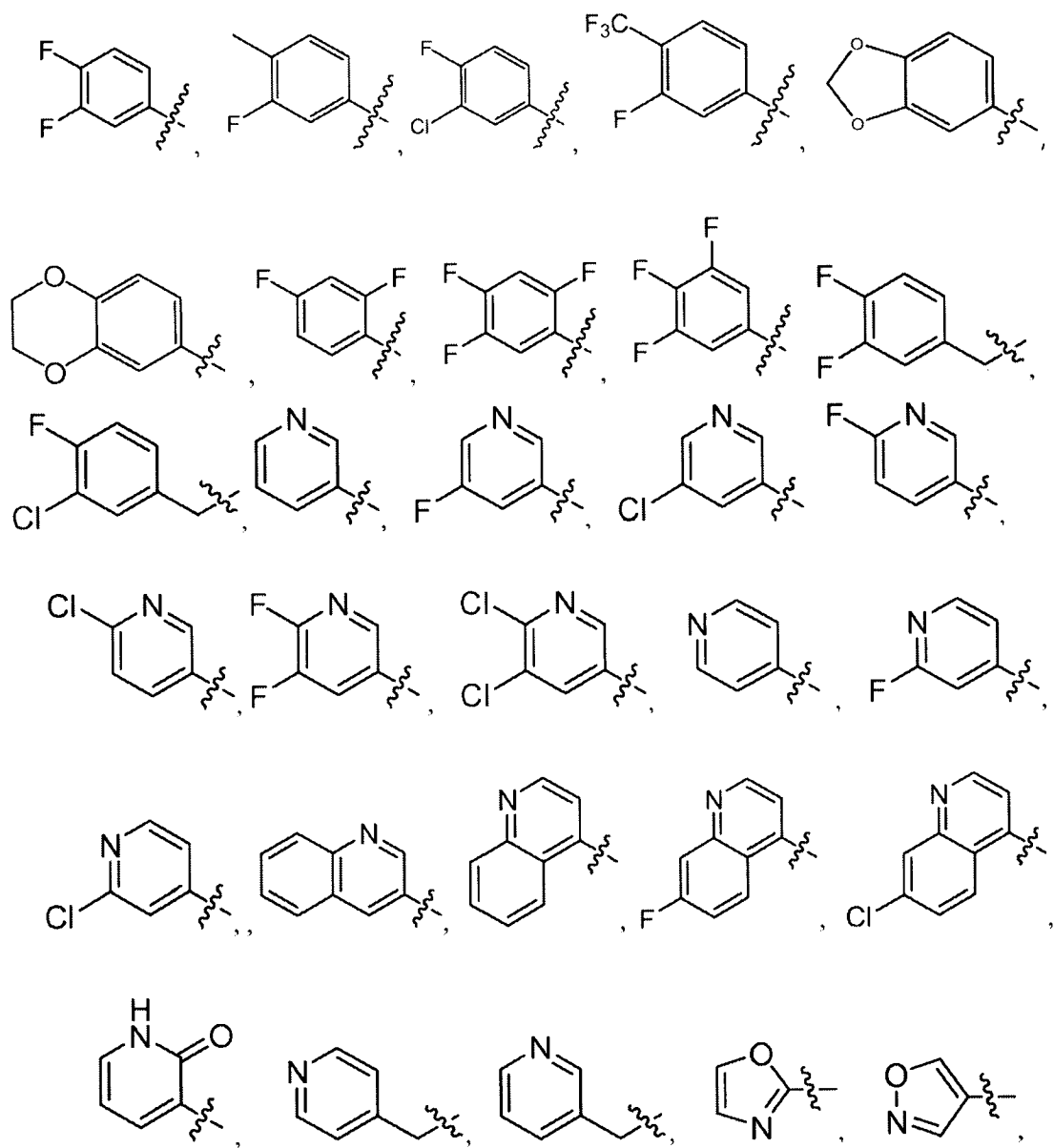
R₅ is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C₁₋₆ alkyl, -O-(C₁₋₆ alkyl), or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

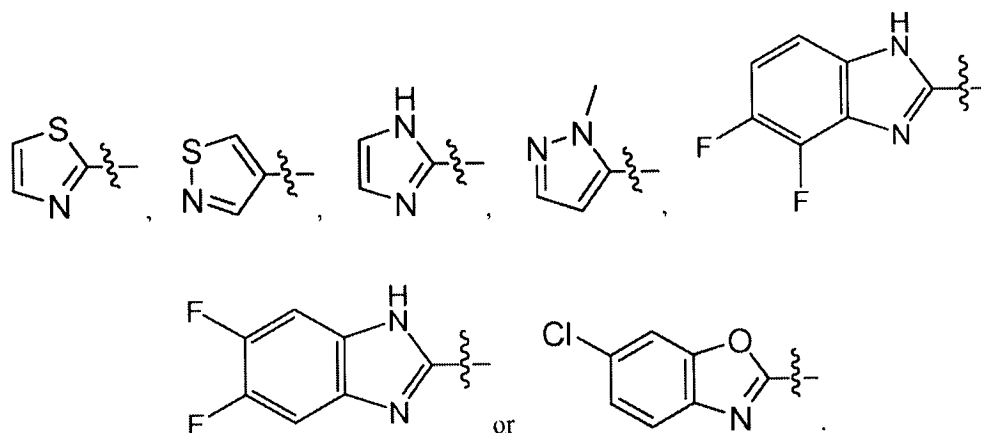
x is 0, 1, 2, or 3.

48. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 47, wherein R¹ is

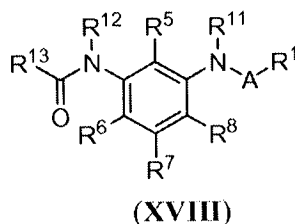


and R³ is





49. A compound comprising a structure of Formula (XVIII), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



(XVIII)

wherein:

A is selected from a group consisting of SO_2 and CO ;

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$; or

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl;

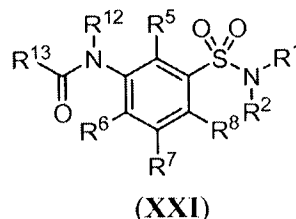
R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

50. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 49, wherein A is SO_2 .

51. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 49, wherein A is carbonyl, CO.

52. A compound comprising a structure of Formula (XXI), or an enantiomer, diastereomer or pharmaceutically accepted salt thereof:



wherein:

R^1 is selected from a group consisting of optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, and optionally substituted benzyl;

R^2 is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{3-7} cycloalkyl, and optionally substituted heterocyclic; or

R^1 and R^2 are taken together with the atoms to which they are bound to form an optionally substituted heterocycle with 3 to 10 atoms;

R^5 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^6 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^7 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$;

R^8 is selected from a group consisting of hydrogen, halogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{1-6} haloalkyl, OR^9 , cyano, and $N(R^9)_2$; or

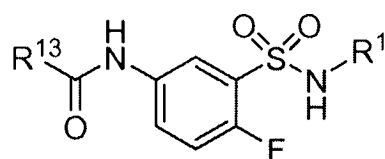
R^2 and R^8 are taken together with the atoms to which they are bound to form an optionally substituted ring with 5 to 6 atoms;

R^9 is independently at each occurrence selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted heterocyclyl, and optionally substituted heteroaryl.

R^{12} is selected from a group consisting of hydrogen, optionally substituted C_{1-6} linear alkyl, optionally substituted C_{1-6} branched alkyl, and optionally substituted C_{3-7} cycloalkyl; and

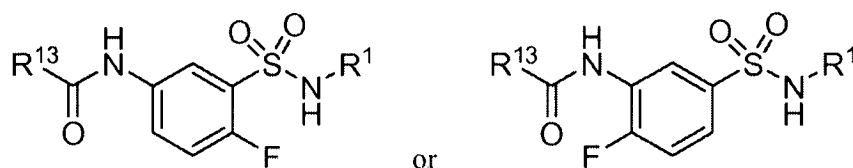
R^{13} is selected from a group consisting of optionally substituted aryl, optionally substituted benzyl, optionally substituted alkylaryl, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl.

53. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 52, the compound comprising a structure of Formulae XXXXVIII:

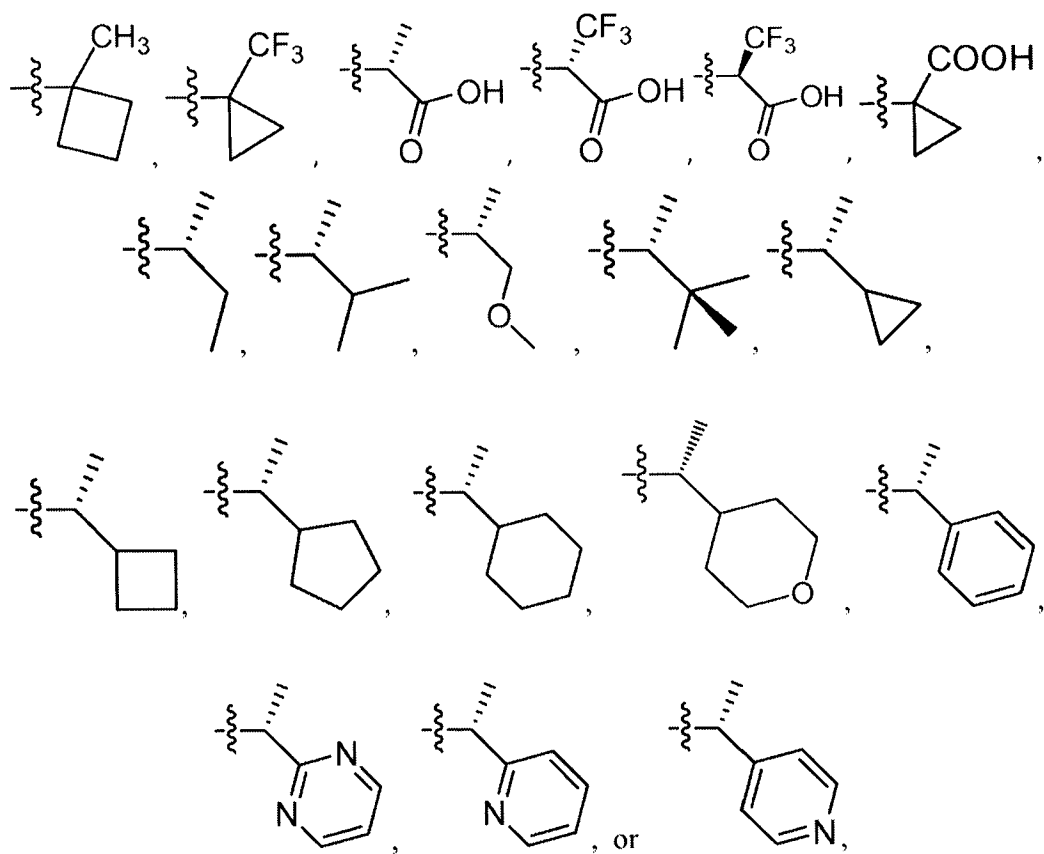


(XXXXVIII)

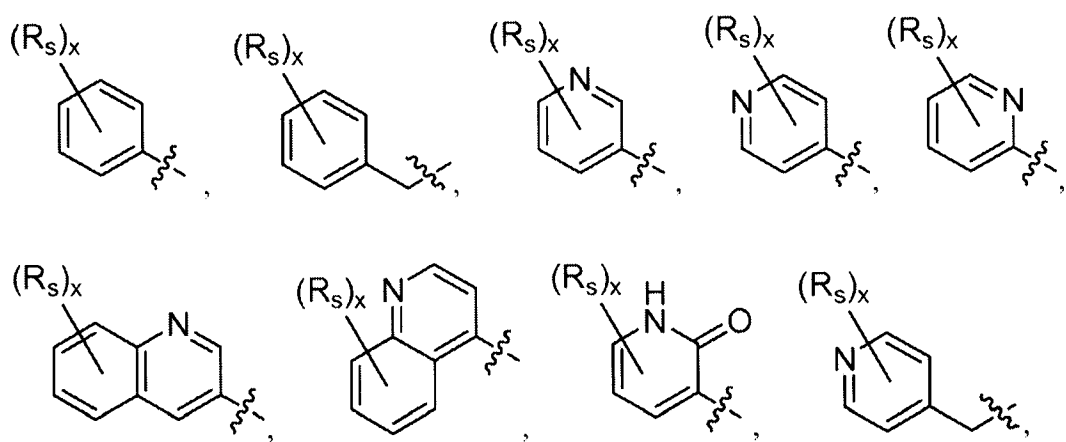
54. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 52, the compound comprising a structure of

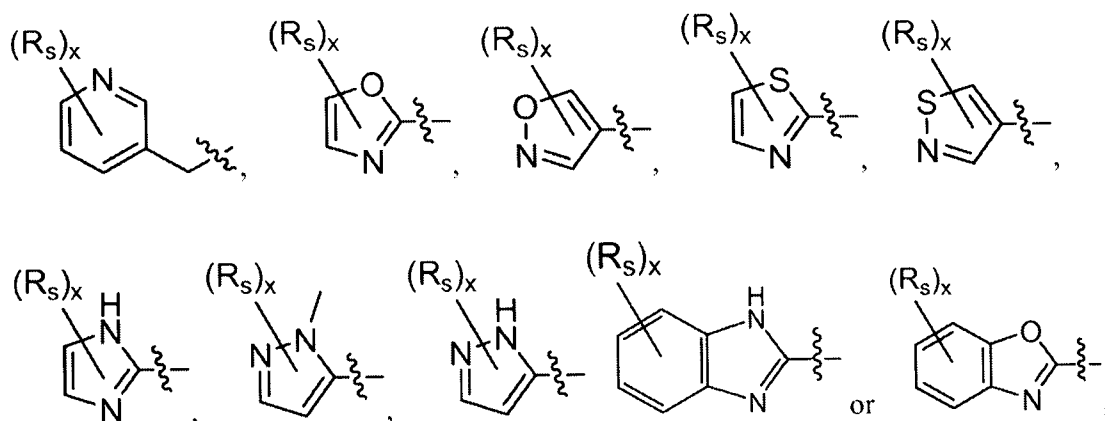


wherein R^1 is



R^{13} is

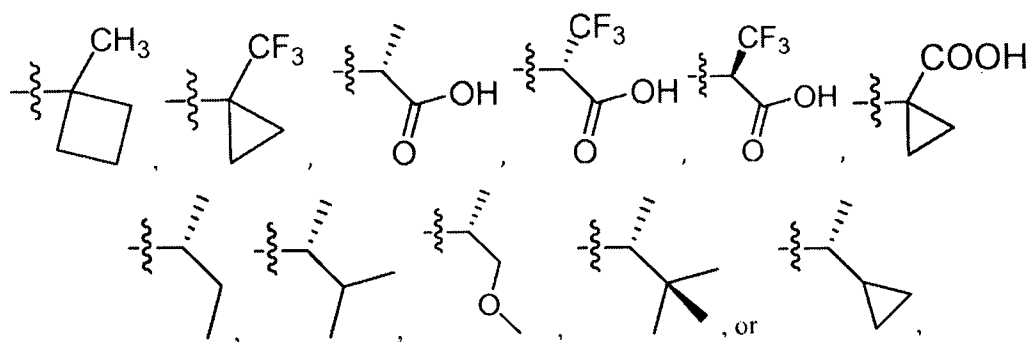




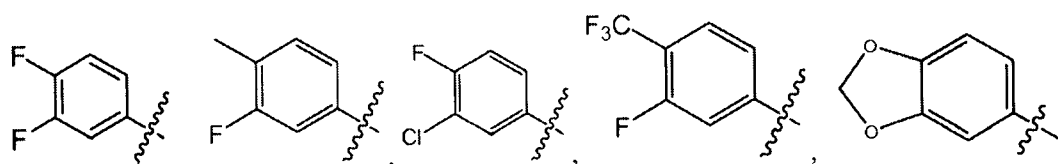
R_s is independently at each occurrence bromo, chloro, fluoro, cyano, hydroxyl, optionally fluorinated C_{1-6} alkyl, $-O-(C_{1-6} \text{ alkyl})$, or when two are taken form a fused cyclic or heterocyclic moiety; and x is 0, 1, 2, or 3.

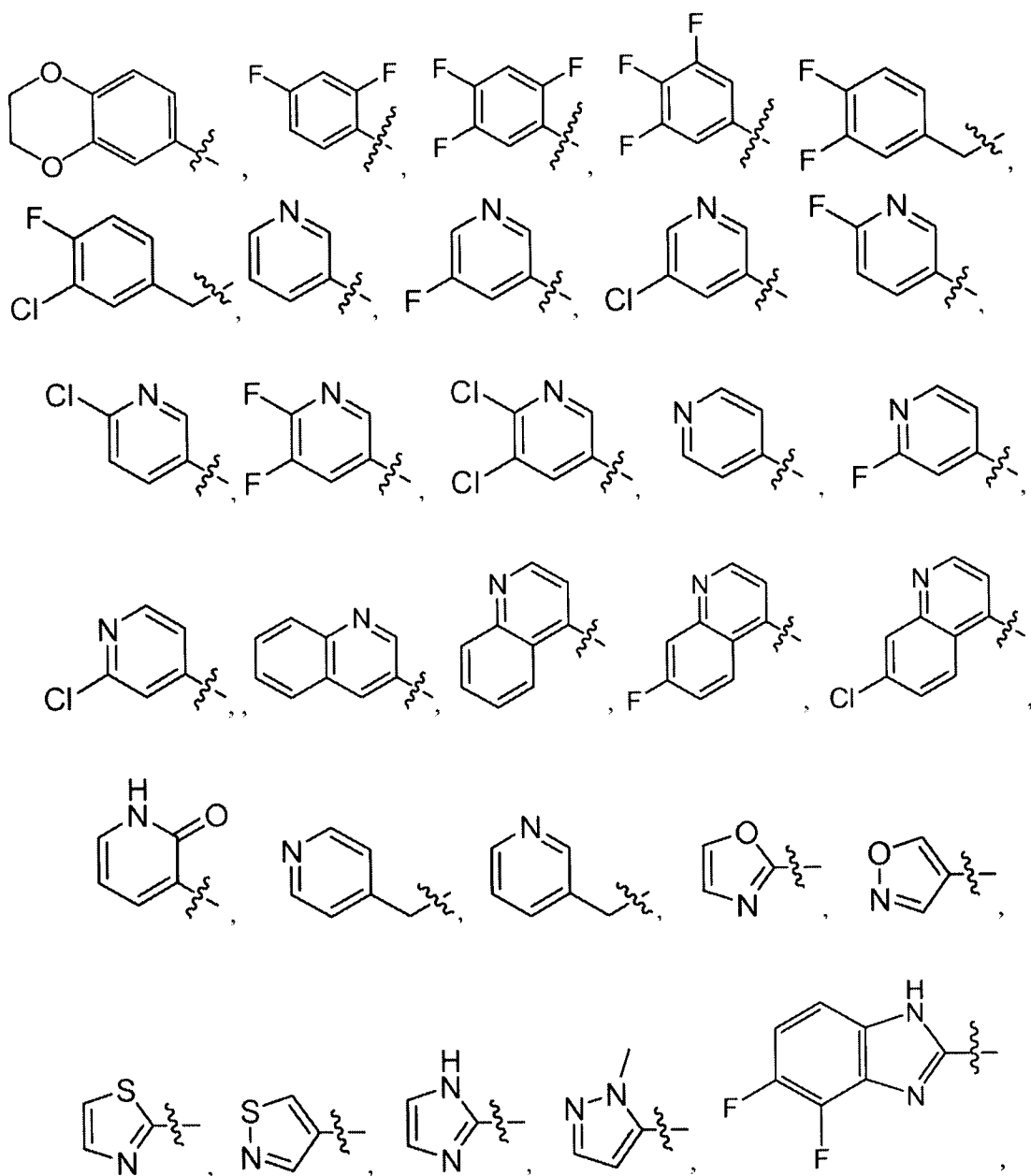
x is 0, 1, 2, or 3.

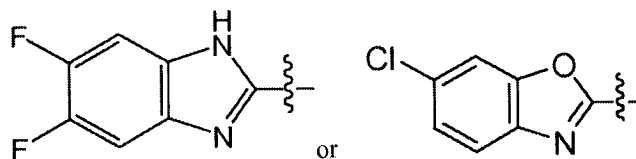
55. The compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 54, wherein R^1 is



and R^{13} is







56. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient
57. A method of treating a disease that involves pregenomic RNA encapsidation, said method comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1.
58. The method of claim 57, wherein the disease that involves pregenomic RNA encapsidation is a Hepatitis B virus infection.
59. A method of treating a Hepatitis B viral infection, said method comprising administering to a patient in need of such treatment an effective amount of at least one compound of claim 1.
60. The method of claim 59, wherein the treatment controls or ameliorates a condition associated with liver disease, including cirrhosis and hepatocellular carcinoma.
61. A method of repressing viral replication, morphogenesis, or both replication and morphogenesis comprising administering to a patient in need thereof a compound, enantiomer, diastereomer or pharmaceutically accepted salt of claim 1.



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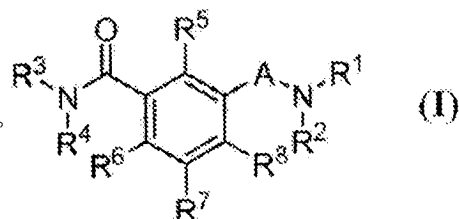
(54) 发明名称

针对 HBV 感染的新型抗病毒剂

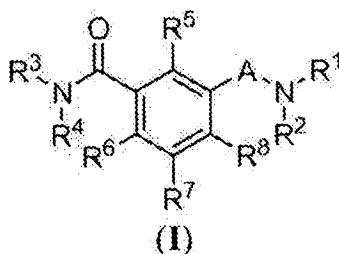
(57) 摘要

本发明涉及式 (I) 的新型化合物和使用所述化合物的新型方法, 所述化合物作用于处理病毒的核衣壳装配抑制剂, 尤其但不限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 前基因组 RNA 衣壳化抑制剂。(式 (I)) 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 A、R¹、R²、R³、R⁴、R⁵、R⁶、R⁷ 和 R⁸ 在本文

中定义。



1. 一种包含式 (I) 结构的化合物或其对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物：



包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

A 选自由 SO_2 和 CO 组成的组；

R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基、任选取代的 3-7 元环杂烷基、任选取代的 C_2 烯基、任选取代的 C_2 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-\text{C}_{1-6}$ 烷氧化物、 $-\text{SO}_2-\text{C}_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基组成的组；

R^2 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{3-7} 环烷基和任选取代的杂环组成的组；或

R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环；并且

R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基、任选取代的烷基杂芳基和任选取代的 C_{1-6} 直链烷基组成的组；

R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组；

R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $\text{N}(\text{R}^9)_2$ 组成的组；

R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $\text{N}(\text{R}^9)_2$ 组成的组；或

R^1 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；并且

R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、 OR^9 、氰基和 $\text{N}(\text{R}^9)_2$ 组成的组；

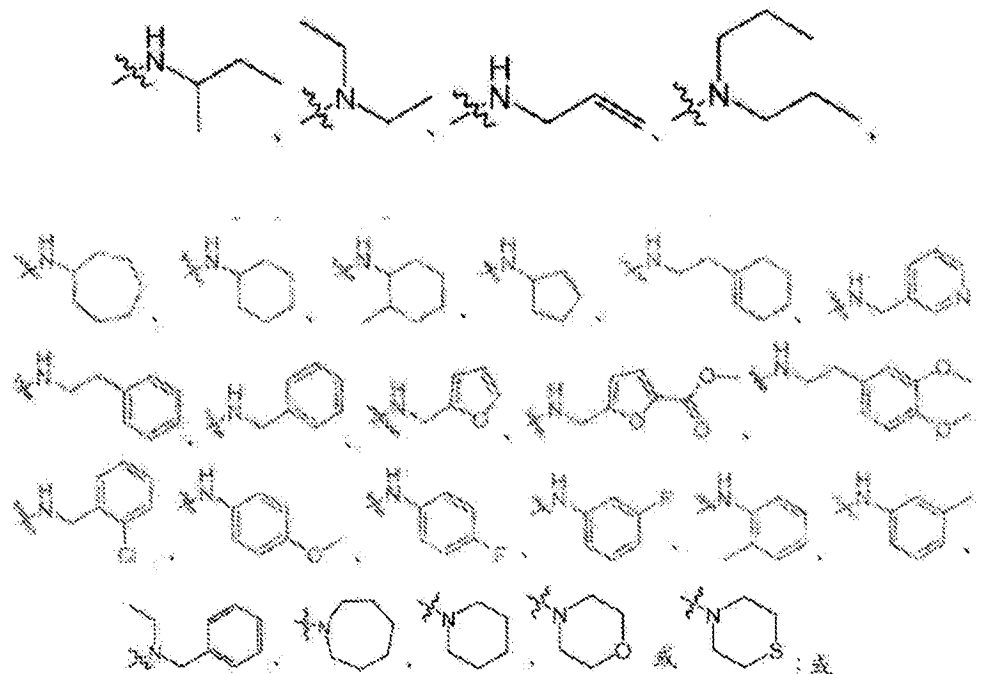
R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、 OR^9 、氰基和 $\text{N}(\text{R}^9)_2$ 组成的组；或

R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的碳环或杂环；并且

R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基、任选取代的苯甲基、任选取代的杂环基和任选取代的杂芳基组成的组；

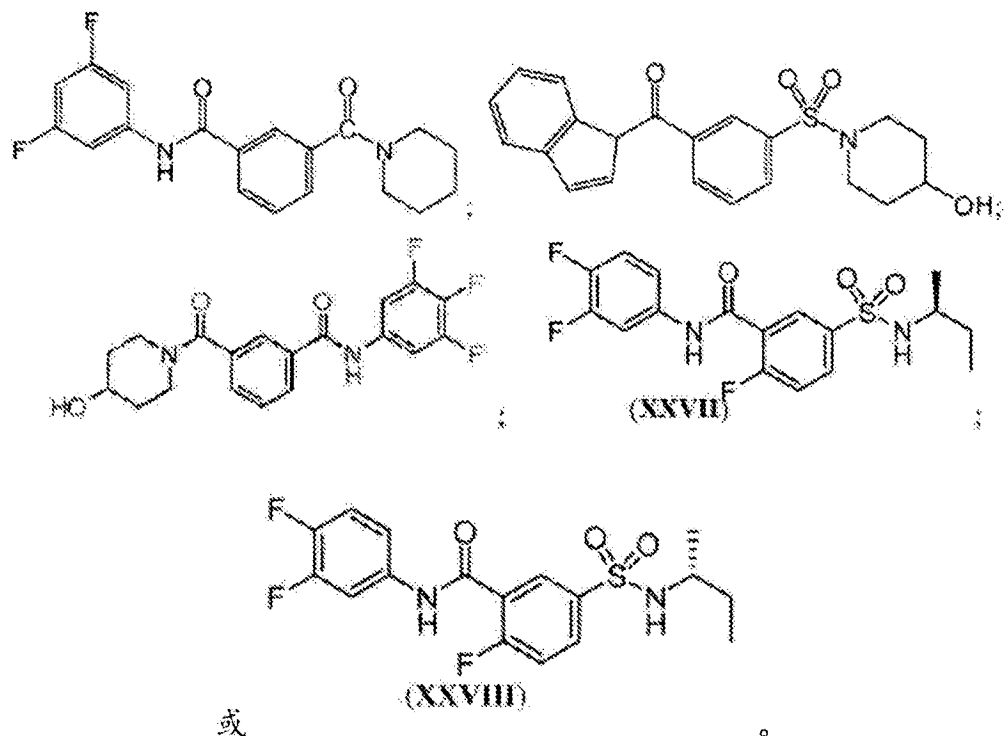
条件是当 A 是 SO_2 ； R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环；并且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环时，那么以下 (a) 至 (d) 都不适用：

(a) R^3 是任选取代的苯基，并且 R^1 或 R^2 单独地或当一起时含有羟基；或



(d) R^3 或 R^4 是未被取代或被单取代的芳基、或未被取代或被单取代的芳烷基、或未被取代或被单取代的杂芳基,并且 R^1 和 R^2 连同它们所结合的原子一起形成具有6至12个原子的任选取代的杂环结构;或

条件是所述化合物不是3-[[(二环丙基甲基) 氨基] 磺酰基]-N-(4-异丙氧基苯基) 苯甲酰胺;或3-[[(2-(1H-苯并咪唑-2-基) 丙基) 氨基] 磺酰基]-N-(4-异丙氧基苯基) 苯甲酰胺;或3-[(环己基氨基) 磺酰基]-N-(4-异丙基苯基) 苯甲酰胺;或3-(苯胺基磺酰基)-N-(4-异丙基苯基) 苯甲酰胺;或5-[[(3-[(4-甲氧基苯基) 氨基] 羰基) 苯基) 磺酰基] 氨基] 戊酸;或3-[(叔丁基氨基) 磺酰基]-N-(4-甲氧基苯基) 苯甲酰胺;或(3S)-1-[(3-[(5-异丙氧基吡啶-2-基) 氨基] 羰基) 苯基) 磺酰基] 哌啶-3-甲酰胺;或(3R)-1-[(3-[(5-异丙氧基吡啶-2-基) 氨基] 羰基) 苯基) 磺酰基] 哌啶-3-甲酰胺;或3-(哌啶-1-基磺酰基)-N-[(1S)-1,2,3,4-四氢萘-1-基] 苯甲酰胺;或N-(5-溴-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺;或N-(3-甲氧基-5-苯基吡啶-2-基)-3-(吡咯烷-1-基磺酰基) 苯甲酰胺;或N-(3-甲氧基-5-苯氧基吡啶-2-基)-3-(吡咯烷-1-基磺酰基) 苯甲酰胺;或N-[3-甲氧基-5-(苯硫基) 吡啶-2-基]-3-(吡咯烷-1-基磺酰基) 苯甲酰胺;或N-(5-乙基-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺;或N-(3-甲氧基-5-乙烯基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺;或

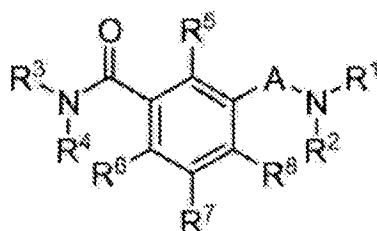


2. 所述式 (I) 化合物, 其中:

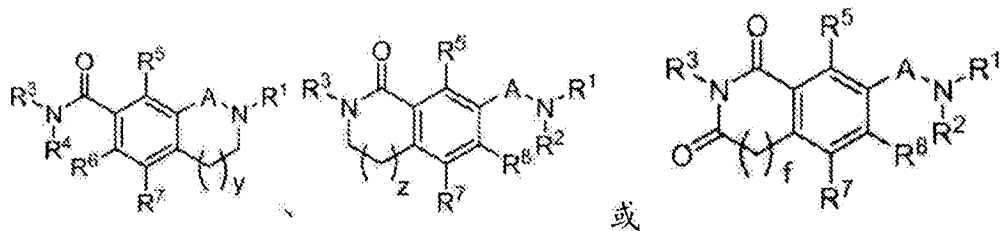
R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环; 并且

R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环;

由此提供具有下式的化合物:



3. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含以下结构之一:



其中, 视情况:

R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环; 并且

R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环; 并且

其中 z 和 f 独立地是 0 或 1, 并且 y 独立地是 0、1 或 2。

4. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物

或溶剂合物,其中 A 是 SO_2 。

5. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中 A 是 CO。

6. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

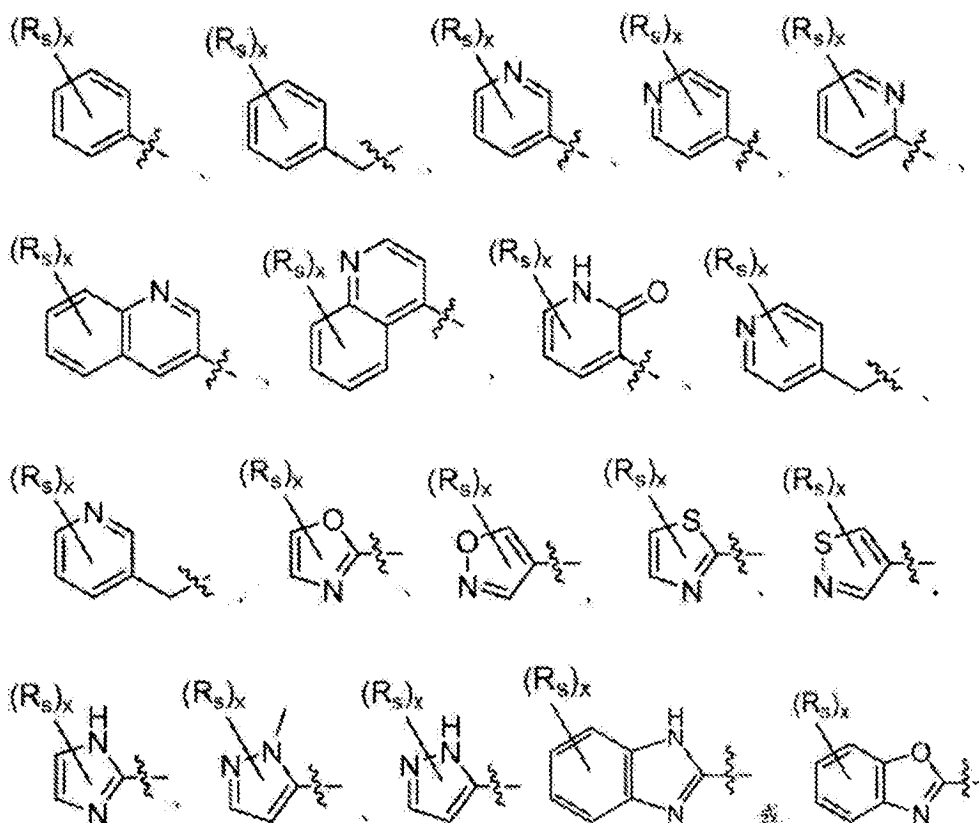
R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组;并且

当存在时, R^1 是氢。

7. 如权利要求 6 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

R^3 选自由任选取代的苯基、任选取代的苯甲基、任选取代的苯并异噁唑基、任选取代的苯并噁唑基、任选取代的呋喃基、任选取代的咪唑基、任选取代的吡咯基、任选取代的异噁唑基、任选取代的异噻唑基、任选取代的噁唑基、任选取代的吡唑基、任选取代的吡啶-2-酮-基、任选取代的吡啶基、任选取代的吡咯基、任选取代的喹啉基、任选取代的噻唑基任选取代的噻吩基和任选取代的甲基吡啶基组成的组。

8. 如权利要求 7 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中 R^3 是



其中

R_5 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化的 C_{1-6} 烷基、 $-\text{O}-$ (C_{1-6} 烷基), 或当两个 R_5 一起形成稠环部分或杂环部分时;并且 x 是 0、1、2 或 3,

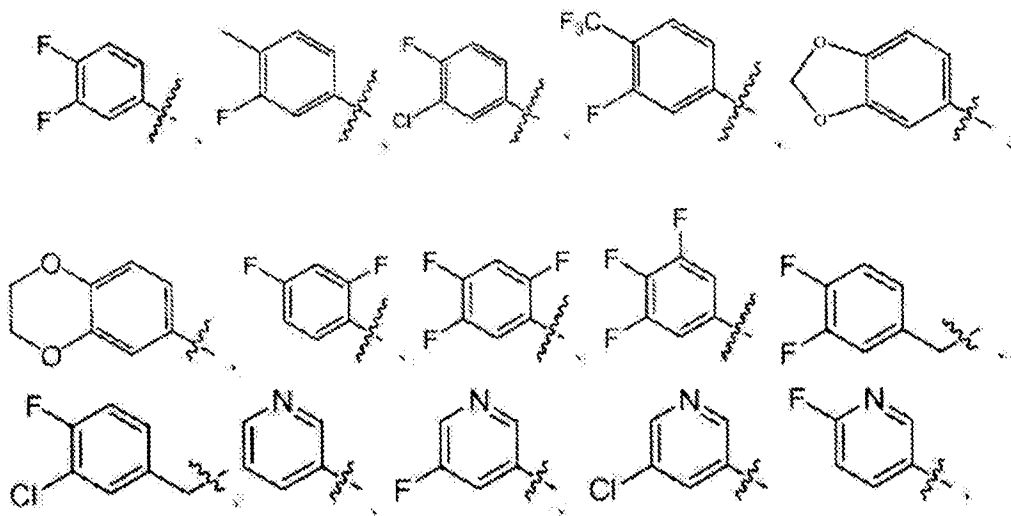
x 是 0、1、2 或 3；并且

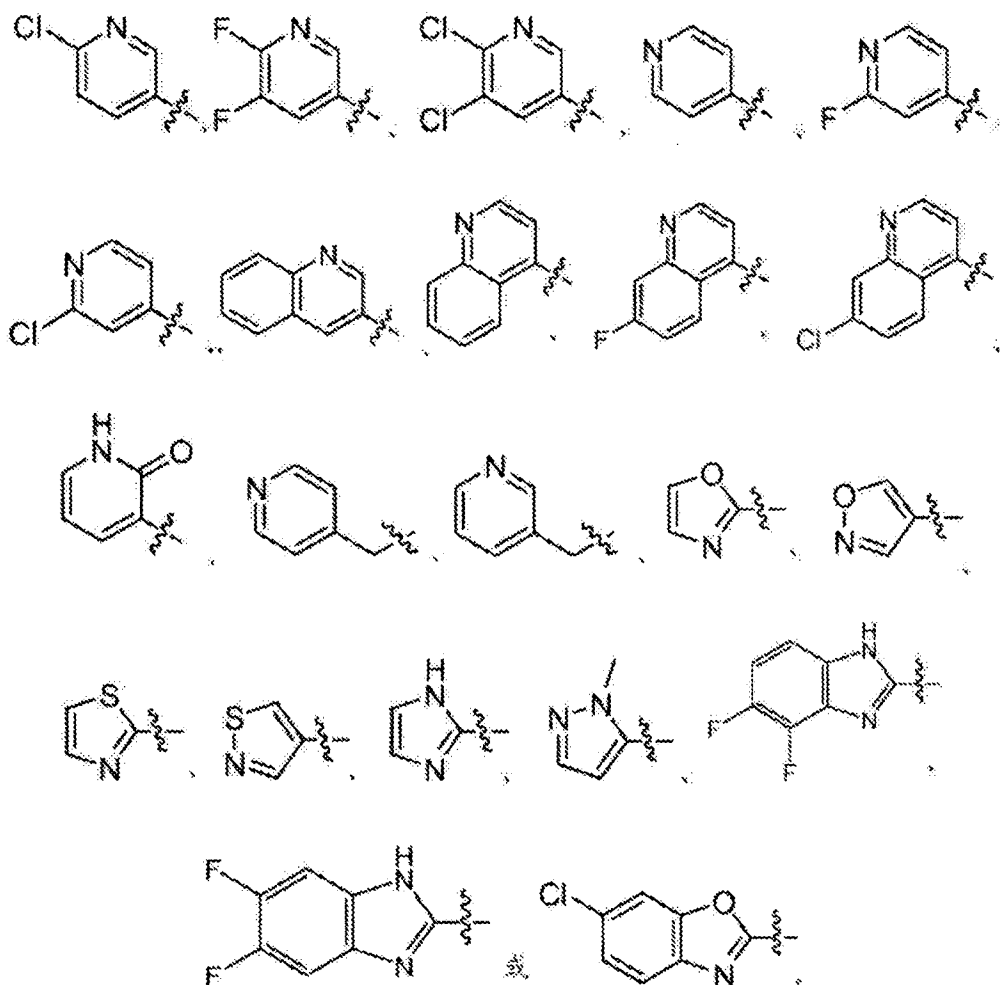
当存在时， R^4 是氢。

9. 如权利要求 7 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其中 R^3 的任选取代包括至少一个卤代或 C_{1-6} 烷基。

10. 如权利要求 9 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其中 R^3 的所述任选取代包括至少一个卤代。

11. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 R^3 是



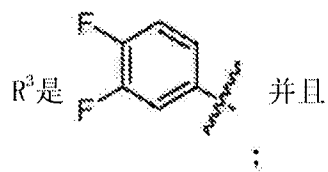


12. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

R^5 和 R^7 在每次出现时都各自独立地是 H 或 F; 并且

R^6 和 R^8 在每次出现时都各自独立地是氢、氯代、氟代或 C_{1-3} 烷基或 C_{1-3} 烷氧基。

13. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中



当存在时, R^1 是氢。

14. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

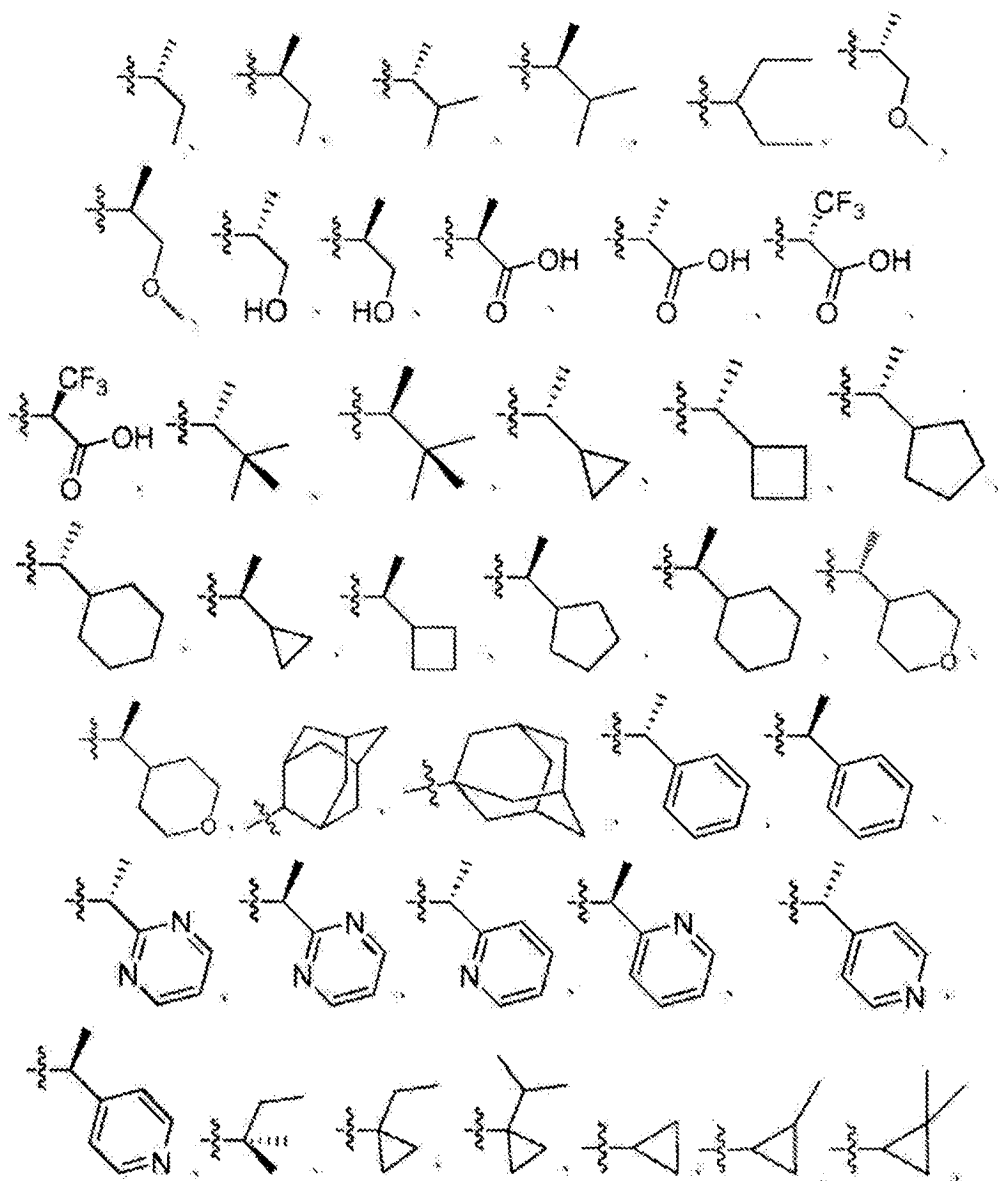
R^5 、 R^7 和 R^8 各自是 H; 并且

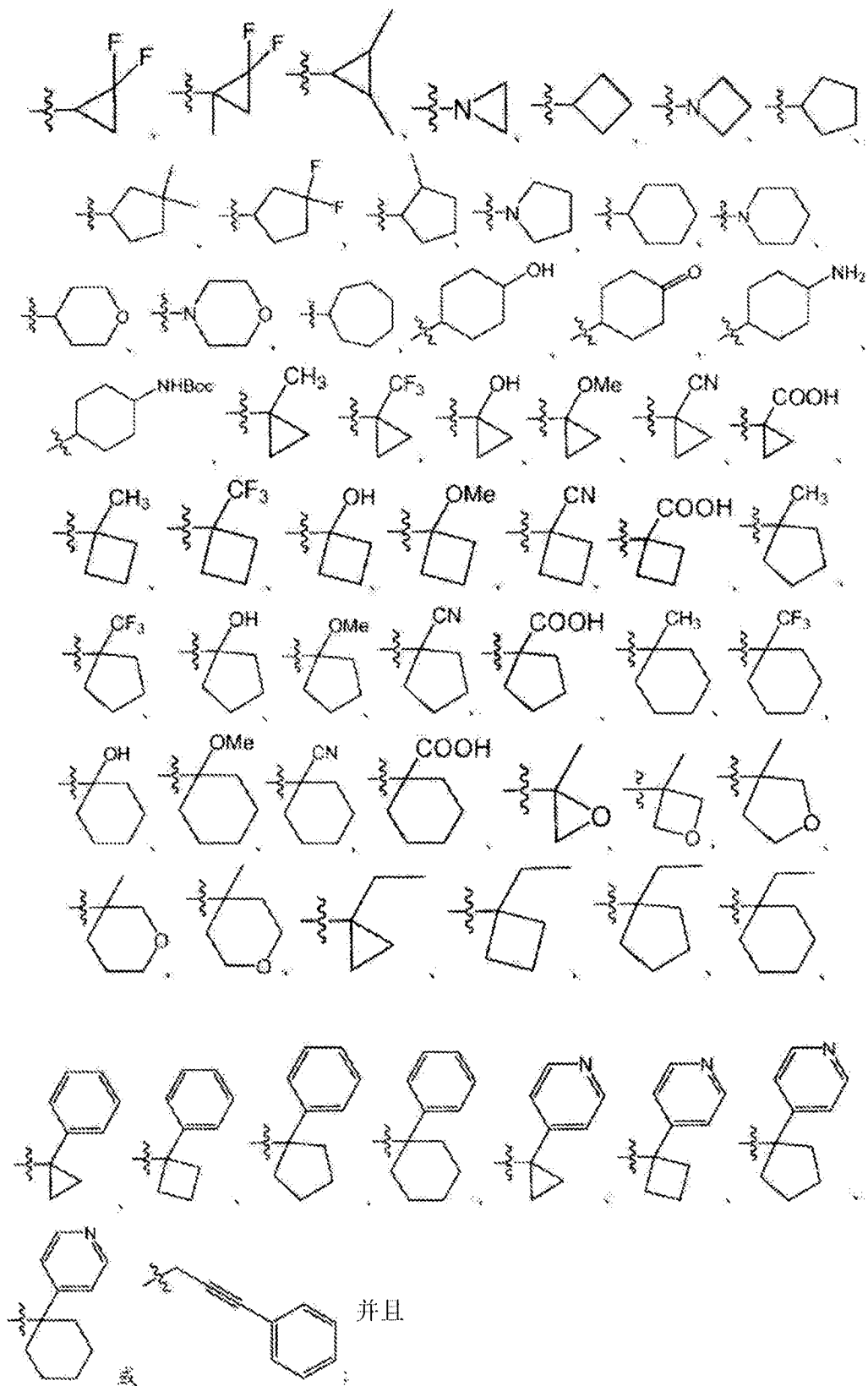
R^6 是氢、氯代、氟代或甲氧基。

15. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中,

R^1 是甲基、甲氧基、乙基、乙氧基、正丙基、正丙氧基、异丙基、异丙氧基、正丁基、正丁氧

基、仲丁基、仲丁氧基、叔丁基、叔丁氧基、任选取代的苯基、任选取代的苯甲基、任选取代的苯并异噁唑基、任选取代的苯并噁唑基、任选取代的呋喃基、任选取代的咪唑基、任选取代的吡咯基、任选取代的异噁唑基、任选取代的异噻唑基、任选取代的噁唑基、任选取代的吡唑基、任选取代的吡啶-2-酮-基、任选取代的吡啶基、任选取代的吡咯基、任选取代的喹啉基、任选取代的噻唑基任选取代的噻吩基和任选取代的甲基吡啶基、

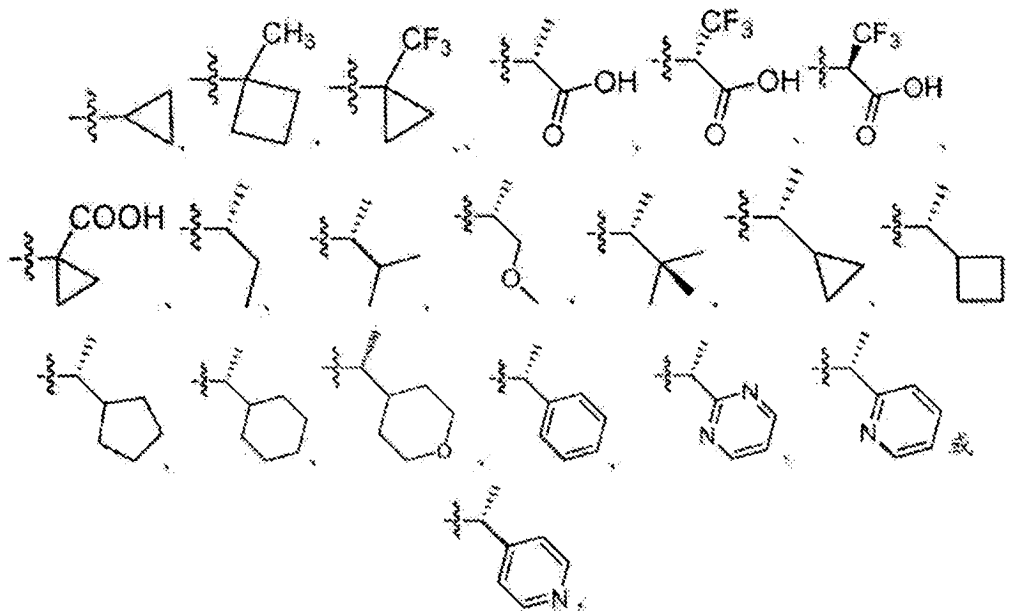




当存在时, R^2 是 H。

16. 如权利要求 15 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、盐或

水合物, 其中 R^1 是异丙基、叔丁基、

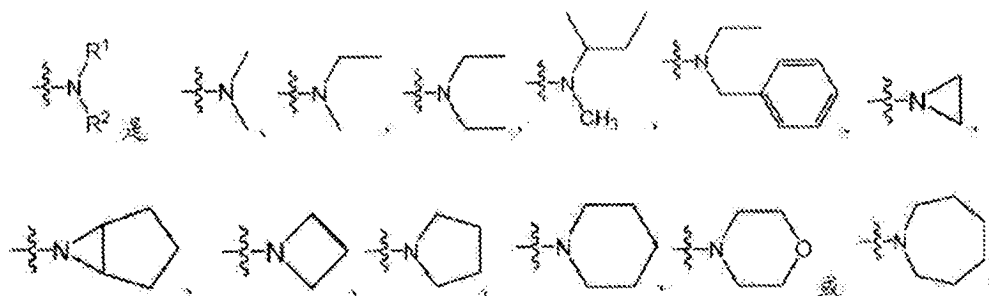


并且, 当存在时, R^2 是 H。

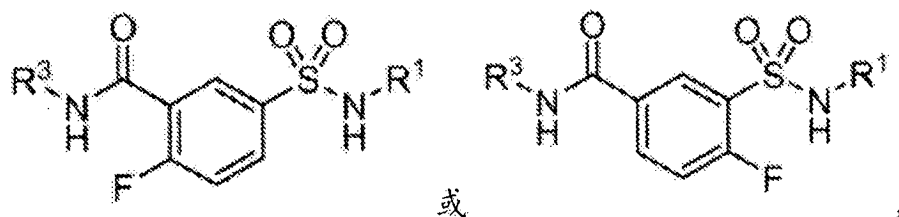
17. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 条件是所述 $-N(R^1)(R^2)$ 部分不含有羟基。

18. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 条件是 R^1 不是环戊基。

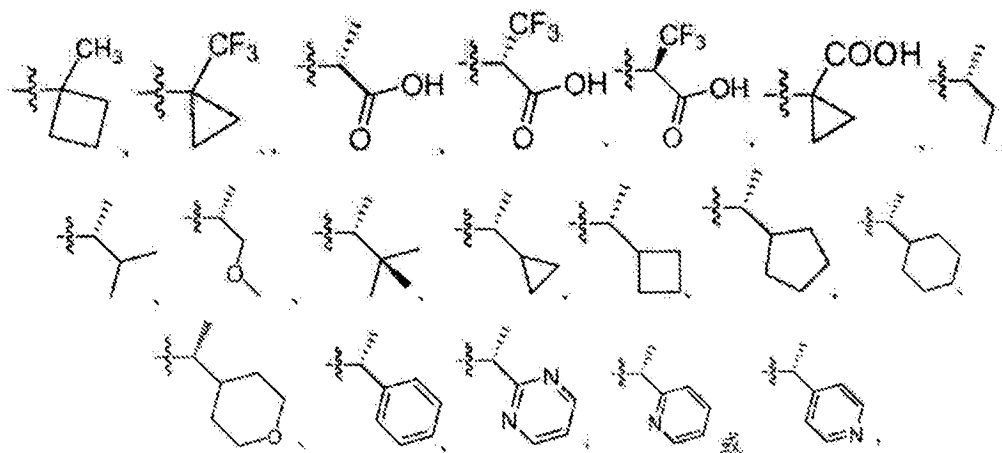
19. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中



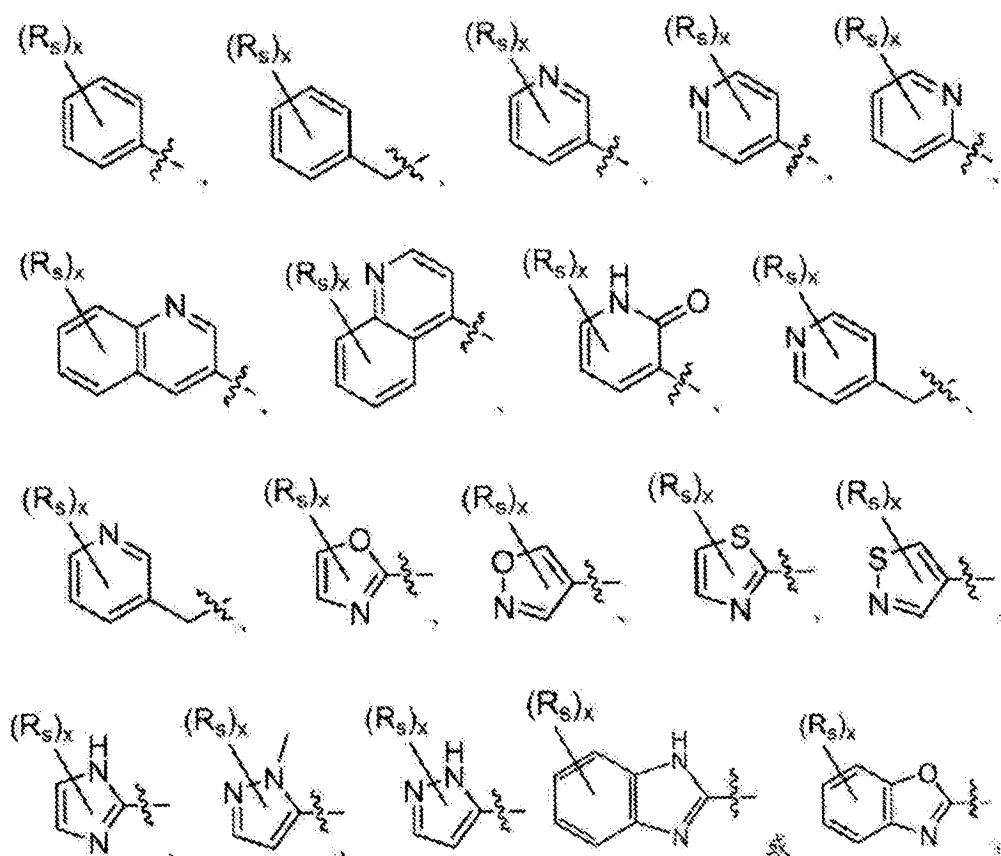
20. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其包含结构



其中 R^1 是



并且 R^3 是

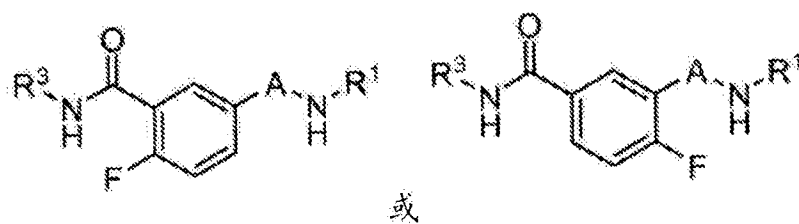


其中

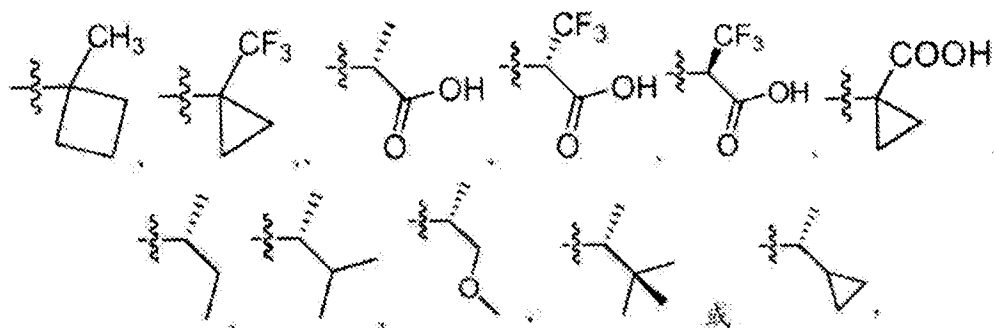
R_5 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化的 C_{1-6} 烷基、 $-O-(C_{1-6}$ 烷基)，或当两个 R_5 一起形成稠环部分或杂环部分；并且 x 是 0、1、2 或 3。

x 是 0、1、2 或 3。

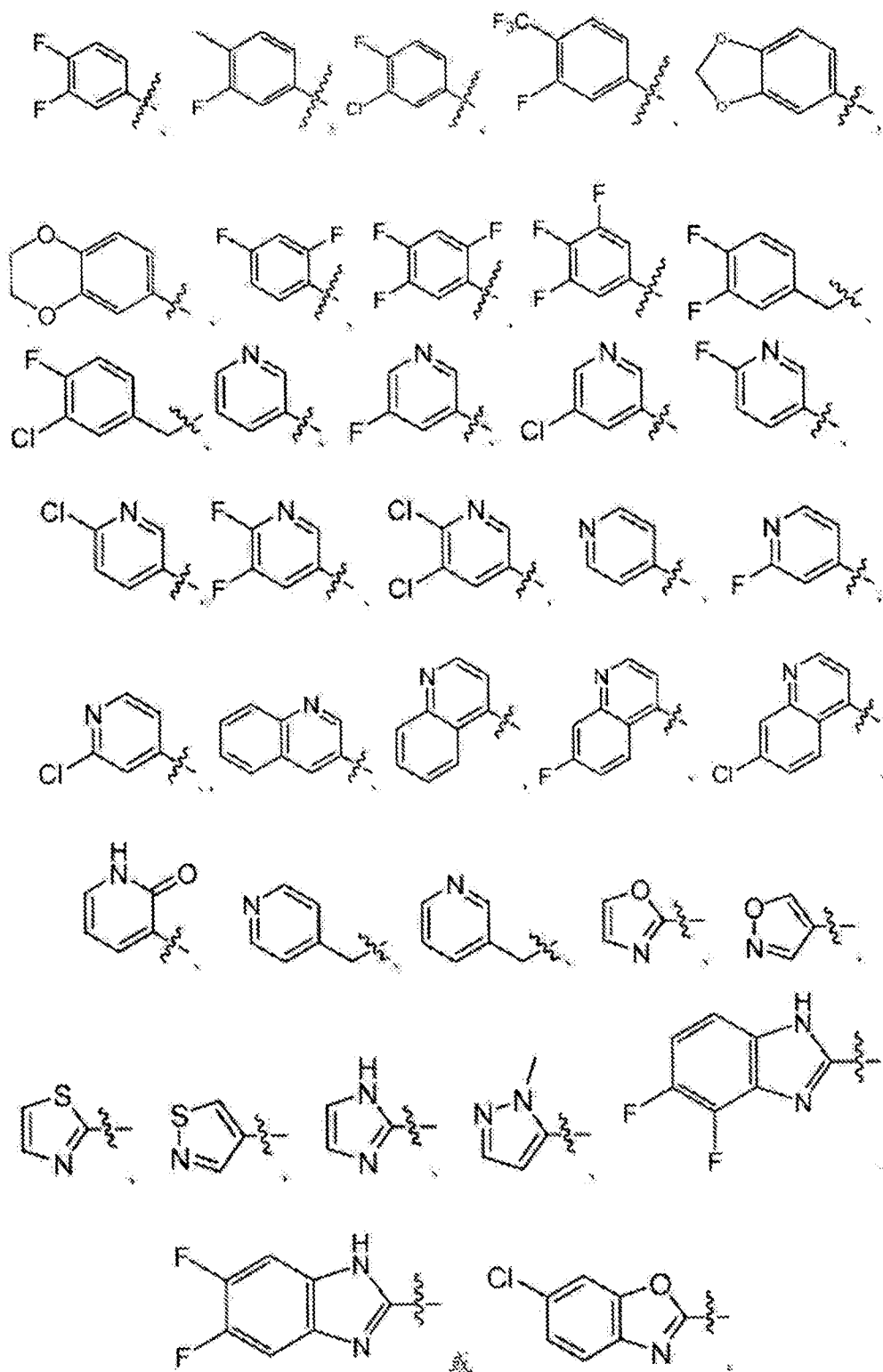
21. 如权利要求 20 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其包含结构



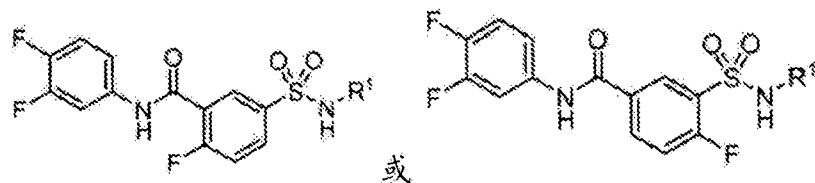
其中 R^1 是



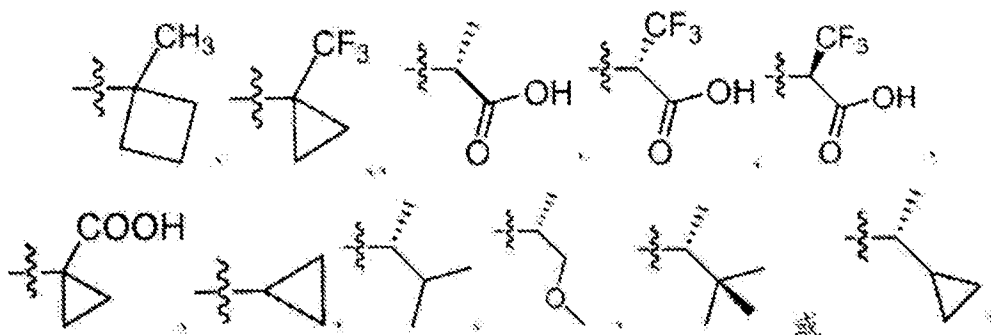
并且 R^3 是



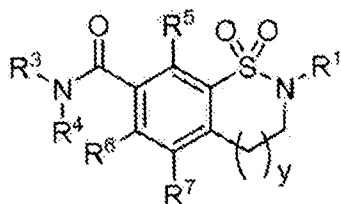
22. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其包含结构



其中 R¹ 是异丙基、叔丁基、



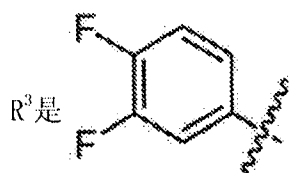
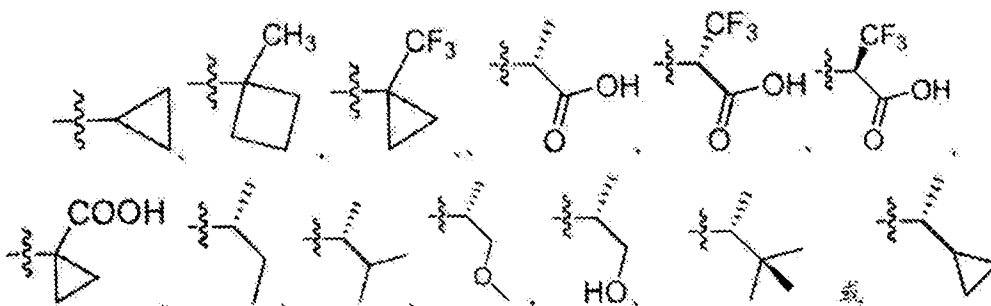
23. 如权利要求 3 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,所述化合物包含结构:



其中 y 是 0、1 或 2。

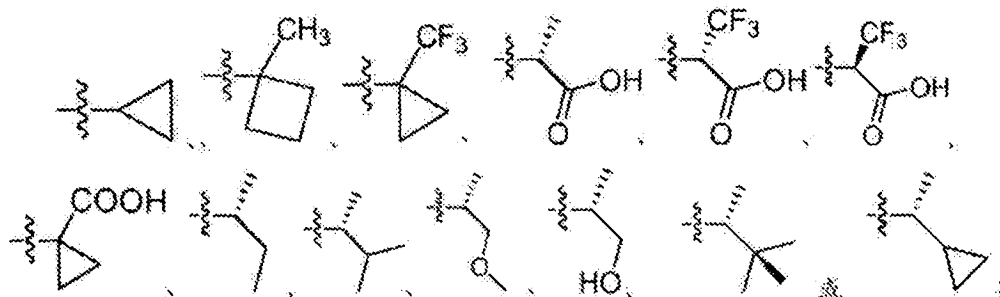
24. 如权利要求 23 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

R¹ 是异丙基、叔丁基、

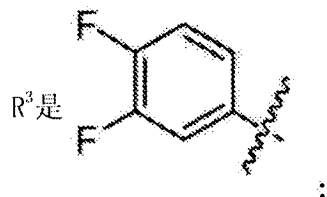


R⁴、R⁵和 R⁷是 H;并且

R⁶是 H 或 F。



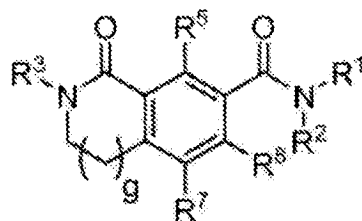
R^2 是 H；



R^5 和 R^7 是 H；并且

R^8 是 H 或 F。

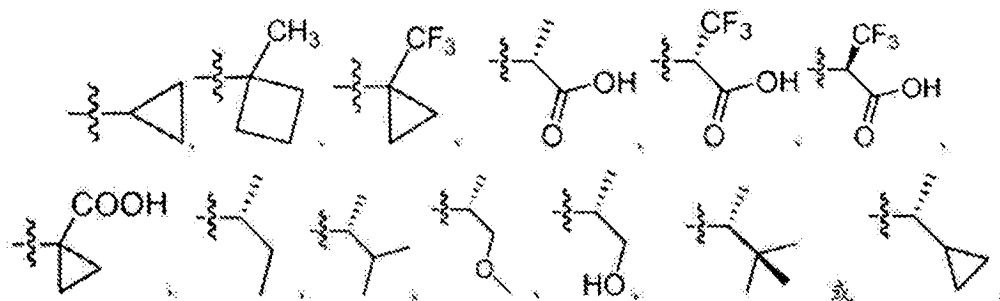
29. 如权利要求 3 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，所述化合物包含结构：



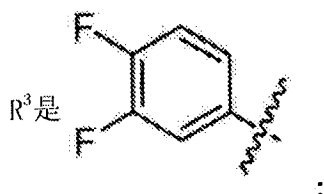
其中 g 是 0 或 1。

30. 如权利要求 29 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其中

R^1 是异丙基、叔丁基、



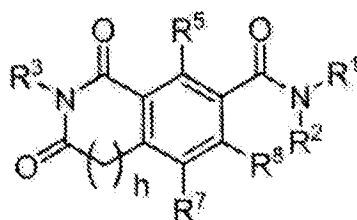
R^2 是 H；



R^5 和 R^7 是 H; 并且

R^8 是 H 或 F。

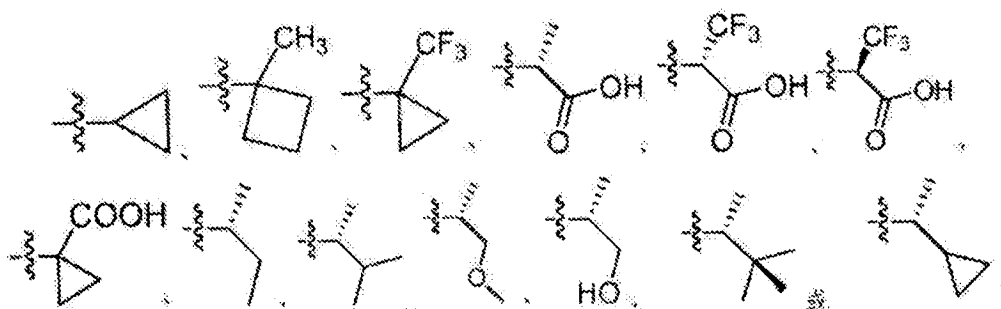
31. 如权利要求 3 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含结构:



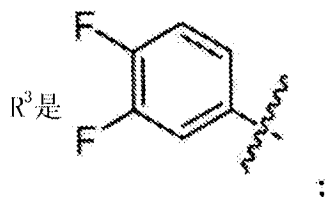
其中 h 是 0 或 1。

32. 如权利要求 31 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

R^1 是异丙基、叔丁基、



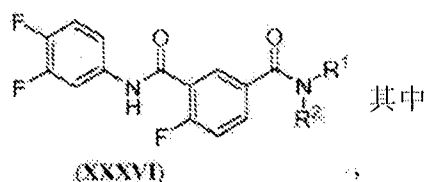
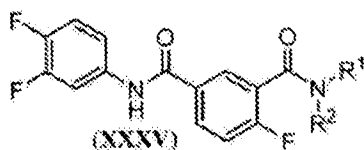
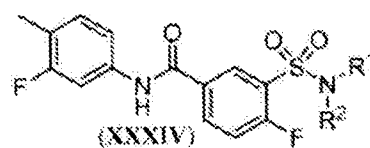
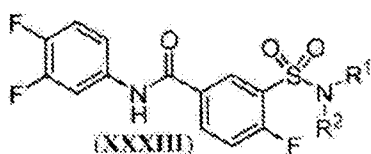
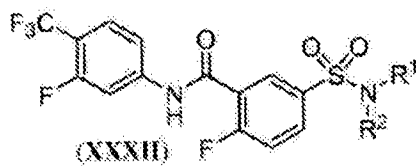
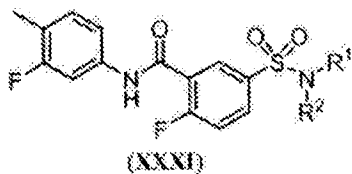
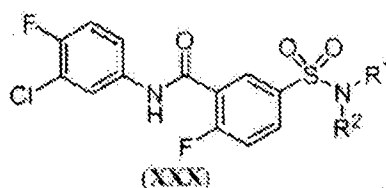
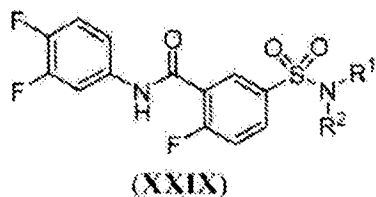
R^2 是 H;



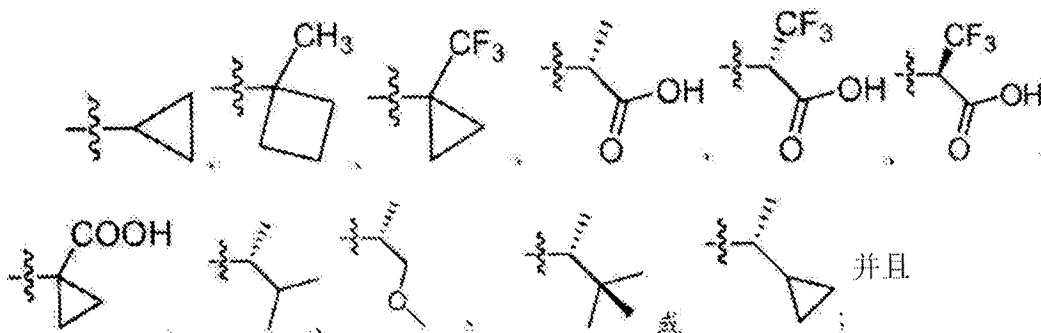
R^5 和 R^7 是 H; 并且

R^8 是 H 或 F。

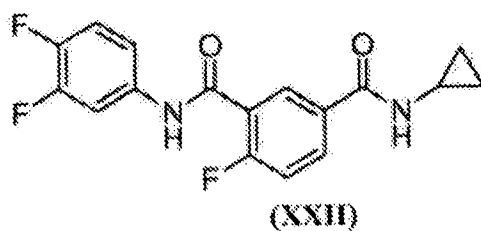
33. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含以下任一结构:



其中

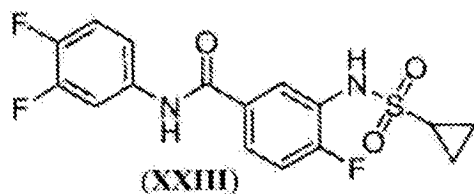
R¹是异丙基、叔丁基、R²是 H。

34. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含具有式 (XXII) 的结构:

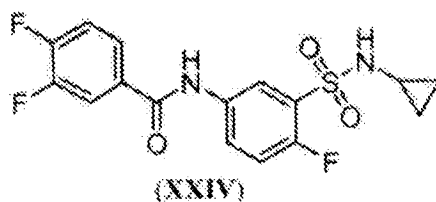


35. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述

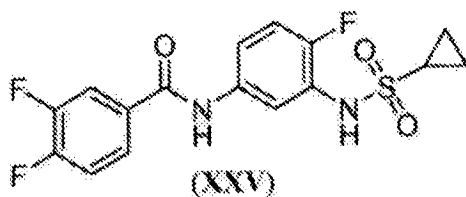
化合物包含具有式 (XXIII) 的结构：



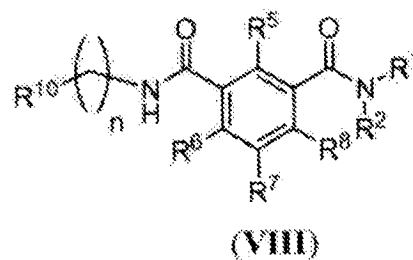
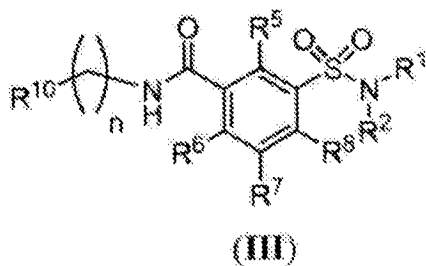
36. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含具有式 (XXIV) 的结构：



37. 如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含具有式 (XXV) 的结构：



38. 一种包含具有式 (III) 或式 (VIII) 的结构的化合物或其对映异构体、非对映异构体或药学上接受的盐：



其中：

R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组；

R^2 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{3-7} 环烷基和任选取代的杂环组成的组；或

R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环；并且

R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^7 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^8 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；或

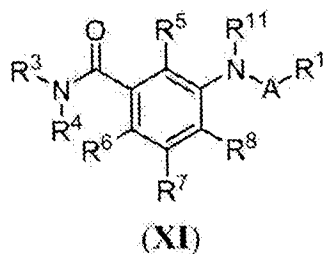
R^2 和 R^8 连同它们所结合的原子一起形成具有5至6个原子的任选取代的环；并且

R^9 在每次出现时都独立地选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基、任选取代的苯甲基、任选取代的杂环基和任选取代的杂芳基组成的组；

R^{10} 选自自由任选取代的芳基和任选取代的杂芳基组成的组；并且

n 是0或1。

39. 一种包含具有式(XI)的结构的化合物或其对映异构体、非对映异构体或药学上接受的盐：



其中：

R^1 选自自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组；

R^3 选自自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基、任选取代的烷基杂芳基；和任选取代的 C_{1-6} 直链烷基组成的组；

R^4 选自自由氢和任选取代的 C_{1-6} 直链烷基组成的组；

R^5 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^6 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；或

R^4 和 R^6 连同它们所结合的原子一起形成具有5至6个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；

R^7 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

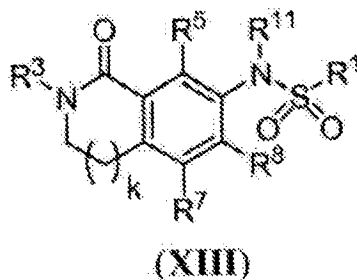
R^8 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^9 在每次出现时都独立地选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基、任选取代的苯甲基、任选取代的杂环基和任选取代的杂芳基组成的组；并且

R^{11} 选自自由以氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组。

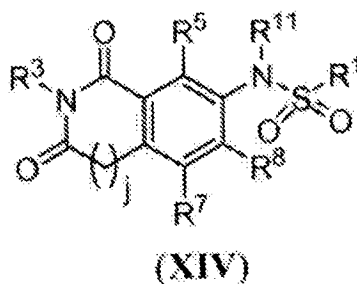
40. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中 A 是 SO_2 。

41. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含具有式 (XIII) 的结构:



其中 k 是 0 或 1。

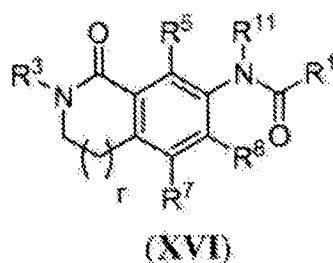
42. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 (XIV) 的结构,



其中 j 是 0 或 1。

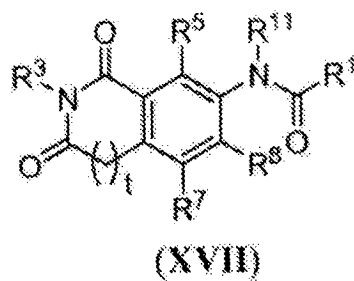
43. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中 A 是羰基、CO。

44. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 (XVI) 的结构:



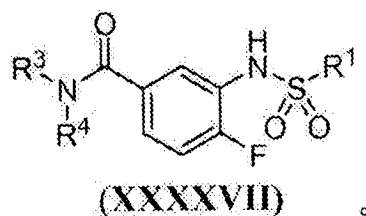
其中 r 是 0 或 1。

45. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 (XVII) 的结构,

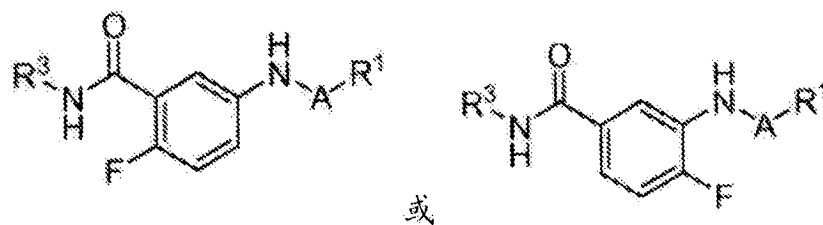


其中 t 是 0 或 1。

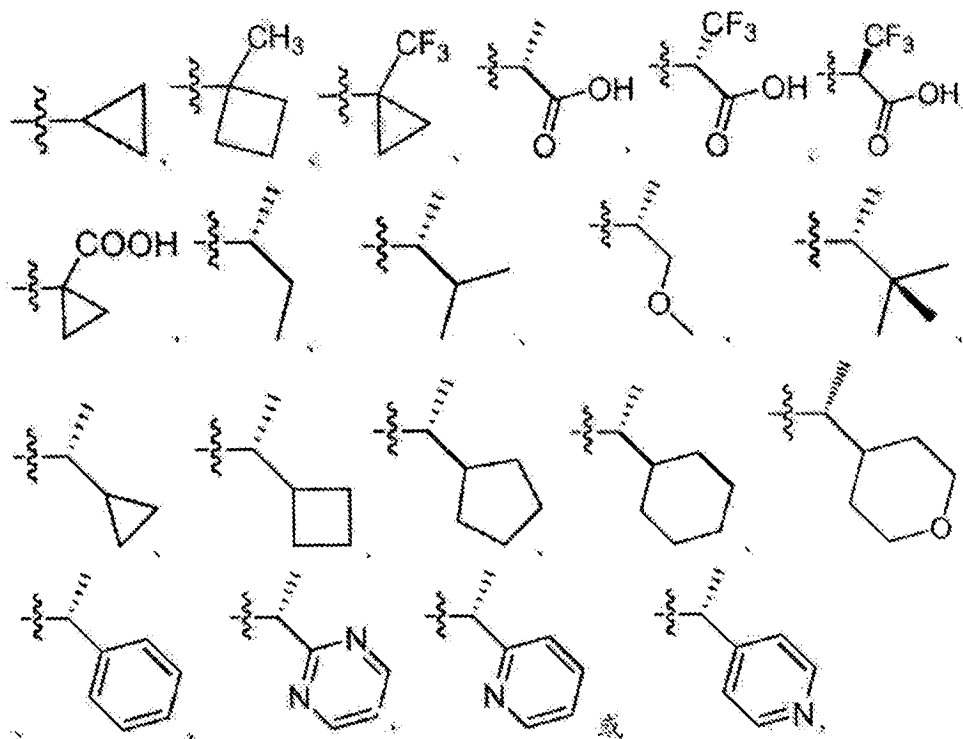
46. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含式 XXXVII 的结构:



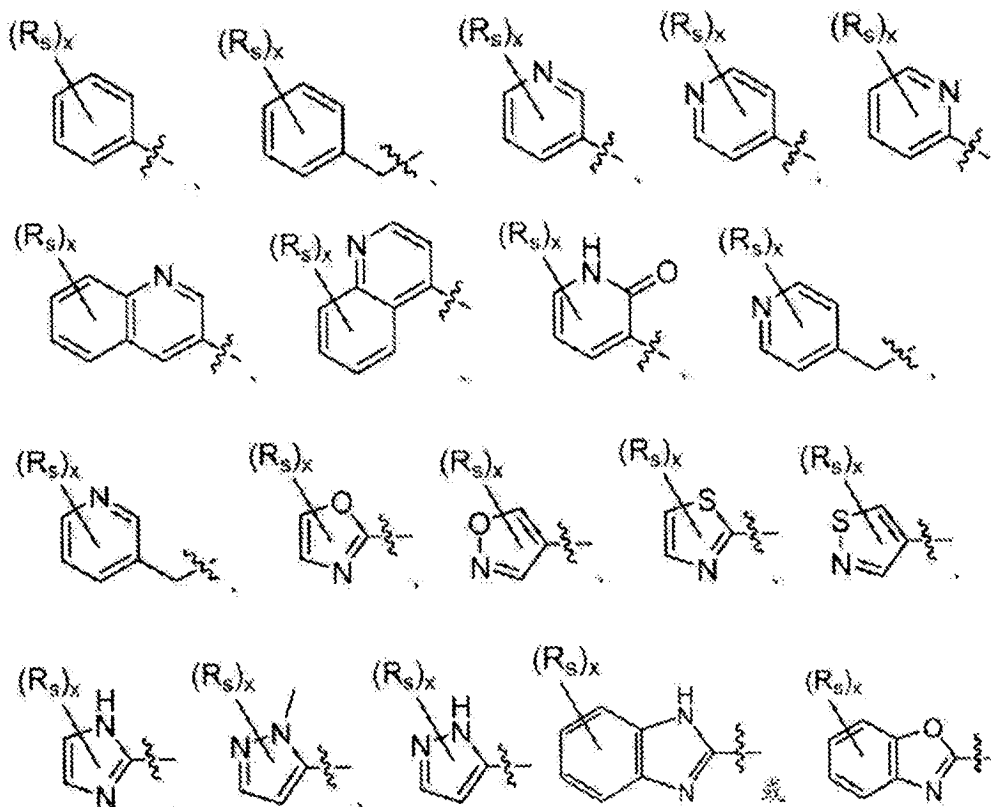
47. 如权利要求 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含结构



其中 R¹ 是异丙基、叔丁基、



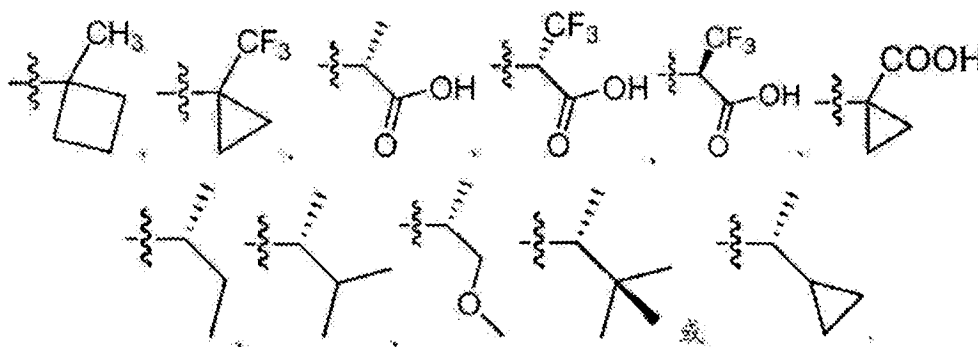
R^3 是



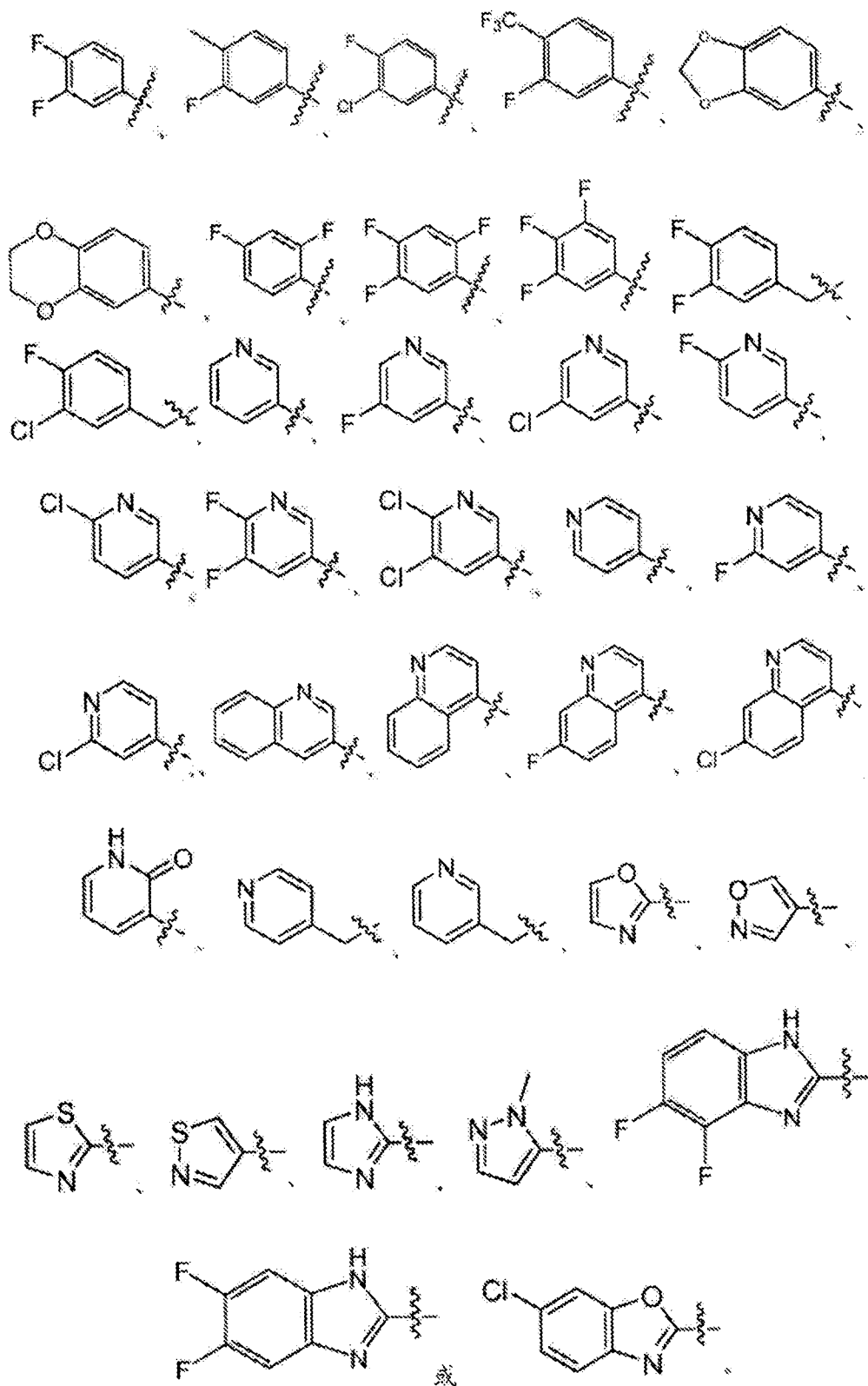
R_5 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化 C_{1-6} 烷基、 $-O-(C_{1-6}$ 烷基)，或当两个 R_5 一起形成稠环部分或杂环部分；并且 x 是 0、1、2 或 3，

x 是 0、1、2 或 3。

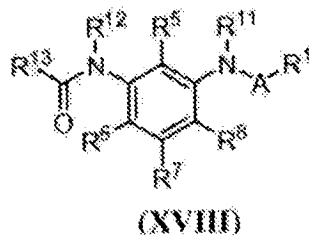
48. 如权利要求 47 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中 R^1 是



并且 R^3 是



49. 一种包含式 (XVIII) 的结构的化合物或其对映异构体、非对映异构体或药学上接受的盐：



其中：

A 选自由 SO₂和 CO 组成的组；

R¹选自由任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₃₋₇环烷基、任选取代的芳基和任选取代的苯甲基组成的组；

R⁵选自由氢、卤素、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₁₋₆卤代烷基、OR⁹、氰基和 N(R⁹)₂组成的组；

R⁶选自由氢、卤素、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₁₋₆卤代烷基、OR⁹、氰基和 N(R⁹)₂组成的组；

R⁷选自由氢、卤素、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₁₋₆卤代烷基、OR⁹、氰基和 N(R⁹)₂组成的组；

R⁸选自由氢、卤素、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₁₋₆卤代烷基、OR⁹、氰基和 N(R⁹)₂组成的组；或

R⁹在每次出现时都独立地选自由氢、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₃₋₇环烷基、任选取代的芳基、任选取代的苯甲基、任选取代的杂环基和任选取代的杂芳基组成的组；

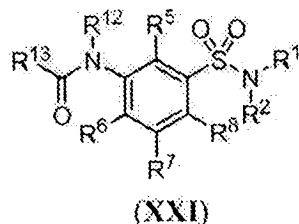
R¹²选自由氢、任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基和任选取代的 C₃₋₇环烷基组成的组；并且

R¹³选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

50. 如权利要求 49 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 A 是 SO₂。

51. 如权利要求 49 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 A 是羰基、CO。

52. 一种包含式 (XXI) 的结构化合物或其对映异构体、非对映异构体或药学上接受的盐：



其中：

R¹选自由任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₃₋₇环烷基、任选取代的芳基和任选取代的苯甲基组成的组；

R^2 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{3-7} 环烷基和任选取代的杂环组成的组；或

R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环；

R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；

R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 、氰基和 $N(R^9)_2$ 组成的组；或

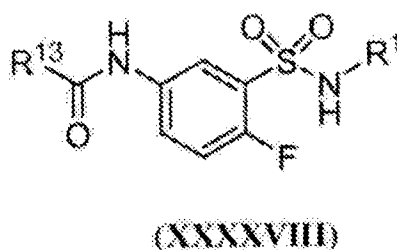
R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的环；

R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基、任选取代的苯甲基、任选取代的杂环基和任选取代的杂芳基组成的组。

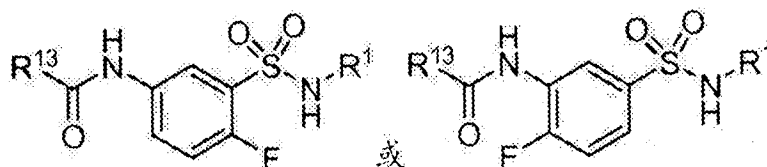
R^{12} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组；并且

R^{13} 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

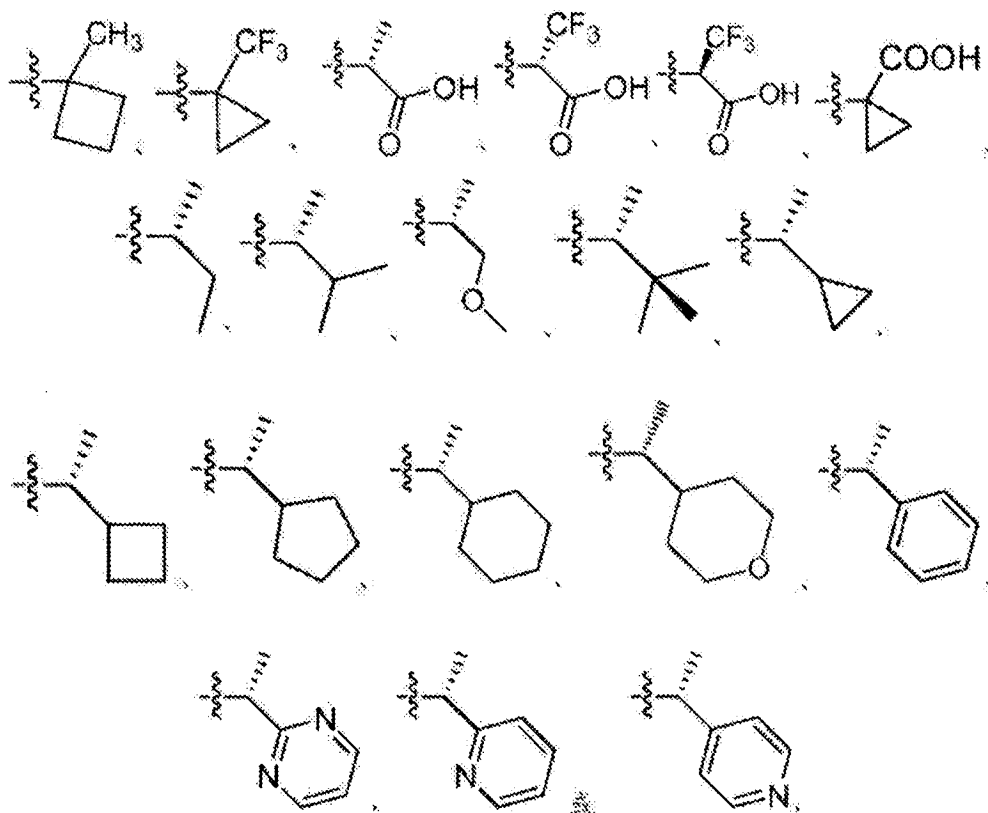
53. 如权利要求 52 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，所述化合物包含式 XXXXVIII 的结构：



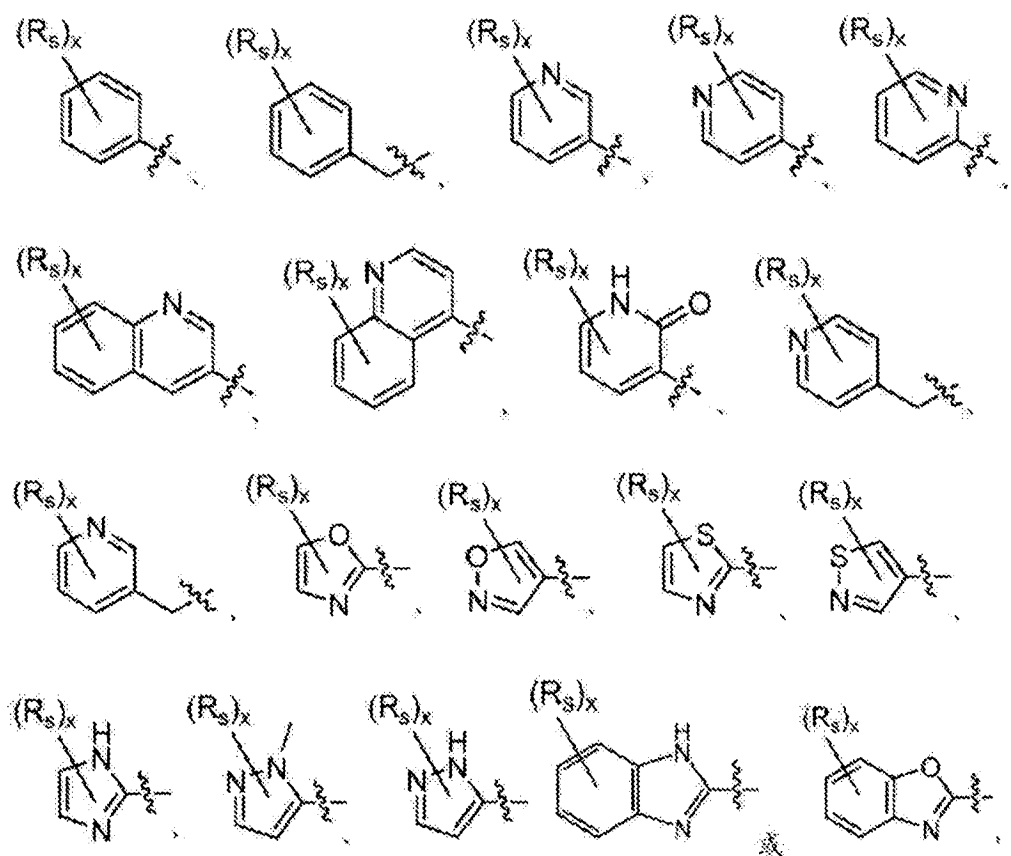
54. 如权利要求 52 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，所述化合物包含结构



其中 R^1 是



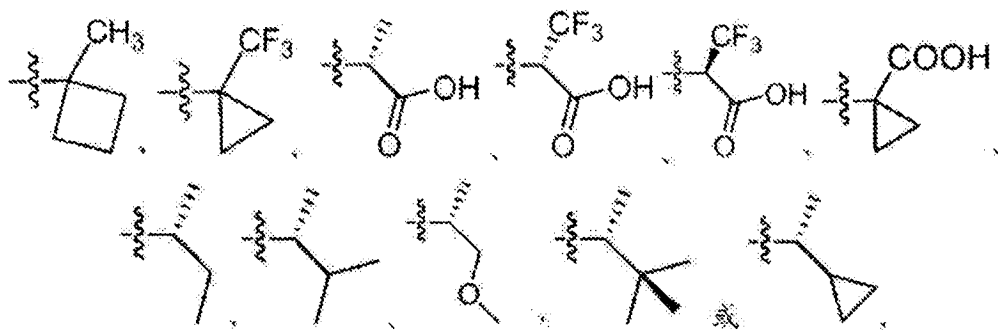
R^{13} 是



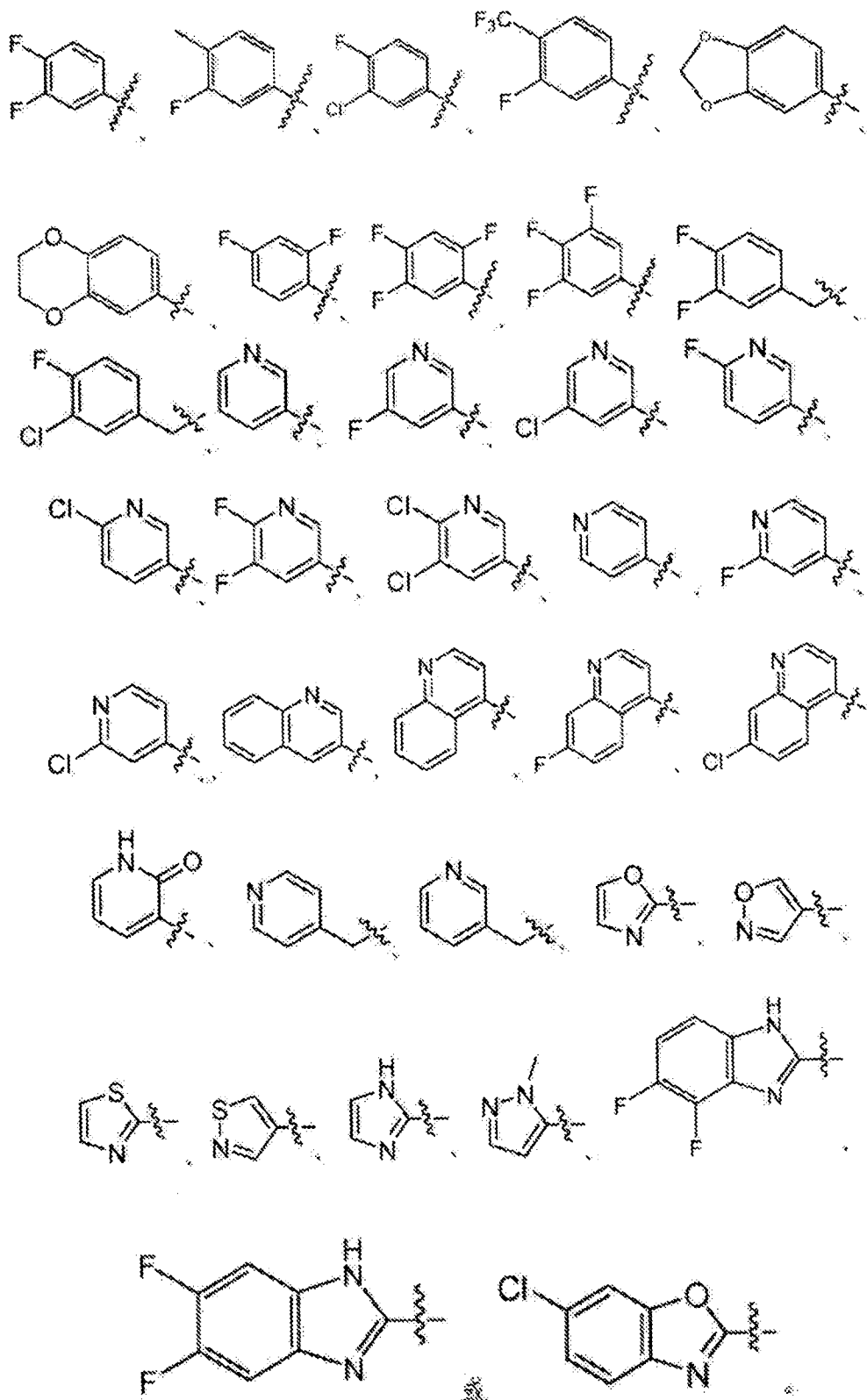
R_5 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化的 C_{1-6} 烷基、 $-O-(C_{1-6}烷基)$ ，或当两个 R_5 一起形成稠环部分或杂环部分时；并且 x 是 0、1、2 或 3。

x 是 0、1、2 或 3。

55. 如权利要求 54 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 R^1 是



并且 R^{13} 是



56. 一种药物组合物,其包含如权利要求 1 所述的化合物以及药学上可接受的赋形剂。

57. 一种治疗涉及前基因组 RNA 衣壳化的疾病的方法,所述方法包括向需要此类治疗的患者施用有效量的至少一种如权利要求 1 所述的化合物。

58. 如权利要求 57 所述的方法, 其中所述涉及前基因组 RNA 衣壳化的疾病是乙型肝炎病毒感染。

59. 一种治疗乙型肝炎病毒性感染的方法, 所述方法包括向需要此类治疗的患者施用有效量的至少一种如权利要求 1 所述的化合物。

60. 如权利要求 59 所述的方法, 其中所述治疗控制或改善与肝病相关的病状, 包括肝硬化和肝细胞癌。

61. 一种阻遏病毒复制、形态发生、或复制与形态发生两者的方法, 其包括向有需要的患者施用如权利要求 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐。

针对 HBV 感染的新型抗病毒剂

[0001] 相关申请的交叉引用

[0002] 本申请要求 2012 年 12 月 27 日提交的美国申请号 61/746,552 的权益,所述申请出于所有目的以引用的方式整体并入本文。

[0003] 政府权利

[0004] 本发明是在政府支持下在由 NIH 的国立过敏和感染性疾病研究所 (NIAID) 颁发的拨款号 R43AI098200、R43AI104066 下进行。政府享有本发明的某些权利。

发明领域

[0005] 本发明描述用作前基因组 RNA 衣壳化抑制剂,用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的化合物和方法。

[0006] 发明背景

[0007] 乙型肝炎病毒 (HBV) 感染仍然是主要公共卫生问题。当前,估计全世界 3.5 亿人以及美国 140 万人被 HBV 慢性感染 (McMahon, 2005)。如果保持未治疗,那么这些个体中约三分之一将死于严重肝病,诸如肝硬化和肝细胞癌 (Lee, 1997 ;Lok, 2004)。

[0008] 七种药物当前可用于管理慢性乙型肝炎,其包括两种 α -干扰素 (标准和聚乙二醇化) 制剂和抑制 HBV DNA 聚合酶的五种核苷类似物 (拉米夫定 (lamivudine)、阿德福韦 (adefovir)、恩替卡韦 (entecavir)、替比夫定 (telbivudine) 和替诺福韦 (tenofovir)) (Keefe 等, 2008)。目前,优选第一线治疗选择是恩替卡韦、替诺福韦或聚乙二醇-干扰素 α -2a。然而,即使采用第一线治疗选项,聚乙二醇-干扰素 α -2a 也仅在三分之一治疗患者中有效达成某些血清学重要事件,并且常伴有严重副作用 (Janssen 等, 2005 ;Lau 等, 2005 ;Perrillo, 2009)。恩替卡韦和替诺福韦是高度有效的 HBV 抑制剂,但连续遏制 HBV 复制需要长期或可能终生治疗,此可最终由于出现耐药性病毒而失败 (Dienstag, 2009)。因此,迫切需要引入用于慢性乙型肝炎的新型、安全且有效疗法,此被国立过敏和感染性疾病研究所 (NIAID) 列为高优先级目标领域。

[0009] HBV 是一种属于肝脱氧核糖核酸病毒科的非细胞病变性、嗜肝性 DNA 病毒。前基因组 (pg)RNA 是 HBV DNA 的逆转录复制的模板,并且它连同病毒 DNA 聚合酶一起衣壳化成核衣壳为随后病毒 DNA 合成所必需。抑制前基因组 RNA (pg) 衣壳化将阻断 HBV 复制,并且提供一种用以治疗 HBV 的新型治疗方法。类似方法也将产生针对其它病毒的新型治疗方法。

[0010] 在临床上,抑制前基因组 RNA (pg) 衣壳化,或更一般来说,抑制核衣壳装配,提供以下治疗优势:首先,抑制前基因组 RNA (pg) 衣壳化将通过对于不耐受或受益于当前药物的患者亚种群提供另一选项来补充当前药物 (Akbar 等, 2009 ;Liaw, 2009 ;Peters, 2009 ;Wiegand, van Bommel 和 Berg)。其次,基于它们的不同抗病毒机理,抑制前基因组 RNA (pg) 衣壳化将有效针对对当前可用的 DNA 聚合酶抑制剂具有抗性的 HBV 变体 (Zoulim 和 Locarnini, 2009)。第三,类似用于人免疫缺陷病毒 (HIV) 感染的高度活性抗逆转录病毒疗法 (HAART) (Este 和 Cihlar),前基因组 RNA (pg) 衣壳化抑制剂与 DNA 聚合酶抑制剂的组合疗法应协同遏制 HBV 复制,并且防止出现耐药性,并且因此提供对慢性乙型肝炎感染的更

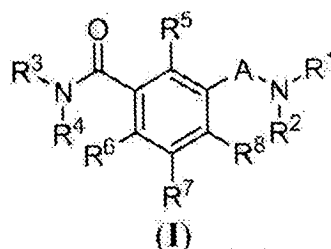
安全且更有效治疗。

[0011] 长期需要具有疾病改善性,并且有效治疗被乙型肝炎病毒和其它病毒感染的患者,或防止其在处于获得相关疾病的风险下的患者中发作的新型抗病毒药物。也明确且目前需要具有疾病改善性,并且有效治疗被耐药性乙型肝炎病毒和其它病毒感染的患者的新型抗病毒药物。本发明解决对具有疾病改善性,并且有效治疗被乙型肝炎病毒和其它病毒感染的患者的新型抗病毒药物的需要。以单药疗法形式或与其它治疗或辅助治疗组合向受感染患者施用这些治疗剂将导致显著改善的预后、减弱疾病进展以及增强血清转化速率。

[0012] 发明概述

[0013] 本发明涉及用于处理病毒的用作核衣壳装配抑制剂,尤其但不仅限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 前基因组 RNA 衣壳化抑制剂的式 (I) 的新型化合物和使用所述化合物的新型方法。

[0014]



[0015] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

[0016] A 选自由 SO_2 和 CO 组成的组;

[0017] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组; R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-\text{C}_{1-6}$ 烷氧化物、 $-\text{SO}_2-\text{C}_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基;

[0018] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组; R^2 也可或者或另外任选包括任选取代的 C_{3-7} 环烷基或任选取代的杂环;或

[0019] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环(包括双环或金刚烷基结构);并且

[0020] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组;在一些实施方案中, R^3 也可包括任选取代的 C_{1-6} 直链烷基;

[0021] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组;

[0022] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组; R^5 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$;

[0023] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 ; R^6 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$ 组成的组;或

[0024] R^1 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环;并且

[0025] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0026] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$;或

[0027] R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的碳环或杂环;并且

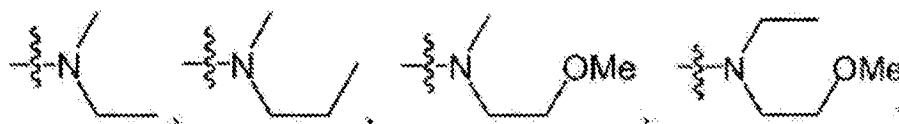
[0028] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基组成的组; R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基;

[0029] 条件是当 A 是 SO_2 ; R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环;并且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环时,那么以下 (a) 至 (d) 都不适用:

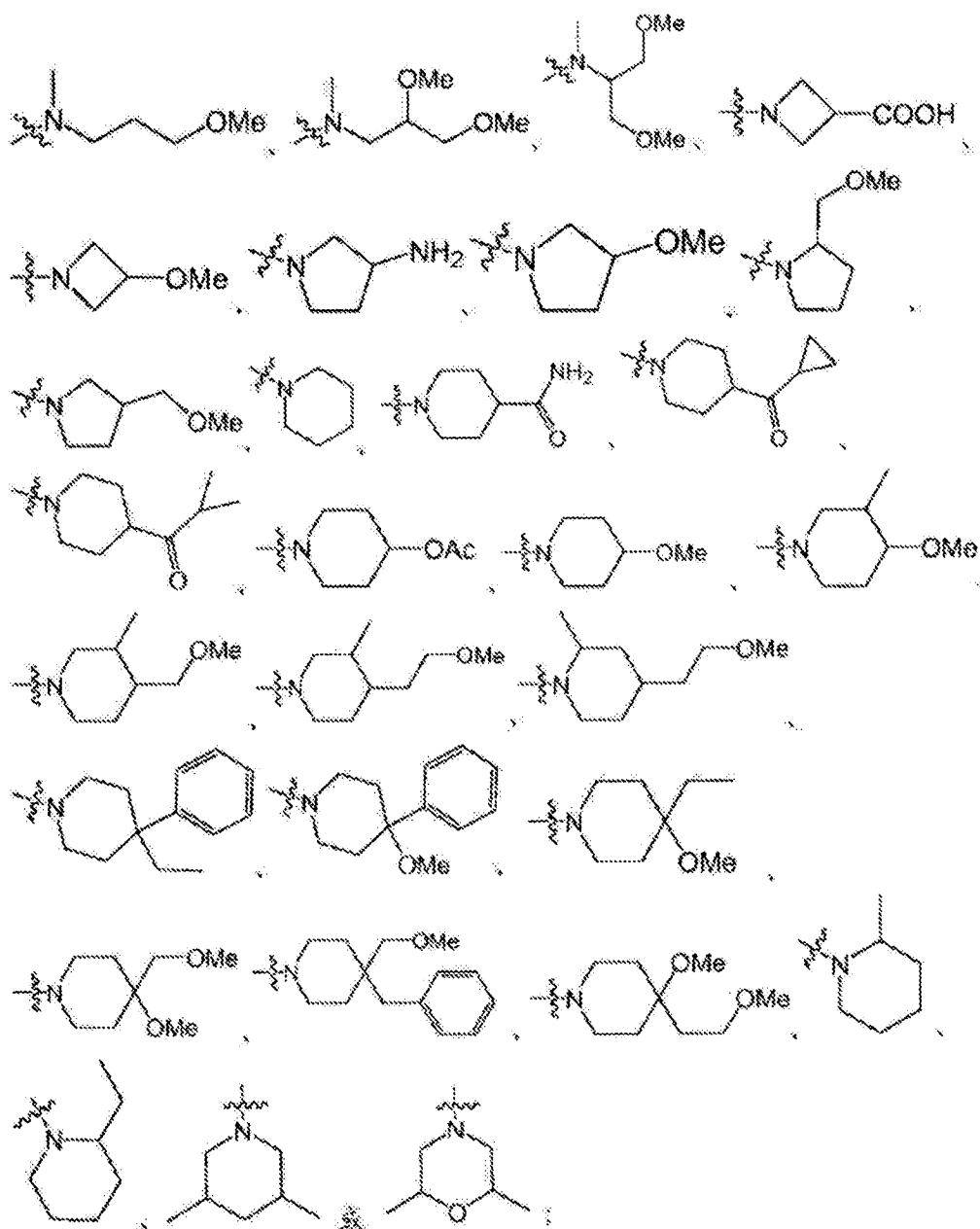
[0030] (a) R^3 是任选取代的苯基,并且 R^1 或 R^2 单独地或当一起时含有羟基,或

[0031] (b) R^3 是任选取代的烷基或苯基,并且 $N(R^1)(R^2)$ 是任选取代的哌嗪或

[0032]

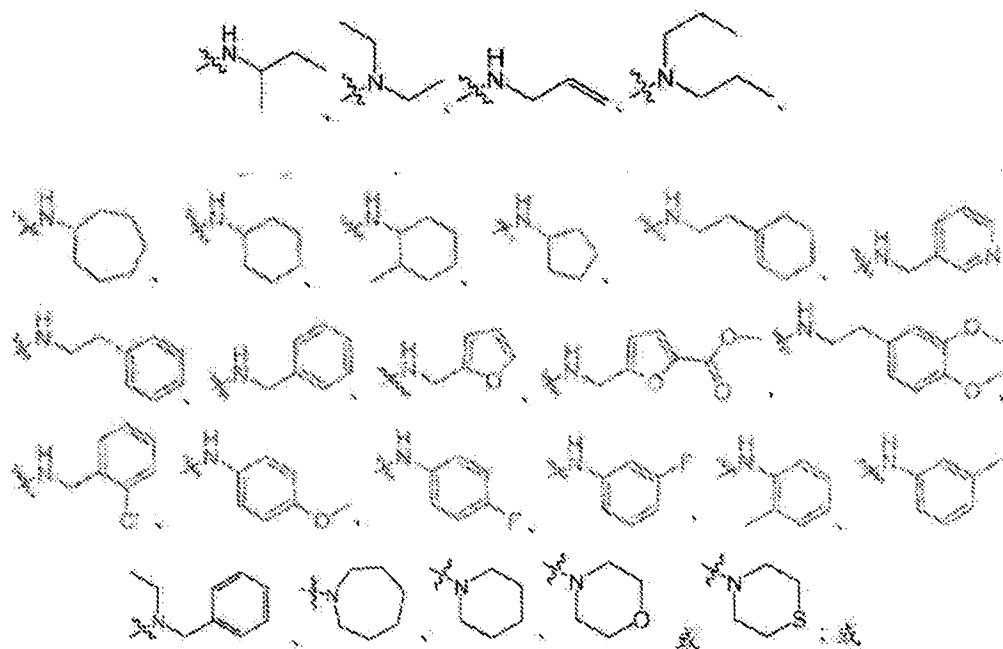


[0033]



[0034] (c) R^3 是任选取代的烷基、芳基或烷芳基, 并且 $N(R^1)(R^2)$ 是

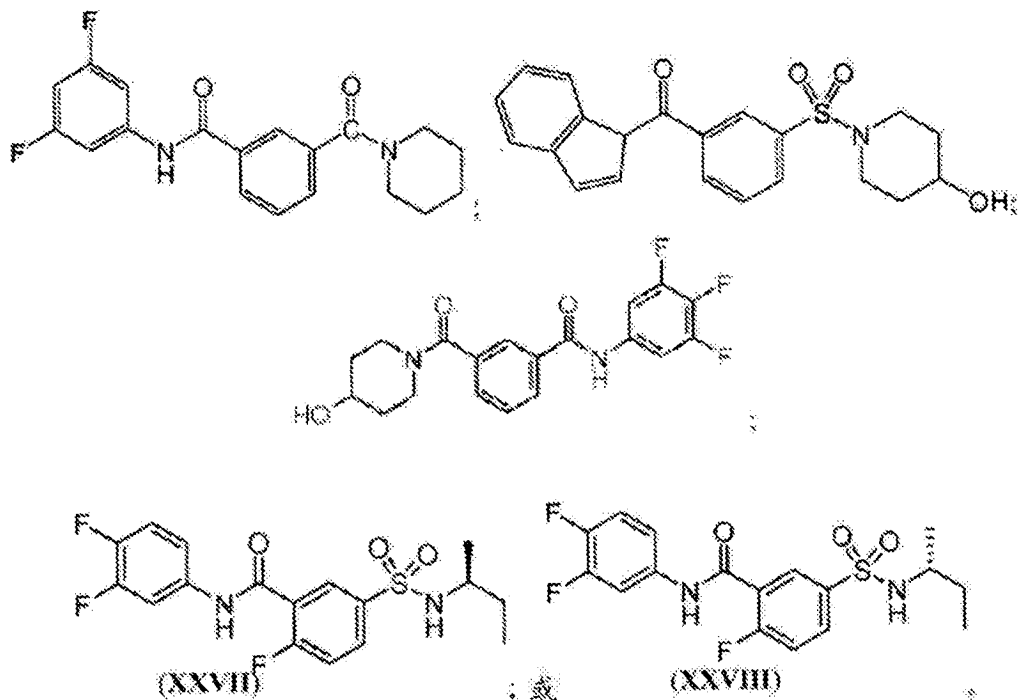
[0035]



[0036] (d) R^3 或 R^4 是未被取代或被单取代的芳基、未被取代或被单取代的芳烷基、或未被取代或被单取代的杂芳基, 并且 R^1 和 R^2 连同它们所结合的原子一起形成具有 6 至 12 个原子的任选取代的杂环结构; 或

[0037] 条件是化合物不是 3-[(二环丙基甲基)氨基]磺酰基)-N-(4-异丙氧基苯基)苯甲酰胺; 或 3-([2-(1H-苯并咪唑-2-基)丙基]氨基)磺酰基)-N-(4-异丙氧基苯基)苯甲酰胺; 或 3-[(环己基氨基)磺酰基]-N-(4-异丙基苯基)苯甲酰胺; 或 3-(苯胺基磺酰基)-N-(4-异丙基苯基)苯甲酰胺; 或 5-[(3-[(4-甲氧基苯基)氨基]羰基)苯基]磺酰基]氨基]戊酸; 或 3-[(叔丁基氨基)磺酰基]-N-(4-甲氧基苯基)苯甲酰胺; 或 (3S)-1-[3-[(5-异丙氧基吡啶-2-基)氨基]羰基)苯基]磺酰基]哌啶-3-甲酰胺; 或 (3R)-1-[3-[(5-异丙氧基吡啶-2-基)氨基]羰基)苯基]磺酰基]哌啶-3-甲酰胺; 或 3-(哌啶-1-基磺酰基)-N-[(1S)-1,2,3,4-四氢萘-1-基]苯甲酰胺; 或 N-(5-溴-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺; 或 N-(3-甲氧基-5-苯基吡啶-2-基)-3-(吡咯烷-1-基磺酰基)苯甲酰胺; 或 N-(3-甲氧基-5-苯氧基吡啶-2-基)-3-(吡咯烷-1-基磺酰基)苯甲酰胺; 或 N-[3-甲氧基-5-(苯硫基)吡啶-2-基]-3-(吡咯烷-1-基磺酰基)苯甲酰胺; 或 N-(5-乙基-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺; 或 N-(3-甲氧基-5-乙烯基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺; 或

[0038]



[0039] 式(I)化合物的一些实施方案也排除当A是SO₂;R⁴和R⁶连同它们所结合的原子一起不形成任选取代的环;并且R²和R⁸连同它们所结合的原子一起不形成任选取代的环时,R³是任选取代的烷基、芳基或烷芳基,并且N(R¹)(R²)是任选取代的哌啶的那些化合物。

[0040] 本发明的实施方案包括式(I)化合物,其中

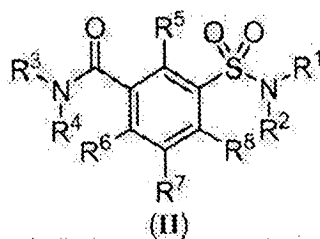
[0041] A是SO₂;

[0042] R⁴和R⁶连同它们所结合的原子一起不形成任选取代的环;并且

[0043] R²和R⁸连同它们所结合的原子一起不形成任选取代的环;

[0044] 由此提供具有式(II)的化合物,

[0045]

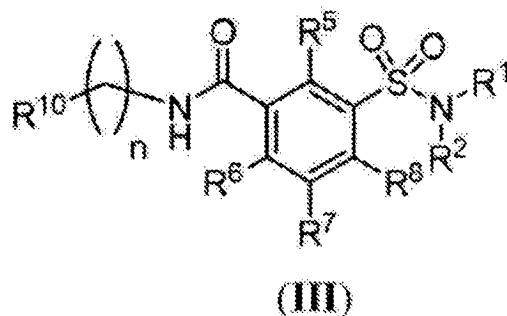


[0046] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0047] 在一些实施方案中,R¹至R⁸是如对于式(I)化合物所定义。在其它独立实施方案中,R¹至R⁸是如下所定义。

[0048] 本发明的实施方案包括式(I)化合物,其中A是SO₂,由此提供具有式(III)的化合物,

[0049]



[0050] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，

[0051] 其中：

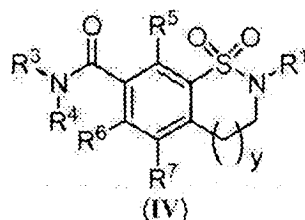
[0052] R^{10} 选自自由任选取代的芳基和任选取代的杂芳基组成的组；并且

[0053] n 是 0 或 1。

[0054] 在一些实施方案中， R^1 、 R^2 以及 R^5 至 R^8 是如对于式 (I) 化合物所定义。在其它独立实施方案中， R^1 、 R^2 以及 R^5 至 R^8 是如下所定义。在一些实施方案中， R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的碳环或杂环。

[0055] 本发明的实施方案包括式 (I) 化合物，具体来说具有式 (IV)，

[0056]

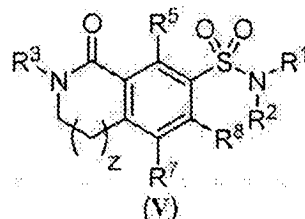


[0057] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中： y 是 0 或 1。在一些实施方案中， y 是 2。

[0058] 在一些实施方案中， R^1 以及 R^3 至 R^8 是如对于式 (I) 化合物所定义。在其它独立实施方案中， R^1 以及 R^3 至 R^8 是如下所定义。在一些实施方案中， R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的碳环或杂环。

[0059] 本发明的实施方案包括其中 A 是 SO_2 的式 (I) 化合物，其具有式 (V)，

[0060]

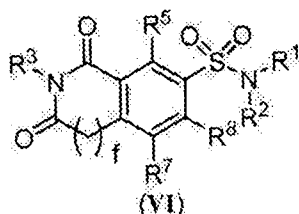


[0061] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中： z 是 0 或 1。

[0062] 在一些实施方案中， R^1 至 R^3 、 R^5 以及 R^7 至 R^8 是如对于式 (I) 化合物所定义。在其它独立实施方案中， R^1 至 R^3 、 R^5 以及 R^7 至 R^8 是如下所定义。在一些实施方案中， R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的碳环或杂环。

[0063] 本发明的实施方案包括其中 A 是 SO_2 的式 (I) 化合物，其具有式 (VI)，

[0064]

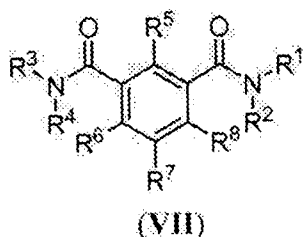


[0065] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:f是0或1。

[0066] 在一些实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 是如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 是如下所定义。在一些实施方案中, R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的碳环或杂环。

[0067] 本发明的实施方案包括其中A是CO的式(I)化合物,其具有式(VII),

[0068]

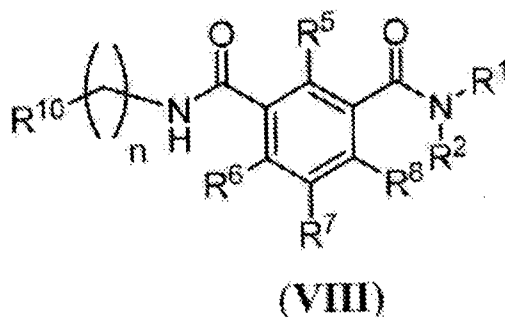


[0069] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0070] 在一些实施方案中, R^1 至 R^8 是如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^8 是如下所定义。[0071] 在式(VII)化合物的一些实施方案中, R^1 和 R^6 连同它们所结合的原子一起不形成任选取代的碳环或杂环;并且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的碳环或杂环;

[0072] 本发明的实施方案包括其中A是CO的式(I)化合物,由此提供具有式(VIII)的化合物,

[0073]



[0074] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

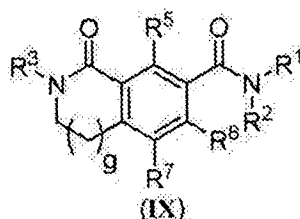
[0075] R^{10} 选自由任选取代的芳基和任选取代的杂芳基组成的组;并且

[0076] n是0或1。

[0077] 在一些实施方案中, R^1 至 R^2 以及 R^5 至 R^8 是如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^2 以及 R^5 至 R^8 如下所定义。

[0078] 本发明的实施方案包括其中 A 是 CO 的式 (I) 化合物, 其具有式 (IX) :

[0079]

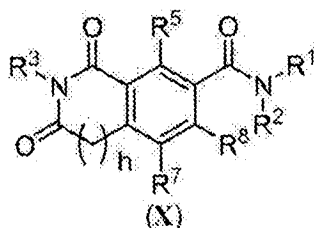


[0080] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 :g 是 0 或 1。

[0081] 在一些实施方案中, R¹至 R³、R⁵以及 R⁷至 R⁸是如对于式 (I) 化合物所定义。在其它实施方案中, R¹至 R³、R⁵以及 R⁷至 R⁸是如下所定义。在一些实施方案中, R²和 R⁸连同它们所结合的原子一起不形成任选取代的碳环或杂环; 并且

[0082] 本发明的实施方案包括其中 A 是 CO 的式 (I) 化合物, 其具有式 (X),

[0083]

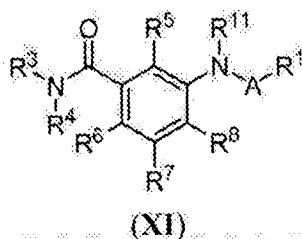


[0084] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 :h 是 0 或 1。

[0085] 在一些实施方案中, R¹至 R³、R⁵以及 R⁷至 R⁸是如对于式 (I) 化合物所定义。在其它独立实施方案中, R¹至 R³、R⁵以及 R⁷至 R⁸如下所定义。

[0086] 本发明的实施方案包括用于处理病毒的用作核衣壳装配抑制剂, 尤其但不仅限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 前基因组 RNA 衣壳化抑制剂的具有式 (XI) 的化合物

[0087]



[0088] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 :

[0089] A 选自由 SO₂和 CO 组成的组 ;

[0090] R¹选自由任选取代的 C₁₋₆直链烷基、任选取代的 C₁₋₆支链烷基、任选取代的 C₃₋₇环烷基、任选取代的芳基和任选取代的苯甲基组成的组 ; R¹也可或者或另外任选包括任选取代的 C₁₋₆卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C₂₋₈烯基、任选取代的 C₂₋₈炔基、任选取代的 C₁₋₆烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 -C₁₋₆- 烷氧化物、-SO₂-C₁₋₆烷基、任选取代的杂环或任选取代的杂芳基 ;

[0091] R³选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的

杂芳基和任选取代的烷基杂芳基组成的组；在一些实施方案中， R^3 也可包括任选取代的 C_{1-6} 直链烷基；

[0092] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组；

[0093] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0094] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；或

[0095] R^4 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；并且

[0096] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

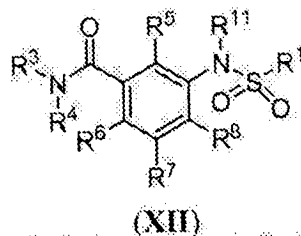
[0097] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0098] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组； R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；并且

[0099] R^{11} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组。

[0100] 本发明的实施方案也包括具有式 (XII) 的化合物，

[0101]

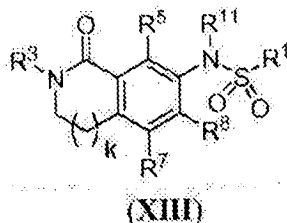


[0102] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0103] 在一些实施方案中， R^1 、 R^3 至 R^8 以及 R^{11} 是如对于式 (XI) 化合物所定义。在其它实施方案中， R^1 、 R^3 至 R^8 以及 R^{11} 是如下所定义。

[0104] 本发明的实施方案包括具有式 (XIII) 的化合物，

[0105]

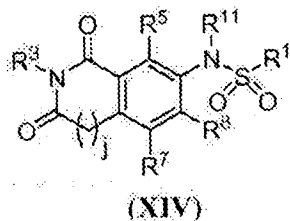


[0106] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中： k 是 0 或 1。

[0107] 在一些实施方案中， R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 是如对于式 (XI) 化合物所定义。在其它独立实施方案中， R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 是如下所定义。

[0108] 本发明的实施方案包括具有式 (XIV) 的化合物,

[0109]

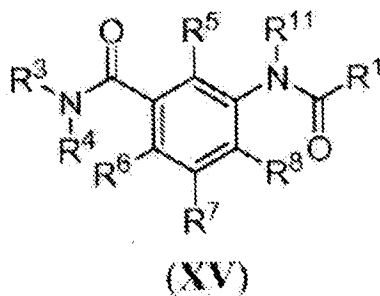


[0110] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:j是0或1。

[0111] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 是如对于式 (XI) 化合物所定义。在其它实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0112] 本发明的实施方案包括具有式 (XV) 的化合物,

[0113]

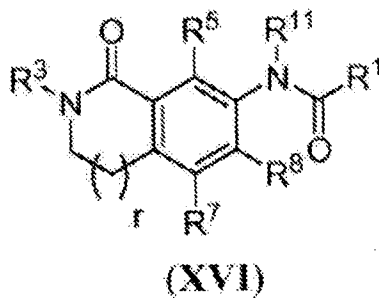


[0114] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0115] 在一些实施方案中, R^1 、 R^3 至 R^8 以及 R^{11} 是如对于式 (XI) 化合物所定义。在其它实施方案中, R^1 、 R^3 至 R^8 以及 R^{11} 如下所定义。

[0116] 本发明的实施方案包括具有式 (XVI) 的化合物,

[0117]

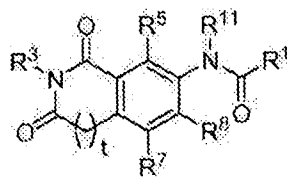


[0118] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:r是0或1。

[0119] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 是如对于式 (XI) 化合物所定义。在其它实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0120] 本发明的实施方案包括具有式 (XVII) 的化合物,

[0121]



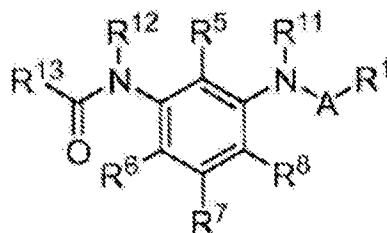
(XVII)

[0122] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：t 是 0 或 1。

[0123] 在一些实施方案中， R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 是如对于式 (XI) 化合物所定义。在其它实施方案中， R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0124] 本发明的实施方案包括用于处理病毒的用作核衣壳装配抑制剂，尤其但不限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 前基因组 RNA 衣壳化抑制剂的具有式 (XVIII) 的化合物

[0125]



(XVIII)

[0126] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

[0127] A 选自由 SO_2 和 CO 组成的组；

[0128] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组； R^1 也可或者或另外任选包括任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-C_{1-6}$ - 烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基；

[0129] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0130] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组； R^6 也可或者或另外任选是氰基或 $N(R^9)_2$ ；

[0131] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0132] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0133] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 组成的组； R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；

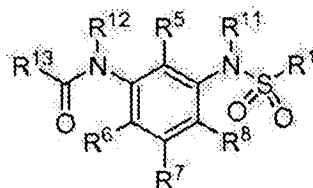
[0134] R^{11} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组；

[0135] R^{12} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组；并且

[0136] R^{13} 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

[0137] 本发明的实施方案包括具有式 (XIX) 的化合物，

[0138]



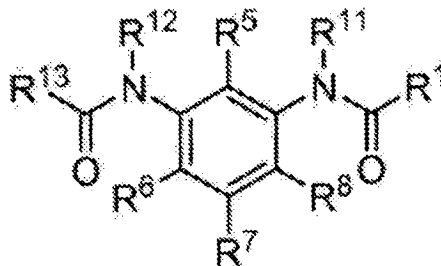
(XIX)

[0139] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0140] 在一些实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 是如对于式 (XVIII) 化合物所定义。在其它实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如下所定义。

[0141] 本发明的实施方案包括具有式 (XX) 的化合物，

[0142]



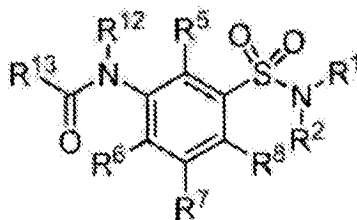
(XX)

[0143] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0144] 在一些实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 是如对于式 (XVIII) 化合物所定义。在其它实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如下所定义。

[0145] 本发明的实施方案包括用于处理病毒的用作核衣壳装配抑制剂，尤其但不仅限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 的前基因组 RNA 衣壳化抑制剂的具有式 (XXI) 的化合物

[0146]



(XXI)

[0147] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

[0148] R^1 选自自由以下组成的组:任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_3-7 环烷基、任选取代的芳基和任选取代的苯甲基; R^1 也可或者或另外任选包括任选取代的 3-7 元环杂烷基、任选取代的 C_2-8 烯基、任选取代的 C_2-8 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-C_{1-6}-$ 烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基;

[0149] R^2 选自自由氢和任选取代的 C_{1-6} 直链烷基组成的组; R^2 也可或者或另外任选包括任选取代的 C_3-7 环烷基或任选取代的杂环;或

[0150] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环(包括双环或金刚烷基结构);

[0151] R^5 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0152] R^6 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0153] R^7 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0154] R^8 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和 OR^9 组成的组; R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0155] R^9 在每次出现时都独立地选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基和任选取代的 C_{1-6} 卤代烷基组成的组; R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基;

[0156] R^{12} 选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基组成的组;并且

[0157] R^{13} 选自自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

[0158] 本发明进一步涉及组合物,其包含:

[0159] 有效量的一种或多种根据本发明的化合物及赋形剂。

[0160] 本发明也涉及一种用于治疗或预防涉及核衣壳装配,尤其但不限于包括前基因组 RNA 衣壳化的疾病,包括例如 HBV 感染的方法,所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0161] 本发明还进一步涉及一种用于治疗或预防涉及核衣壳装配,尤其但不限于包括前基因组 RNA 衣壳化的疾病,包括例如 HBV 感染的方法,其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物以及赋形剂的组合物。

[0162] 本发明也涉及一种用于治疗或预防与 HBV 感染相关的疾病或病状以及涉及核衣壳装配,尤其但不限于包括前基因组 RNA 衣壳化的疾病的方法。所述方法包括向受试者施用有效量的根据本发明的化合物或组合物。

[0163] 本发明还进一步涉及一种用于治疗或预防与 HBV 感染相关的疾病或病状以及涉及核衣壳装配,尤其但不限于包括前基因组 RNA 衣壳化的疾病的方法,其中所述方法包括向受试者施用包含有效量的一种或多种根据本发明的化合物以及赋形剂的组合物。

[0164] 这些和其它目标、特征和优势将由阅读以下详细描述和随附权利要求而变得为本领域普通技术人员显而易见。除非另外规定,否则本文所有百分比、比率和比例都是以重量计。除非另外规定,否则所有温度都是以摄氏度(°C)计。所有文件在相关部分引用,以引用的方式并入本文;对任何文件的引用都不应解释为认可它是关于本发明的现有技术。

[0165] 发明详述

[0166] 在不意图受任何特定理论的正确性或不正确性束缚下,据信本发明化合物一般来说通过抑制核衣壳装配,并且具体来说通过抑制含有病毒基因组 RNA/DNA 的衣壳的形成(即 HBV 前基因组 RNA 衣壳化抑制剂)来起作用。术语“HBV 的前基因组 RNA 衣壳化抑制剂”是指一类干扰病毒核酸和它的与那个病毒特异性相关的衣壳蛋白质缔合的化合物。通过干扰衣壳形成,这个机理提供一种一般来说有效遏制病毒复制,并且具体来说关于 HBV 的策略。尽管本申请中使用的措辞主要针对可能通过抑制肝脱氧核糖核酸病毒前基因组 RNA 和衣壳的缔合来处理 HBV,但使用本文所述的化合物干扰其它病毒的必需 RNA 或 DNA 和它们的衣壳的缔合的相同策略也将是有效抗病毒策略(例如 HIV)。也就是说,在化合物或治疗明确涉及处理 HBV 的各情况下,其它实施方案规定其它病毒也可通过施加本文所述的化合物,例如通过干扰衣壳形成;通过干扰核酸与衣壳缔合;通过干扰 RNA 与衣壳蛋白质缔合;干扰前基因组 RNA 缔合和衣壳;以及通过干扰核酸衣壳缔合,特别是通过干扰肝脱氧核糖核酸形成和 HBV 衣壳形成来阻遏病毒复制和形态发生来处理。

[0167] 本发明的前基因组 RNA 衣壳化抑制剂能够治疗和预防与前基因组 RNA 衣壳化相关的疾病,例如 HBV 感染。前基因组 (pg)RNA 是 HBV DNA 的逆转录复制的模板,并且它连同病毒 DNA 聚合酶一起衣壳化成核衣壳为随后病毒 DNA 合成所必需。在不希望受理论限制下,据信抑制前基因组 RNA 衣壳化可改善、缓解与前基因组 RNA 衣壳化相关的疾病(例如 HBV 感染)或另外导致所述疾病被控制。本发明的前基因组 RNA 衣壳化抑制剂解决对鉴定在化学方面以及在机理方面不同于当前临床使用的 HBV 抗病毒药物的用于治疗 HBV 感染的新型且安全抗病毒剂的明确且未满足需要。

[0168] 在临床上,本发明的前基因组 RNA 衣壳化抑制剂通过对不耐受或受益于当前药物的患者亚种群提供另一选项来补充当前药物(Akbar 等,2009;Liaw,2009;Peters,2009;Wiegand, van Bommel 和 Berg)。此外,本发明的前基因组 RNA 衣壳化抑制剂可对当前可用的 DNA 聚合酶抑制剂具有抗性的 HBV 变体有效(Zoulim 和 Locarnini,2009)。此外,本发明的前基因组 RNA 衣壳化抑制剂与 DNA 聚合酶抑制剂的组合疗法可协同遏制 HBV 复制,并且防止出现耐药性,从而提供对慢性乙型肝炎的更安全且更有效治疗(Billioud 等,2011)。

[0169] 通过参照以下描述结合形成本公开的一部分的附图和实施例,本发明可更易于被理解。应了解,本发明不限于本文描述和/或显示的特定产物、方法、条件或参数,并且本文使用的术语是出于仅通过举例方式描述特定实施方案的目的,而不意图限制任何要求保护的发明。类似地,除非另外明确陈述,否则关于可能的作用机理或模式或改进原因的任何描述都意图仅具有说明性,并且在本文中本发明不受任何所述表明的作用机理或模式或改进原因的正确性或不正确性约束。在整篇本文本中,认识到描述涉及以下两方面:化合物和组合物;以及制备、配制化合物和组合物本身的方法和使用化合物和组合物本身进行治疗的方法,并且反之亦然。

[0170] 在本公开中,单数形式“一”和“所述”包括复数个提及物,并且除非上下文另外明

确指示,否则提及特定数值包括至少那个特定值。因此,举例来说,提及“一种物质”是指为本领域技术人员所知的所述物质及其等效物中的至少一个,等。

[0171] 当通过使用描述词“约”来将值表示为近似值时,应了解,特定值形成另一实施方案。一般来说,使用术语“约”指示近似值可视设法通过公开的主题获得的所需性质而变化,并且应基于它的功能来在它所使用的特定情形下加以解释。本领域技术人员将能够将此作为常规事项进行解释。在一些情况下,用于特定值的有效数字的数目可为一种确定用词“约”的程度的非限制性方法。在其它情况下,用于一系列值中的分级可用于确定各值可用于术语“约”的预定范围。当存在时,所有范围都具有包括性,并且可组合。也就是说,提及范围内陈述的值包括那个范围内的每个值。

[0172] 应了解,为明晰起见在本文中在单独实施方案的情形下描述的本发明的某些特征也可在单一实施方案中组合提供。也就是说,除非明显不相容或明确排除,否则各个别实施方案被视为可与任何其它实施方案组合,并且所述组合被视为另一实施方案。相反,为简洁起见在单一实施方案的情形下描述的本发明的各种特征也可单独或以任何子组合提供。最后,尽管实施方案可描述为一系列步骤的一部分或更一般性结构的一部分,但各所述步骤本身也可被视为可与其它实施方案组合的独立实施方案。

[0173] 过渡术语“包含”、“基本上由...组成”和“由...组成”意图暗示它们在专利行话中通常被接受的含义;也就是说(i)与“包括”、“含有”或“特征在于”同义的“包含”具有包括性或是开端的,并且不排除其它未叙述要素或方法步骤;(ii)“由...组成”排除未在权利要求中指定的任何要素、步骤或成分;并且(iii)“基本上由...组成”将权利要求的范围限于指定物质或步骤“和不实质上影响要求保护的发明的基本和新型特征的那些物质或步骤”。以短语“包含”(或它的等效语)描述的实施方案也提供以“由...组成”和“基本上由...组成”独立描述的那些实施方案作为实施方案。对于以“基本上由...组成”提供的那些实施方案,基本和新型特征是方法(或用于所述方法中的系统或由其获得的组合物)在治疗本文所述的病状方面的容易可操作性。

[0174] 当呈现清单时,除非另外陈述,否则应了解,那个清单的各个别要素以及那个清单的每个组合都是单独实施方案。举例来说,呈现为“A、B或C”的实施方案的清单应解释为包括实施方案“A”、“B”、“C”、“A或B”、“A或C”、“B或C”、或“A、B或C”。类似地,碳或环结构的下标描述,诸如 C_{1-6} 烷基,应理解成包括那个清单的各个别要素以及那个清单的每个组合作为单独实施方案,例如 C_1 -烷基、 C_2 -烷基、 C_3 -烷基、 C_4 -烷基、 C_5 -烷基、 C_6 -烷基、 C_{1-2} -烷基、 C_{1-3} -烷基、 C_{1-4} -烷基、 C_{1-5} -烷基、 C_{1-6} -烷基、 C_{2-3} -烷基、 C_{2-4} -烷基、 C_{2-5} -烷基、 C_{2-6} -烷基、 C_{3-4} -烷基、 C_{3-5} -烷基、 C_{3-6} -烷基、 C_{4-5} -烷基、 C_{4-6} -烷基和 C_{5-6} -烷基。

[0175] 除非另外定义,否则本文所用的所有技术和科学术语都与本发明所属领域普通技术人员通常所理解具有相同含义。尽管在实施或测试本发明时也可使用与本文所述的那些方法和材料类似或等效的任何方法和材料,但本文描述了代表性说明性方法和材料。

[0176] 如本文所用,术语“治疗(treating/treatment)”疾病或病症是指向患者施加或施用治疗剂,即本发明化合物(单独或与另一药物制剂组合),或向自具有HBV感染、HBV感染的症状或可能显现HBV感染的患者分离的组织或细胞系施加或施用治疗剂(例如供诊断或离体应用),以达成控制疾病的进展(即遏止或降低疾病或其至少一种临床症状的发展),或改善疾病的影响的目的。在另一实施方案中,所述术语是指在身体上(例如使可辨别症

状稳定化)、在生理上(例如使身体参数稳定化)或在两方面调节疾病或病症。在另一实施方案中,“治疗”是指延迟疾病或病症的发作,或甚至防止所述发作。

[0177] 术语“预防(preventing/prevention)”意图暗示治疗或化合物降低本文所述的疾病或病状的风险的能力。在其它实施方案中,这些术语也可指降低获得疾病或病症的风险(即导致疾病的至少一种临床症状不在尚未暴露于疾病或易患疾病,以及尚未经受或显示疾病的症状的受试者中显现)。

[0178] 在整篇描述中,当组合物被描述为具有、包括或包含特定组分时,或当方法被描述为具有、包括或包含特定方法步骤时,预期本教义的组合物的基本上由所述组分组成,或由所述组分组成,并且本教义的方法也基本上由所述方法步骤组成,或由所述处理步骤组成。

[0179] 在本申请中,当要素或组分据称包括在所述要素或组分的清单中和/或选自所述要素或组分的清单时,应了解,要素或组分可为所述要素或组分中的任一个,并且可选自由所述要素或组分中的两个或更多个组成的组。

[0180] 除非另外明确陈述,否则在本文中使用的单数包括复数(并且反之亦然)。此外,当在定量值之前使用术语“约”时,除非另外明确陈述,否则本教义也包括特定定量值自身。

[0181] 应了解,步骤的顺序或执行某些动作的顺序是不重要的,只要本教义保持可操作即可。此外,两个或更多个步骤或动作可同时进行。

[0182] 如本文所用,术语“卤素”将指氯、溴、氟和碘。

[0183] 如本文所用,除非另外指示,否则“烷基”和/或“脂族”无论单独或作为取代基的一部分使用都是指具有1至20个碳原子或这个范围内的任何数目的碳原子,例如1至6个碳原子或1至4个碳原子的直碳链和支碳链两者。指定的碳原子数(例如C₁₆)将独立地指烷基部分或较大含烷基取代基的烷基部分中的碳原子数。烷基的非限制性实例包括甲基、乙基、正丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基等。烷基可任选取代。被取代的烷基的非限制性实例包括羟基甲基、氯甲基、三氟甲基、氨基甲基、1-氯乙基、2-羟基乙基、1,2-二氟乙基、3-羧基丙基等。在具有多个烷基的取代基如(C₁₆烷基)₂氨基中,烷基可相同或不同。任选取代的烷基包括以下作为特定个别实施方案:卤代烷基,并且特别是部分氟化或全氟化烷基,例如-CH₂F、-CHF₂和-CF₃。

[0184] 如本文所用,术语“烯基”和“炔基”无论单独或作为取代基的一部分使用都是指具有2个或更多个碳原子,优选2至20个碳原子的直碳链和支碳链,其中烯基链在链中具有至少一个双键,而炔基链在链中具有至少一个三键。烯基和炔基可任选取代。烯基的非限制性实例包括乙烯基、3-丙烯基、1-丙烯基(也是2-甲基乙烯基)、异丙烯基(也是2-甲基乙烯-2-基)、丁烯-4-基等。经取代的烯基的非限制性实例包括2-氯乙烯基(也是2-氯乙烯基)、4-羟基丁烯-1-基、7-羟基-7-甲基辛-4-烯-2-基、7-羟基-7-甲基辛-3,5-二烯-2-基等。炔基的非限制性实例包括乙炔基、丙-2-炔基(也是炔丙基)、丙炔-1-基和2-甲基-己-4-炔-1-基。经取代的炔基的非限制性实例包括5-羟基-5-甲基己-3-炔基、6-羟基-6-甲基庚-3-炔-2-基、5-羟基-5-乙基庚-3-炔基等。

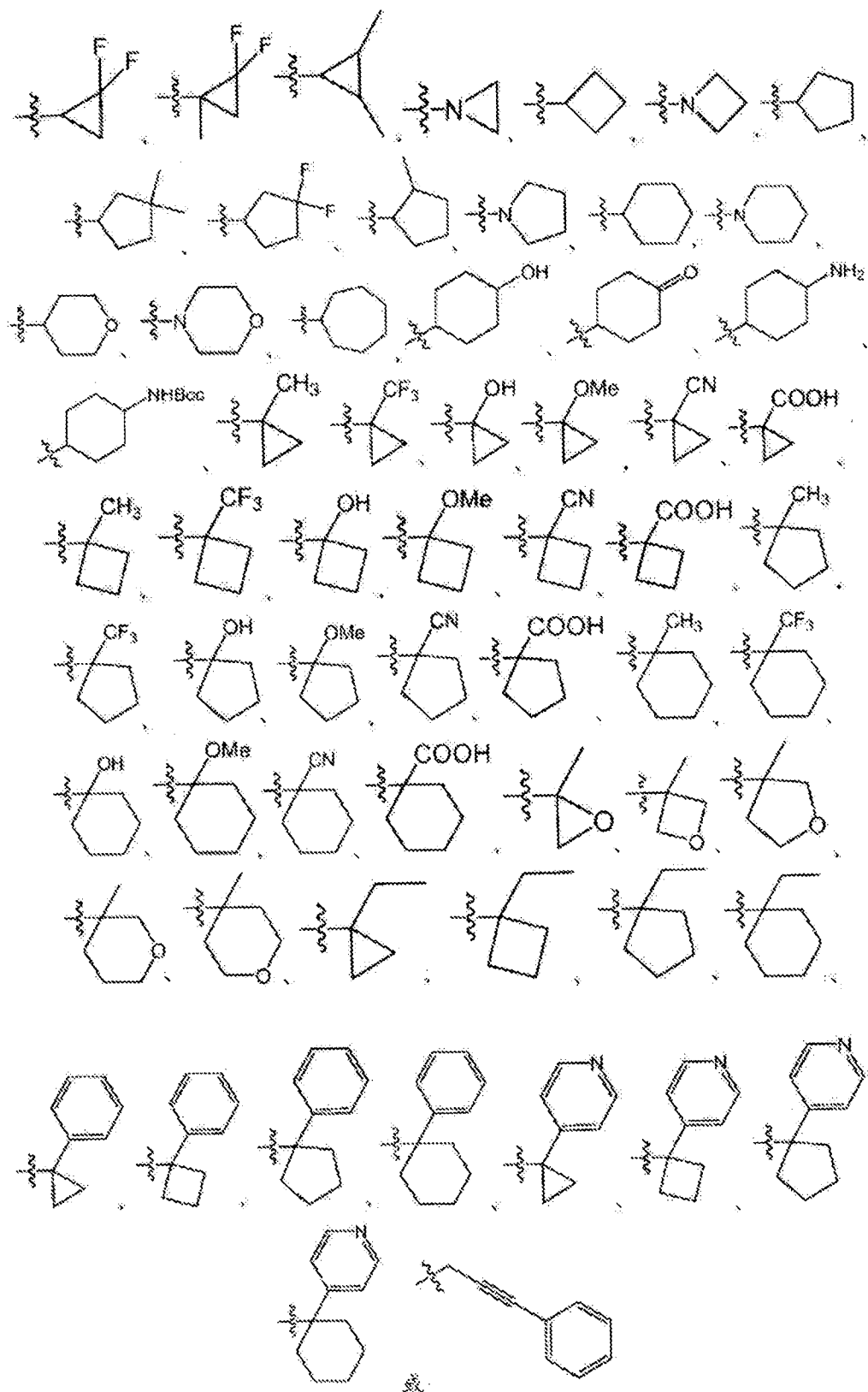
[0185] 术语“羧基胺”和“羧基-烷氧化物”分别是指结构-C(O)N(R¹⁵)₂和-C(O)-OR¹⁵。本发明的优选羧基胺和羧基-烷氧化物部分包括其中R¹⁵在每次出现时都独立地是H、C₁₋₆烷基、C₂₋₈烯基、C₂₋₈炔基、环烷基(例如C₃₋₆环烷基)、芳基、杂环基或杂芳基的那些。仅举一个实例来说,-C(O)N(R¹⁵)₂可为-C(O)N(CH₃)₂。

[0186] 如本文所用,“环烷基”无论单独或作为另一基团的一部分使用都是指例如具有 3 至 14 个环碳原子,优选 3 至 7 或 3 至 6 个环碳原子,或甚至 3 至 4 个环碳原子,并且任选含有一个或多个(例如 1、2 或 3 个)双键或三键的非芳族含碳环,包括环化烷基、烯基和炔基。环烷基可为单环(例如环己基)或多环(例如含有稠环,桥环和/或螺环系统),其中碳原子位于环系统的内部或外部。环烷基的任何适合环位置都可共价连接于定义的化学结构。环烷基环可任选取代。环烷基的非限制性实例包括:环丙基、2-甲基-环丙基、环丙烯基、环丁基、2,3-二羟基环丁基、环丁烯基、环戊基、环戊烯基、环戊二烯基、环己基、环己烯基、环庚基、环辛烷基、十氢萘基、2,5-二甲基环戊基、3,5-二氯环己基、4-羟基环己基、3,3,5-三甲基环己-1-基、八氢并环戊二烯基、八氢-1H-茚基、3a,4,5,6,7,7a-六氢-3H-茚-4-基、十氢甘菊环基;双环[6.2.0]癸基、十氢萘基和十二氢-1H-茚基。术语“环烷基”也包括是双环烃环的碳环,其非限制性实例包括双环-[2.1.1]己烷基、双环[2.2.1]庚烷基、双环[3.1.1]庚烷基、1,3-二甲基[2.2.1]庚烷-2-基、双环[2.2.2]辛烷基和双环[3.3.3]十一烷基。

[0187] “卤代烷基”意图包括具有指定数目的碳原子,被 1 个或多个卤素取代的支链饱和脂族烃基团与直链饱和脂族烃基团两者。卤代烷基包括全卤代烷基,其中烷基的所有氢都被卤素置换(例如 $-\text{CF}_3$ 、 $-\text{CF}_2\text{CF}_3$)。除卤素之外,卤代烷基也可任选被一个或多个取代基取代。卤代烷基的实例包括但不限于氟甲基、二氯乙基、三氟甲基、三氯甲基、五氟乙基和五氯乙基。

[0188] 烷基、烯基、炔基、环烷基和环杂烷基的非限制性实例包括至少以下:甲基、甲胺(或其经保护的类似物)、甲氧基、乙基、乙胺(或其经保护的类似物)、乙氧基、正丙基、丙胺(或其经保护的类似物)、正丙氧基、异丙基、异丙胺(或其经保护的类似物)、异丙氧基、正丁基、正丁胺(或其经保护的类似物)、正丁氧基、仲丁基、仲丁胺(或其经保护的类似物)、仲丁氧基、叔丁基、叔丁胺(或其经保护的类似物)、叔丁氧基、乙烯基、

[0189]



[0191] 术语“烷氧基”是指基团 -O- 烷基, 其中烷基如上所定义。烷氧基任选可被取代。术语 C₃-C₆ 环状烷氧基是指含有 3 至 6 个碳原子以及至少一个氧原子的环 (例如四氢呋喃、

四氢-2H-吡喃)。C₃-C₆环状烷氧基任选可被取代。

[0192] 术语“脒”是指式 -C(NR¹⁵)(R¹⁵)₂ 的结构,其中 R¹⁵是在以下定义。本发明的优选脒部分包括其中 R¹⁵在每次出现时都独立地是 H、C₁₋₆烷基、C₁₋₆卤代烷基、C₂₋₈烯基、C₂₋₈炔基、环烷基(例如 C₃₋₆环烷基)、芳基、杂环基或杂芳基的那些。

[0193] 其中单独或作为另一基团的一部分使用的术语“芳基”在本文中定义为具有 6 个碳成员的不饱和芳族单环或具有 10 至 14 个碳成员的不饱和芳族多环。芳基环可为例如苯基或萘基环,各自任选被一个或多个能够置换一个或多个氢原子的部分取代。芳基的非限制性实例包括:苯基、亚萘-1-基、亚萘-2-基、4-氟苯基、2-羟基苯基、3-甲基苯基、2-氨基-4-氟苯基、2-(N,N-二乙基氨基)苯基、2-氰基苯基、2,6-二-叔丁基苯基、3-甲氧基苯基、8-羟基亚萘-2-基、4,5-二甲氧基亚萘-1-基和 6-氰基-亚萘-1-基。芳基也包括例如与一个或多个饱和或部分饱和碳环耦合的苯基或萘基环(例如双环[4.2.0]辛-1,3,5-三烯基、苯并[1,3]间二氧杂环戊烯基、茚满基),其可在芳族和/或饱和或部分饱和环的一个或多个碳原子处被取代。

[0194] 术语“芳基烷基”或“芳烷基”是指基团-烷基-芳基,其中烷基和芳基是如本文所定义。本发明的芳烷基被任选地取代。芳基烷基的实例包括例如苯甲基、1-苯基乙基、2-苯基乙基、3-苯基丙基、2-苯基丙基、苄基甲等。

[0195] 术语“杂环(heterocyclic/heterocycle)”和/或“杂环基”无论单独或作为另一基团的一部分使用都在本文中定义为一个或多个具有 3 至 20 个原子的环,其中至少一个环中的至少一个原子是选自氮(N)、氧(O)或硫(S)的杂原子,并且其中此外,包括杂原子的环是非芳族。在包括 2 个或更多个稠环的杂环基团中,携带非杂原子的环可为芳基(例如吡啶基、四氢喹啉基、苯并二氢吡喃基)。示例性杂环基团具有 3 至 14 个环原子,其中 1 至 5 个是独立地选自氮(N)、氧(O)或硫(S)的杂原子。杂环基团中的一个或多个 N 或 S 原子可被氧化。杂环基团可被任选取代。

[0196] 具有单环的杂环单元的非限制性实例包括:二氮杂环丙烯基、氮杂环丙烷基、尿唑基、氮杂环丁烷基、噻唑烷基、噁唑烷酮基、噻唑烷酮基、乙内酰脲基、四氢呋喃基、吡咯烷基、吗啉基、哌嗪基、哌啶基、二氢吡喃基、四氢吡喃基、哌啶-2-酮基(戊内酰胺)、2,3,4,5-四氢-1H-氮杂卓基、2,3-二氢-1H-吡啶和 1,2,3,4-四氢-喹啉。具有 2 个或更多个环的杂环单元的非限制性实例包括:六氢-1H-吡咯嗪基、3a,4,5,6,7,7a-六氢-1H-苯并[d]咪唑基、3a,4,5,6,7,7a-六氢-1H-吡啶基、1,2,3,4-四氢喹啉基、苯并二氢吡喃基、异苯并二氢吡喃基、吡啶基、异吡啶基和十氢-1H-环辛并[b]吡咯基。

[0197] 术语“杂芳基”无论单独或作为另一基团的一部分使用都在本文中定义为一个或多个具有 5 至 20 个原子的环,其中至少一个环中的至少一个原子是选自氮(N)、氧(O)或硫(S)的杂原子,并且其中此外,至少一个包括杂原子的环是芳族。在包括 2 个或更多个稠环的杂芳基中,携带非杂原子的环可为碳环(例如 6,7-二氢-5H-环戊并噻啶)或芳基(例如苯并呋喃基、苯并苯硫基、吡啶基)。示例性杂芳基具有 5 至 14 个环原子,并且含有 1 至 5 个独立地选自氮(N)、氧(O)或硫(S)的杂原子。杂芳基中的一个或多个 N 或 S 原子可被氧化。杂芳基可被取代。含有单环的杂芳基环的非限制性实例包括:1,2,3,4-四唑基、[1,2,3]三唑基、[1,2,4]三唑基、三嗪基、噻唑基、1H-咪唑基、噁唑基、呋喃基、噻吩基、噻啶基、2-苯基噻啶基、吡啶基、3-甲基吡啶基和 4-二甲基氨基吡啶基。含有 2 个或更多个

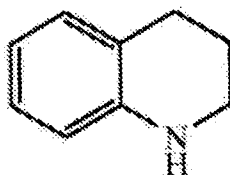
稠环的杂芳基环的非限制性实例包括：苯并呋喃基、苯并苯硫基、苯并噁唑基、苯并噻唑基、苯并三唑基、噌啉基、蔡啶基、菲啶基、7H- 嘌呤基、9H- 嘌呤基、6- 氨基 -9H- 嘌呤基、5H- 吡咯并 [3, 2-d] 嘧啶基、7H- 吡咯并 [2, 3-d] 嘧啶基、吡啶并 [2, 3-d] 嘧啶基、2- 苯基苯并 [d] 噻唑基、1H- 吡啶基、4, 5, 6, 7- 四氢 -1-H- 吡啶基、喹啉基、5- 甲基喹啉基、喹啉基、喹啉基、8- 羟基 - 喹啉基和异喹啉基。

[0198] 如上所述的杂芳基的一个非限制性实例是 C_1 - C_5 杂芳基，其具有 1 至 5 个碳环原子以及至少一个是独立地选自氮 (N)、氧 (O) 或硫 (S) 的杂原子的其它环原子（优选 1 至 4 个是杂原子的其它环原子）。 C_1 - C_5 杂芳基的实例包括但不限于三嗪基、噻唑 -2- 基、噻唑 -4- 基、咪唑 -1- 基、1H- 咪唑 -2- 基、1H- 咪唑 -4- 基、异噁唑啉 -5- 基、呋喃 -2- 基、呋喃 -3- 基、噻吩 -2- 基、噻吩 -4- 基、嘧啶 -2- 基、嘧啶 -4- 基、嘧啶 -5- 基、吡啶 -2- 基、吡啶 -3- 基和吡啶 -4- 基。

[0199] 除非另外指示，否则当两个取代基一起形成具有指定数目的环原子的碳环或杂环（例如 R^2 和 R^3 连同它们所连接的氮 (N) 一起形成具有 3 至 7 个环成员的环）时，环可具有碳原子以及任选一个或多个（例如 1 至 3 个）独立地选自氮 (N)、氧 (O) 或硫 (S) 的其它杂原子。碳环或杂环可为饱和的或部分饱和的，并且可任选取代。

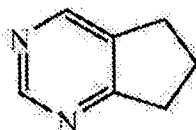
[0200] 出于本发明的目的，包含单一杂原子的稠环单元以及螺环、双环等将被视为属于对应于含杂原子环的环家族。举例来说，具有下式的 1, 2, 3, 4- 四氢喹啉：

[0201]



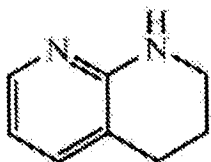
[0202] 出于本发明的目的被视为杂环单元。具有下式的 6, 7- 二氢 -5H- 环戊并嘧啶：

[0203]



[0204] 出于本发明的目的被视为杂芳基单元。当稠环单元在饱和环与芳基环两者中均含有杂原子时，芳基环将占主导地位，并且决定环所归于的种类类型。举例来说，具有下式的 1, 2, 3, 4- 四氢 -[1, 8] 蔡啶：

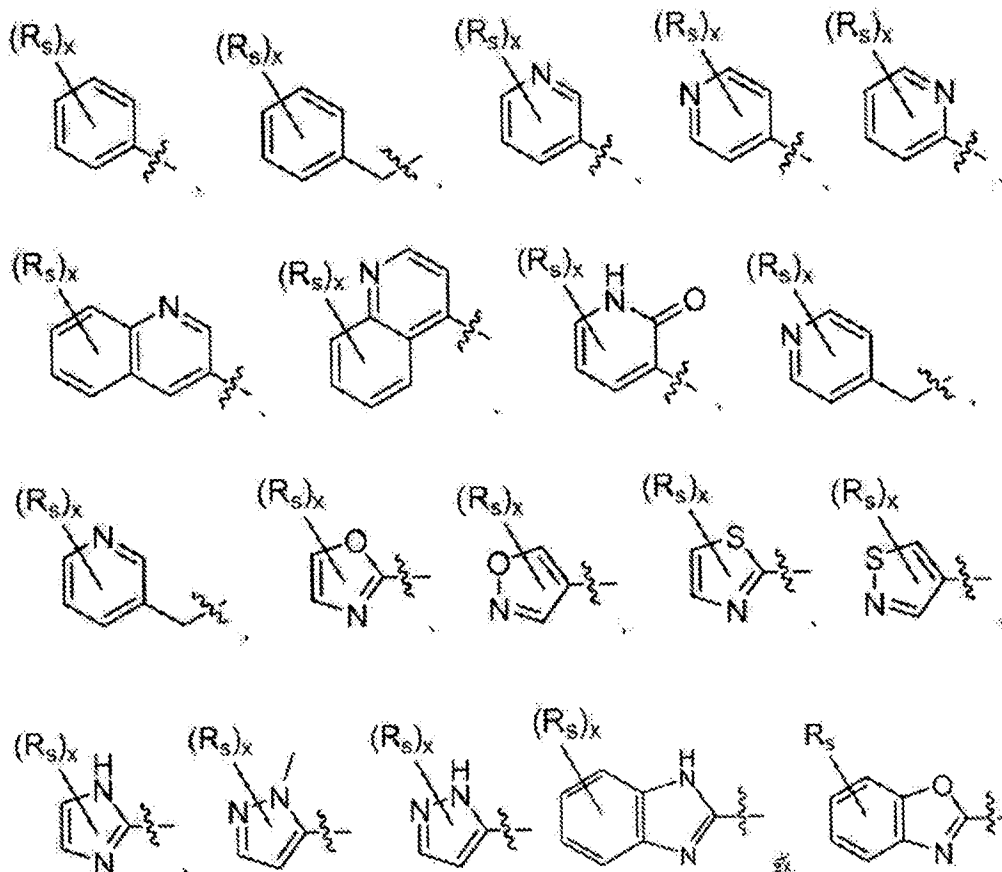
[0205]



[0206] 出于本发明的目的被视为杂芳基单元。

[0207] 芳基、杂芳基、烷芳基和烷基杂芳基（或杂烷芳基）的非限制性实例包括至少以下结构：

[0208]



[0209] 其中

[0210] R_s 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化 C_{1-6} 烷基（例如 $-CH_3$ 、 $-CH_2F$ 、 $-CF_2H$ 、 $-CF_3$ ）、 $-O-(C_{1-6}$ 烷基），或当两个 R_s 一起形成稠环部分或杂环部分时；并且

[0211] x 是 0、1、2 或 3。

[0212] 应了解，当使用时，指示符  指示当化合价允许时，取代基可存在于任何可用环成员上（包括在氮上进行烷基取代）。对于稠合双环系统，相同指示符暗示当化合价允许时，取代基可存在于任一环的环成员上。类似地，尽管以上显示的连接点是针对特定碳原子，但应了解，芳基或杂芳基环可连接于化合价允许的任何碳或杂原子。

[0213] 无论何时术语或它们的任一前缀词根出现在取代基的名称中，所述名称都应解释为包括本文提供的那些限制。举例来说，无论何时术语“烷基”或“芳基”或它们的任一前缀词根出现在取代基的名称（例如芳基烷基、烷基氨基）中，所述名称都应解释为包括以上对“烷基”和“芳基”给出的那些限制。

[0214] 术语“被取代”在整篇说明书中使用。术语“被取代”在本文中定义无论是非环部分还是环状部分的一个或多个氢原子被一个取代基或若干个（例如 1 至 10 个）取代基置换，所述取代基如本文在以下所定义。取代基能够一次置换单一部分的一个或两个氢原子。此外，这些取代基可置换两个邻近碳上的两个氢原子以形成所述取代基、新部分或单元。举例来说，需要单一氢原子置换的经取代单元包括卤素、羟基等。两个氢原子置换包括羰基、

脲基等。自邻近碳原子进行两个氢原子置换包括环氧基等。术语“被取代”在整篇本说明书中用于指示一部分的一个或多个氢原子可被取代基置换。当一部分被描述为“被取代”时，可置换任何数目的氢原子。举例来说，二氟甲基是被取代的 C_1 烷基；三氟甲基是被取代的 C_1 烷基；4-羟基苯基是被取代的芳族环；(N,N-二甲基-5-氨基)辛烷基是被取代的 C_8 烷基；3-胍基丙基是被取代的 C_3 烷基；并且 2-羧基吡啶基是被取代的杂芳基。

[0215] 本文定义的可变基团（例如本文定义的烷基、烯基、炔基、环烷基、烷氧基、芳基氧基、芳基、杂环和杂芳基）无论单独还是作为另一基团的一部分使用都可被任选取代。将如此指示任选取代的基团。术语“任选 (optional/optionally)”在取代基的情形下暗示指定的取代基可或可不存在，并且这些条件各自代表本发明的单独实施方案。

[0216] 以下是可取代一部分上的氢原子的取代基的非限制性实例：卤素（氯 (Cl)、溴 (Br)、氟 (F) 和碘 (I)）、 $-CN$ 、 $-NO_2$ 、氧代 ($=O$)、 $-OR^{14}$ 、 $-SR^{14}$ 、 $-N(R^{14})_2$ 、 $-NR^{14}C(O)R^{14}$ 、 $-SO_2R^{14}$ 、 $-SO_2OR^{14}$ 、 $-SO_2N(R^{14})_2$ 、 $-C(O)R^{14}$ 、 $-C(O)OR^{14}$ 、 $-C(O)N(R^{14})_2$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 烷氧基、 C_{2-8} 烯基、 C_{2-8} 炔基、 C_{3-11} 环烷基、芳基、杂环或杂芳基，其中烷基、卤代烷基、烯基、炔基、烷氧基、环烷基、芳基、杂环和杂芳基各自任选被 1-10 个（例如 1-6 个或 1-4 个）独立地选自卤素、 $-CN$ 、 $-NO_2$ 、氧代和 R^{14} 的基团取代；其中 R^{14} 在每次出现时都独立地是氢、 $-OR^{15}$ 、 $-SR^{15}$ 、 $-C(O)R^{15}$ 、 $-C(O)OR^{15}$ 、 $-C(O)N(R^{15})_2$ 、 $-SO_2R^{15}$ 、 $-S(O)_2OR^{15}$ 、 $-N(R^{15})_2$ 、 $-NR^{15}C(O)R^{15}$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{2-8} 烯基、 C_{2-8} 炔基、环烷基（例如 C_{3-6} 环烷基）、芳基、杂环或杂芳基，或两个 R^{14} 单元连同它们所结合的原子一起形成任选取代的碳环或杂环，其中所述碳环或杂环具有 3 至 7 个环原子；其中 R^{15} 在每次出现时都独立地是氢、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{2-8} 烯基、 C_{2-8} 炔基、环烷基（例如 C_{3-6} 环烷基）、芳基、杂环或杂芳基，或两个 R^{15} 单元连同它们所结合的原子一起形成任选取代的碳环或杂环，其中所述碳环或杂环优选具有 3 至 7 个环原子。视可取代氢原子的数目而定，可存在 0、1、2、3、4、5 或 6 个独立地取代部分上的氢原子的取代基。

[0217] 在一些实施方案中，取代基选自

[0218] i) $-OR^{16}$ ；例如 $-OH$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-OCH_2CH_2CH_3$ ；

[0219] ii) $-C(O)R^{16}$ ；例如 $-COCH_3$ 、 $-COCH_2CH_3$ 、 $-COCH_2CH_2CH_3$ ；

[0220] iii) $-C(O)OR^{16}$ ；例如 $-CO_2CH_3$ 、 $-CO_2CH_2CH_3$ 、 $-CO_2CH_2CH_2CH_3$ ；

[0221] iv) $-C(O)N(R^{16})_2$ ；例如 $-CONH_2$ 、 $-CONHCH_3$ 、 $-CON(CH_3)_2$ ；

[0222] v) $-N(R^{16})_2$ ；例如 $-NH_2$ 、 $-NHCH_3$ 、 $-N(CH_3)_2$ 、 $-NH(CH_2CH_3)$ ；

[0223] vi) 卤素： $-F$ 、 $-Cl$ 、 $-Br$ 和 $-I$ ；

[0224] vii) $-CH_eX_m$ ；其中 X 是卤素， m 是 0 至 2， $e+m=3$ ；例如 $-CH_2F$ 、 $-CHF_2$ 、 $-CF_3$ 、 $-CCl_3$ 或 $-CBr_3$ ；

[0225] viii) $-SO_2R^{16}$ ；例如 $-SO_2H$ 、 $-SO_2CH_3$ 、 $-SO_2C_6H_5$ ；

[0226] ix) C_1-C_6 直链、支链或环状烷基；

[0227] x) 氰基

[0228] xi) 硝基；

[0229] xii) $N(R^{16})C(O)R^{16}$ ；

[0230] xiii) 氧代 ($=O$)；

[0231] xiv) 杂环；以及

[0232] xv) 杂芳基。

[0233] 其中各 R^{16} 独立地是氢、任选取代的 C_1-C_6 直链或支链烷基（例如任选取代的 C_1-C_4 直链或支链烷基）、或任选取代的 C_3-C_6 环烷基（例如任选取代的 C_3-C_4 环烷基）；或两个 R^{16} 单元可一起形成包含 3-7 个环原子的环。在某些方面，各 R^{16} 独立地是氢、任选被卤素取代的 C_1-C_6 直链或支链烷基、或 C_3-C_6 环烷基或 $C_{0-6}-[C_3-C_6$ 环烷基]。

[0234] 在本说明书中的各处，以群组或范围形式公开化合物的取代基。所述描述特别意在包括所述群组和范围的成员的各个和每个个别子组合。举例来说，术语“ C_{1-6} 烷基”特别意图单独地公开 C_1 、 C_2 、 C_3 、 C_4 、 C_5 、 C_6 、 C_1-C_6 、 C_1-C_5 、 C_1-C_4 、 C_1-C_3 、 C_1-C_2 、 C_2-C_6 、 C_2-C_5 、 C_2-C_4 、 C_2-C_3 、 C_3-C_6 、 C_3-C_5 、 C_3-C_4 、 C_4-C_6 、 C_4-C_5 和 C_5-C_6 烷基。

[0235] 出于本发明的目的，术语“化合物”、“类似物”和“物质组合物”同样代表核衣壳装配抑制剂，尤其但不仅限于包括本文所述的前基因组 RNA 衣壳化抑制剂，包括所有对映异构形式、非对映异构形式、盐等，并且术语“化合物”、“类似物”和“物质组合物”在整篇本说明书中可互换使用。

[0236] 本文所述的化合物可含有不对称原子（也称为手性中心），并且一些化合物可含有一个或多个不对称原子或中心，此可因此产生光学异构体（对映异构体）和非对映异构体。本教义和本文公开的化合物包括所述对映异构体和非对映异构体、以及外消旋和拆分对映异构体纯 R 和 S 立体异构体、以及 R 和 S 立体异构体的其它混合物及其药学上可接受的盐。光学异构体可通过为本领域技术人员所知的标准程序以纯形式获得，所述程序包括但不限于形成非对映异构盐、动力学拆分和不对称合成。本教义也涵盖含有烯基部分（例如烯和亚胺）的化合物的顺式和反式异构体。也应了解，本教义涵盖所有可能的区域异构体及其混合物，其可通过为本领域技术人员所知，并且包括但不限于柱色谱法、薄层色谱法和高效液相色谱法的标准分离程序以纯形式获得。对于描述为光学异构体或可包括光学异构体的那些化合物，各种实施方案包括至少个别异构体或其增浓或外消旋混合物。

[0237] 可使用有机和无机碱形成本教义的可具有酸性部分的化合物的药学上可接受的盐。视可用于去质子化的酸性氢的数目而定，涵盖单阴离子盐与多阴离子盐两者。用碱形成的适合盐包括金属盐，如碱金属或碱土金属盐，例如钠盐、钾盐或镁盐；氨盐和有机胺盐，如用吗啉、硫代吗啉、哌啶、吡咯烷、单低级烷基胺、二低级烷基胺或三低级烷基胺（例如乙基-叔丁胺、二乙胺、二异丙胺、三乙胺、三丁胺或二甲基丙胺）、或单羟基低级烷基胺、二羟基低级烷基胺或三羟基低级烷基胺（例如单乙醇胺、二乙醇胺或三乙醇胺）形成的那些。无机碱的特定非限制性实例包括 $NaHCO_3$ 、 Na_2CO_3 、 $KHCO_3$ 、 K_2CO_3 、 $CaCO_3$ 、 $LiOH$ 、 $NaOH$ 、 KOH 、 NaH_2PO_4 、 Na_2HPO_4 和 Na_3PO_4 。也可形成内盐。类似地，当本文公开的化合物含有碱性部分时，可使用有机酸和无机酸形成盐。举例来说，可由以下酸形成盐：乙酸、丙酸、乳酸、苯磺酸、苯甲酸、樟脑磺酸、柠檬酸、酒石酸、丁二酸、二氯乙酸、乙烯磺酸、甲酸、反丁烯二酸、葡萄糖酸、谷氨酸、马尿酸、氢溴酸、盐酸、羟乙磺酸、乳酸、顺丁烯二酸、苹果酸、丙二酸、杏仁酸、甲烷磺酸、粘液酸、茶磺酸、硝酸、草酸、帕莫酸、泛酸、磷酸、邻苯二甲酸、丙酸、丁二酸、硫酸、酒石酸、甲苯磺酸和樟脑磺酸以及其它已知的药学上可接受的酸。

[0238] 如本文所用的术语“治疗 (treat/treating/treatment)”是指部分或完全减轻、抑制、改善和 / 或缓和怀疑患者所罹患的病症。

[0239] 如本文所用，“治疗有效”和“有效剂量”是指引发所需生物活性或作用的物质或

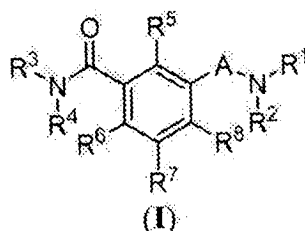
量。“治疗有效量”是指化合物的当向受试者施用以治疗疾病或病状时,足以实现对所述疾病或病状的所述治疗的量。“治疗有效量”可视化合物、疾病或病状和它的严重性、以及待治疗的受试者的年龄、重量等而变化。

[0240] 除当指示时之外,术语“受试者”或“患者”可互换使用,并且是指如人患者和非人灵长类动物的哺乳动物、以及如兔、大鼠和小鼠的实验动物和其它动物。因此,如本文所用的术语“受试者”或“患者”是指可向其施用本发明化合物的任何哺乳动物患者或受试者。在本发明的一示例性实施方案中,为鉴定用于根据本发明方法治疗的主题患者,接受的筛选方法用于确定与靶向或怀疑的疾病或病状相关的风险因素,或确定受试者的现存疾病或病状的状态。这些筛选方法包括例如常规病情检查以确定可与靶向或怀疑的疾病或病状相关的风险因素。这些和其它常规方法允许临床医师选择需要使用本发明的方法和化合物治疗的患者。

[0241] 化合物和组合物

[0242] 用于治疗病毒(包括乙型肝炎病毒(HBV))感染和相关病状的本发明的化合物和组合物包括具有式(I)的所有对映异构和非对映异构形式及其药学上接受的盐:

[0243]



[0244] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

[0245] A 选自由 SO_2 和 CO 组成的组;

[0246] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组; R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-\text{C}_{1-6}-$ 烷氧化物、 $-\text{SO}_2-\text{C}_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基;

[0247] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组; R^2 也可或者或另外任选包括任选取代的 C_{3-7} 环烷基或任选取代的杂环;或

[0248] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环(包括双环或金刚烷基结构);并且

[0249] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组; R^3 也可任选包括任选取代的 C_{1-6} 直链烷基;

[0250] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组;

[0251] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组; R^5 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$;

[0252] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组;在一些实施方案中, R^6 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$; R^6 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$;或

[0253] R^4 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；并且

[0254] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0255] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；或

[0256] R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的碳环或杂环；并且

[0257] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基组成的组； R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；

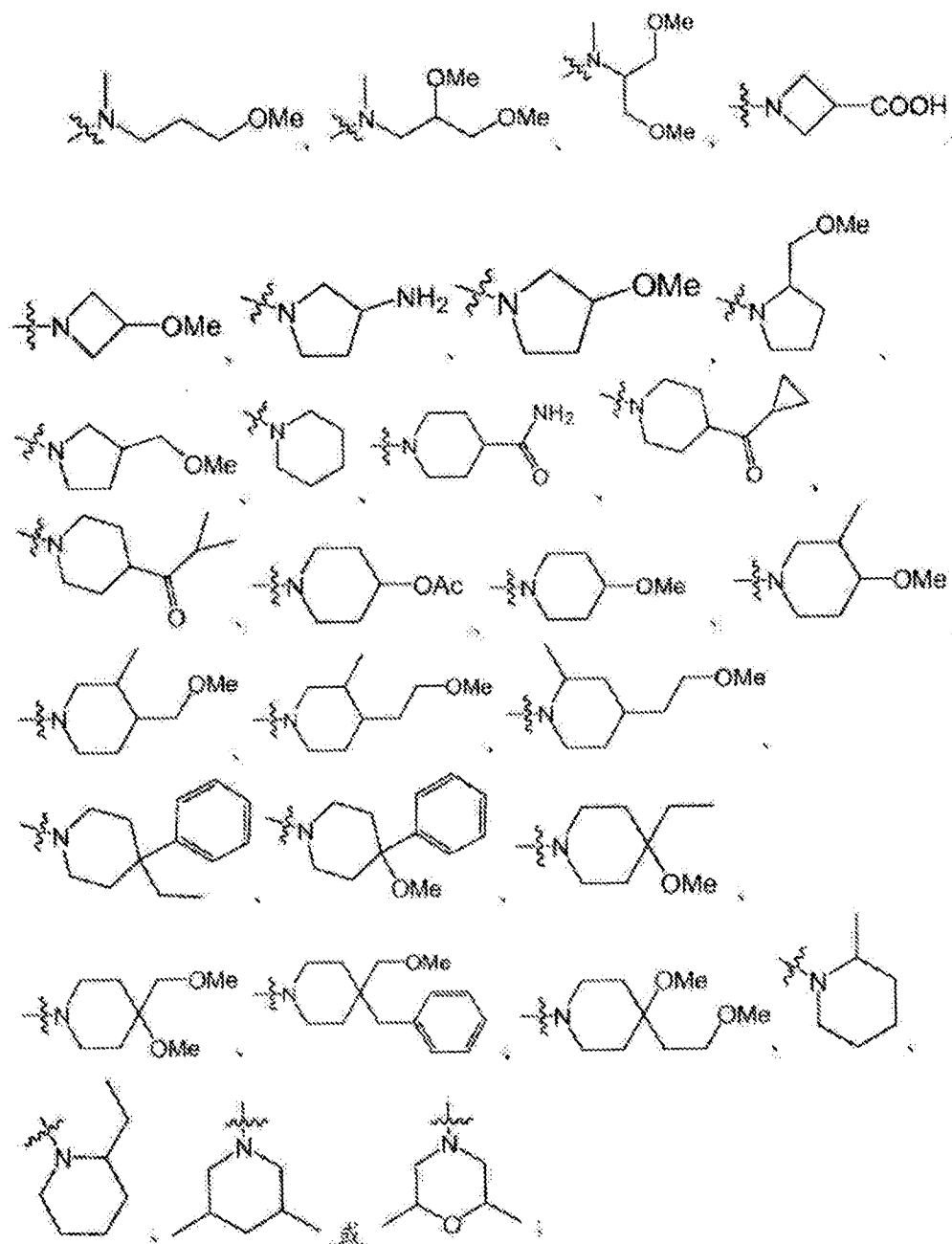
[0258] 条件是当 A 是 SO_2 ； R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环；并且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环时，那么以下 (a) 至 (d) 任何一个都不适用：

[0259] (a) R^3 是任选取代的苯基，并且 R^1 或 R^2 单独地或当一起时含有羟基，或

[0260] (b) R^3 是任选取代的烷基或苯基，并且 $N(R^1)(R^2)$ 是任选取代的哌嗪或

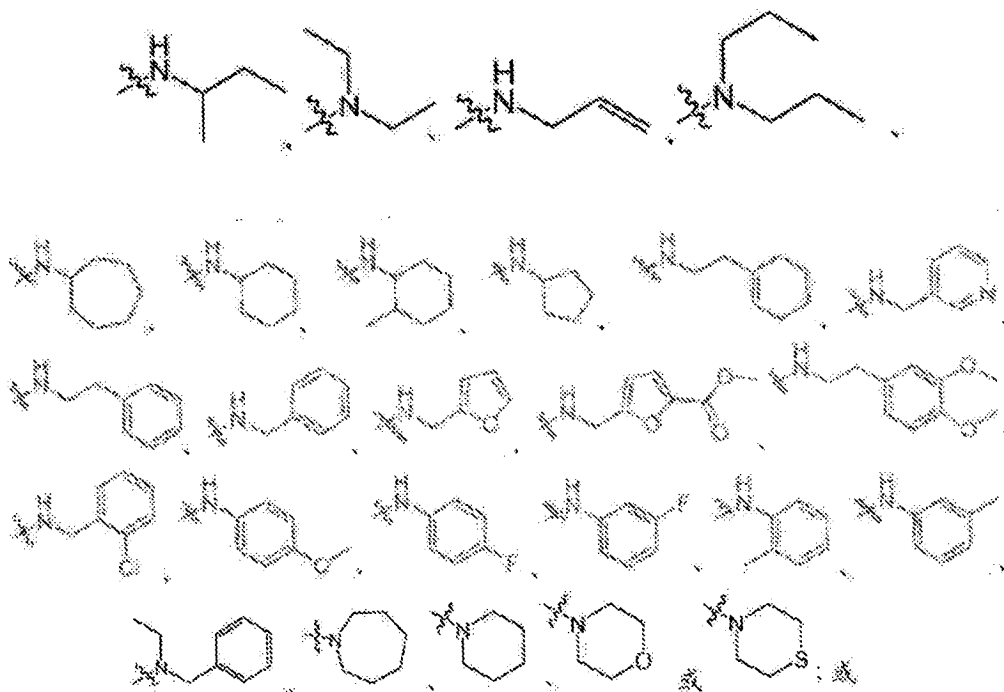


[0261]



[0262] (c) R^3 是任选取代的烷基、芳基或烷芳基, 并且 $N(R^1)(R^2)$ 是

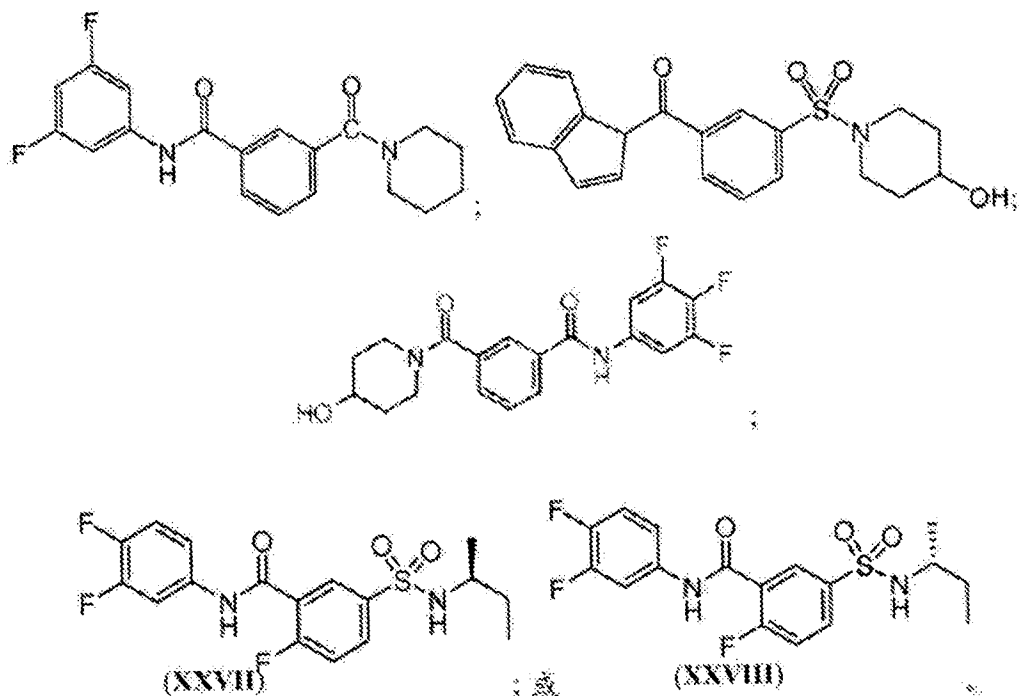
[0263]



[0264] (d) R^3 或 R^4 是未被取代或被单取代的芳基、或未被取代或被单取代的芳烷基、或未被取代或被单取代的杂芳基,并且 R^1 和 R^2 连同它们所结合的原子一起形成具有6至12个原子的任选取代的杂环结构;或

[0265] 条件是化合物不是3-([(二环丙基甲基)氨基]磺酰基)-N-(4-异丙氧基苯基)苯甲酰胺;或3-([2-(1H-苯并咪唑-2-基)丙基]氨基)磺酰基)-N-(4-异丙氧基苯基)苯甲酰胺;或3-[(环己基氨基)磺酰基]-N-(4-异丙基苯基)苯甲酰胺;或3-(苯胺基磺酰基)-N-(4-异丙基苯基)苯甲酰胺;或5-[(3-[(4-甲氧基苯基)氨基]羰基)苯基]磺酰基]氨基]戊酸;或3-[(叔丁基氨基)磺酰基]-N-(4-甲氧基苯基)苯甲酰胺;或(3S)-1-[3-[(5-异丙氧基吡啶-2-基)氨基]羰基)苯基]磺酰基]哌啶-3-甲酰胺;或(3R)-1-[3-[(5-异丙氧基吡啶-2-基)氨基]羰基)苯基]磺酰基]哌啶-3-甲酰胺;或3-(哌啶-1-基磺酰基)-N-[(1S)-1,2,3,4-四氢萘-1-基]苯甲酰胺;或N-(5-溴-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺;或N-(3-甲氧基-5-苯基吡啶-2-基)-3-(吡咯烷-1-基磺酰基)苯甲酰胺;或N-(3-甲氧基-5-苯氧基吡啶-2-基)-3-(吡咯烷-1-基磺酰基)苯甲酰胺;或N-[3-甲氧基-5-(苯硫基)吡啶-2-基]-3-(吡咯烷-1-基磺酰基)苯甲酰胺;或N-(5-乙基-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺;或N-(3-甲氧基-5-乙烯基吡啶-2-基)-3-(哌啶-1-基磺酰基)苯甲酰胺;或

[0266]



[0267] 式 (I) 化合物的一些实施方案也排除当 A 是 SO_2 ; R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环; 并且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环, R^3 是任选取代的烷基、芳基或烷芳基, 并且 $\text{N}(\text{R}^1)(\text{R}^2)$ 是任选取代的哌啶时的那些化合物。

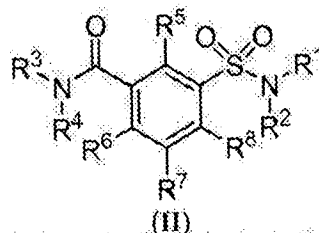
[0268] 本发明的实施方案包括式 (I) 化合物, 其中 A 是 SO_2 ;

[0269] R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的碳环或杂环; 并且

[0270] R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的碳环或杂环;

[0271] 由此提供具有式 (II) 的化合物,

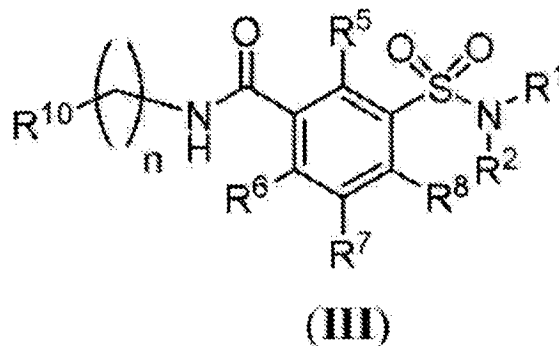
[0272]



[0273] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 并且考虑上述排除。在一些实施方案中, R^1 至 R^8 如对于式 (I) 化合物所定义。在其它独立实施方案中, R^1 至 R^8 如下所定义。

[0274] 本发明的实施方案包括其中 A 是 SO_2 的式 (I) 化合物, 由此提供具有式 (III) 的化合物,

[0275]



[0276] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

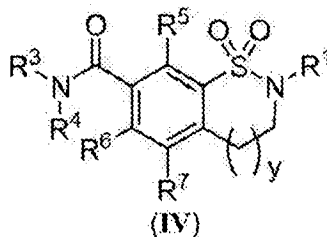
[0277] R^{10} 选自由任选取代的芳基和任选取代的杂芳基组成的组;并且

[0278] n 是 0 或 1。

[0279] 在一些实施方案中, R^1 、 R^2 以及 R^5 至 R^8 如对于式(I)化合物所定义。在其它独立实施方案中, R^1 、 R^2 以及 R^5 至 R^8 如下所定义。

[0280] 本发明的实施方案包括其中 A 是 SO_3 的式(I)化合物,由此提供具有式(IV)的化合物,

[0281]

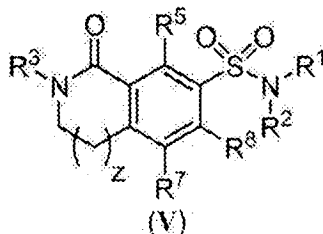


[0282] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中: y 是 0 或 1。在一些实施方案中, y 是 2。

[0283] 在一些实施方案中, R^1 以及 R^3 至 R^8 如对于式(I)化合物所定义。在其它独立实施方案中, R^1 以及 R^3 至 R^8 如下所定义。

[0284] 本发明的实施方案包括其中 A 是 SO_2 的式(I)化合物,由此提供具有式(V)的化合物,

[0285]



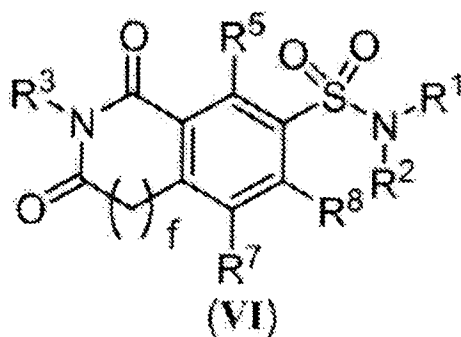
[0286] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

[0287] z 是 0 或 1。

[0288] 在一些实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 是如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如下所定义。

[0289] 本发明的实施方案包括具有式(VI)的化合物,

[0290]

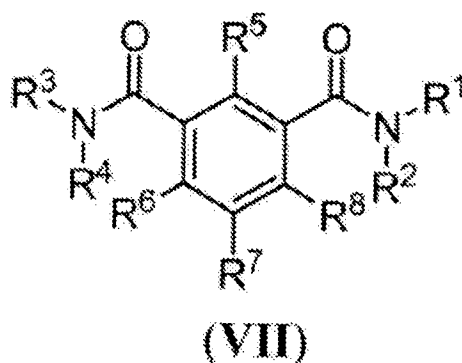


[0291] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:f是0或1。

[0292] 在一些实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如下所定义。

[0293] 本发明的实施方案包括其中A是CO的式(I)化合物,由此提供具有式(VII)的化合物,

[0294]

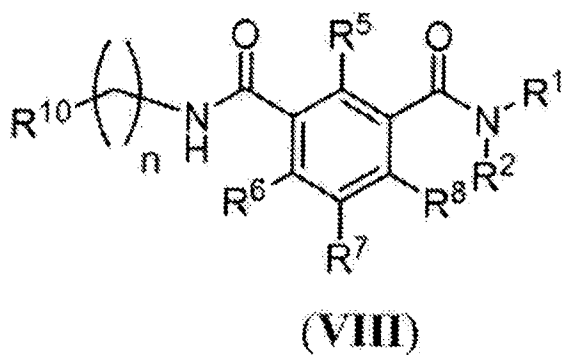


[0295] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0296] 在一些实施方案中, R^1 至 R^8 是如对于式(I)化合物所定义。在其它独立实施方案中, R^1 至 R^8 如下所定义。

[0297] 本发明的实施方案包括其中A是CO的式(I)化合物,由此提供具有式(VIII)的化合物,

[0298]



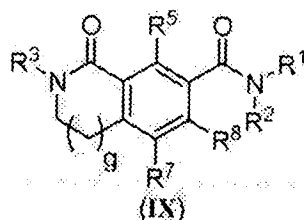
[0299] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

[0300] R^{10} 选自由任选取代的芳基和任选取代的杂芳基组成的组;并且n是0或1。

[0301] 在一些实施方案中, R^1 至 R^2 以及 R^5 至 R^8 如对于式 (I) 化合物所定义。在其它独立实施方案中, R^1 至 R^2 以及 R^5 至 R^8 如下所定义。

[0302] 本发明的实施方案包括具有式 (IX) 的化合物,

[0303]

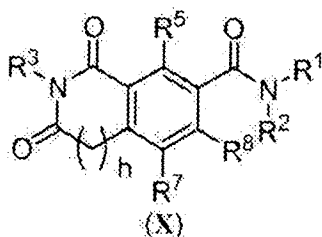


[0304] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 :g 是 0 或 1。

[0305] 在一些实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如对于式 (I) 化合物所定义。在其它实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如下所定义。

[0306] 本发明的实施方案包括其中 A 是 CO 的式 (I) 化合物, 由此提供具有式 (X) 的化合物,

[0307]

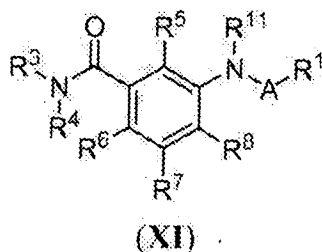


[0308] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中 :h 是 0 或 1。

[0309] 在一些实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如对于式 (I) 化合物所定义。在其它独立实施方案中, R^1 至 R^3 、 R^5 以及 R^7 至 R^8 如下所定义。

[0310] 本发明的实施方案包括用作核衣壳装配抑制剂, 尤其但不仅限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 的前基因组 RNA 衣壳化抑制剂的具有式 (XI) 的化合物,

[0311]



[0312] 包括其所有对映异构形式、非对映异构形式、水合物、溶剂合物、药学上可接受的盐、前药和复合物,

[0313] 其中:

[0314] A 选自由 SO_2 和 CO 组成的组;

[0315] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环

烷基、任选取代的芳基和任选取代的苯甲基组成的组；

[0316] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基；在一些实施方案中， R^3 也可包括任选取代的 C_{1-6} 直链烷基组成的组；

[0317] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组；

[0318] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0319] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；或

[0320] R^4 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；并且

[0321] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

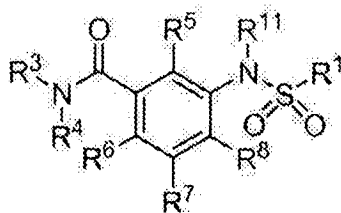
[0322] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0323] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基和任选取代的 C_{1-6} 卤代烷基组成的组； R^9 也可在每次出现时都或者或另外任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；并且

[0324] R^{11} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_3-7 环烷基组成的组。

[0325] 本发明的实施方案包括具有式 (XII) 的化合物，

[0326]



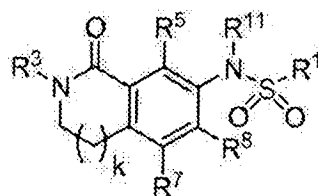
(XII)

[0327] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0328] 在一些实施方案中， R^1 、 R^3 至 R^8 以及 R^{11} 如对于式 (XI) 化合物所定义。在其它实施方案中， R^1 、 R^3 至 R^8 以及 R^{11} 如下所定义。

[0329] 本发明的实施方案包括具有式 (XIII) 的化合物，

[0330]



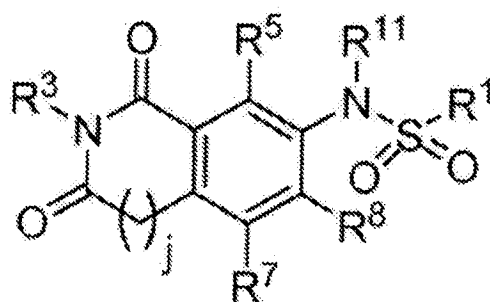
(XIII)

[0331] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:k是0或1。

[0332] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如对于式(XI)化合物所定义。在其它独立实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0333] 本发明的实施方案包括具有式(XIV)的化合物,

[0334]



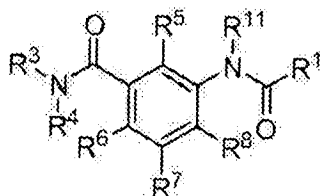
(XIV)

[0335] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:j是0或1。

[0336] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如对于式(XI)化合物所定义。在其它实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0337] 本发明的实施方案包括具有式(XV)的化合物,

[0338]



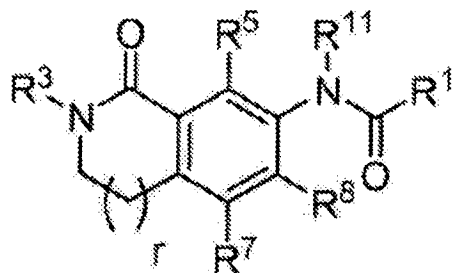
(XV)

[0339] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0340] 在一些实施方案中, R^1 、 R^3 至 R^8 以及 R^{11} 如对于式(XI)化合物所定义。在其它实施方案中, R^1 、 R^3 至 R^8 以及 R^{11} 如下所定义。

[0341] 本发明的实施方案包括具有式(XVI)的化合物,

[0342]



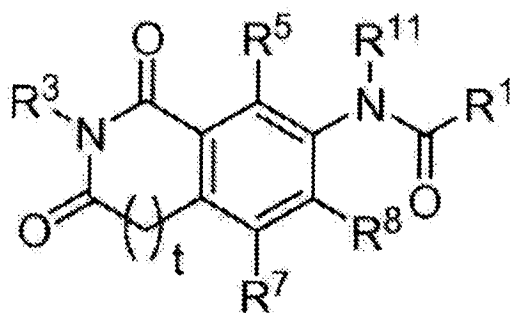
(XVI)

[0343] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:r 是 0 或 1。

[0344] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如对于式 (XI) 化合物所定义。在其它实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0345] 本发明的实施方案包括具有式 (XVII) 的化合物,

[0346]



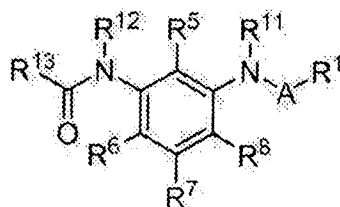
(XVII)

[0347] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:t 是 0 或 1。

[0348] 在一些实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如对于式 (XI) 化合物所定义。在其它实施方案中, R^1 、 R^3 、 R^5 、 R^7 、 R^8 和 R^{11} 如下所定义。

[0349] 本发明的实施方案包括用作核衣壳装配抑制剂,尤其但不限于包括用于治疗乙型肝炎病毒 (HBV) 感染和相关病状的 HBV 的前基因组 RNA 衣壳化抑制剂的具有式 (XVIII) 的化合物,

[0350]



(XVIII)

[0351] 包括其所有对映异构形式、非对映异构形式、水合物、溶剂合物、药学上可接受的盐、前药和复合物,其中:

[0352] A 选自由 SO_2 和 CO 组成的组;

[0353] R^4 选自由任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基、任取代的 C_{3-7} 环烷基、任取代的芳基和任取代的苯甲基组成的组；

[0354] R^5 选自由氢、卤素、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基、任取代的 C_{1-6} 卤代烷基和 OR^9 ； R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$ 组成的组；

[0355] R^6 选自由氢、卤素、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基、任取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0356] R^7 选自由氢、卤素、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基、任取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0357] R^8 选自由氢、卤素、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基、任取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0358] R^9 在每次出现时都独立地选自由氢、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基和任取代的 C_{3-7} 环烷基组成的组； R^9 也可在每次出现时都或者或另外任选独立地包括任取代的芳基、任取代的苯甲基、任取代的杂环基或任取代的杂芳基；

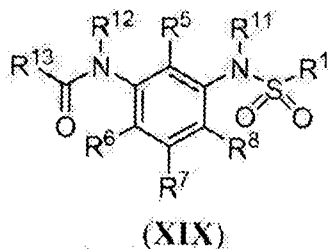
[0359] R^{11} 选自由氢、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基和任取代的 C_{3-7} 环烷基组成的组；

[0360] R^{12} 选自由氢、任取代的 C_{1-6} 直链烷基、任取代的 C_{1-6} 支链烷基和任取代的 C_{3-7} 环烷基组成的组；并且

[0361] R^{13} 选自由任取代的芳基、任取代的苯甲基、任取代的烷基芳基、任取代的杂芳基和任取代的烷基杂芳基组成的组。

[0362] 本发明的实施方案包括具有式 (XIX) 的化合物，

[0363]

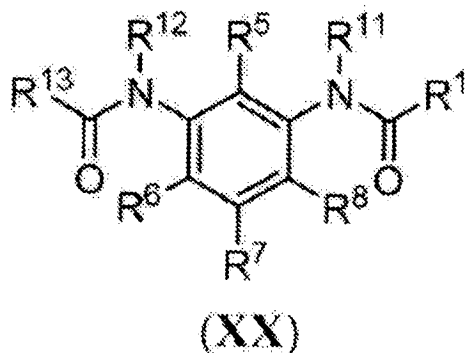


[0364] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0365] 在一些实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如对于式 (XVIII) 化合物所定义。在其它实施方案中， R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如下所定义。

[0366] 本发明的实施方案包括具有式 (XX) 的化合物，

[0367]

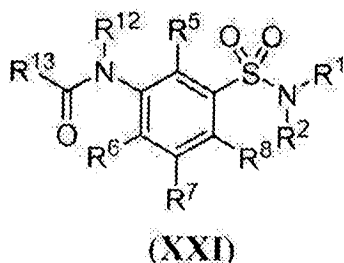


[0368] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物。

[0369] 在一些实施方案中, R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如对于式(XVIII)化合物所定义。在其它实施方案中, R^1 、 R^5 至 R^8 以及 R^{11} 至 R^{13} 如下所定义。

[0370] 本发明的实施方案包括用作核衣壳装配抑制剂, 尤其但不仅限于包括用于治疗乙型肝炎病毒(HBV)感染和相关病状的HBV的前基因组RNA衣壳化抑制剂的具有式(XXI)的化合物,

[0371]



[0372] 包括其所有对映异构形式、非对映异构形式、水合物、溶剂合物、药学上可接受的盐、前药和复合物, 其中:

[0373] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组; R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的3-7元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基- C_{1-6} -烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基;

[0374] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组; R^2 也可或者或另外任选包括任选取代的 C_{3-7} 环烷基或任选取代的杂环;或

[0375] R^1 和 R^2 连同它们所结合的原子一起形成具有3至10个原子的任选取代的杂环(包括环状结构和杂环结构);

[0376] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组; R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0377] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组; R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0378] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 ; R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ 组成的组;

[0379] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

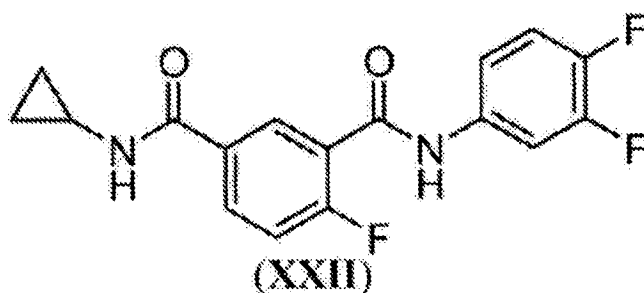
[0380] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基和任选取代的 C_{1-6} 卤代烷基组成的组； R^9 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；

[0381] R^{12} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组；并且

[0382] R^{13} 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

[0383] 出于说明在本文中命名以及提及本发明化合物所依的方式的目的，具有式 (XXII) 的化合物：

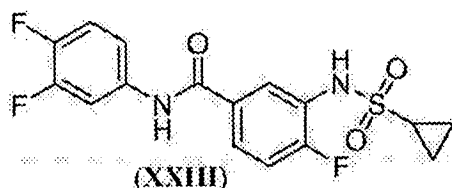
[0384]



[0385] 具有化学名称 N^1 -环丙基-N³-(3,4-二氟苯基)-4-氟间苯二甲酰胺。

[0386] 出于说明在本文中命名以及提及本发明化合物所依的方式的目的，具有式 (XXIII) 的化合物：

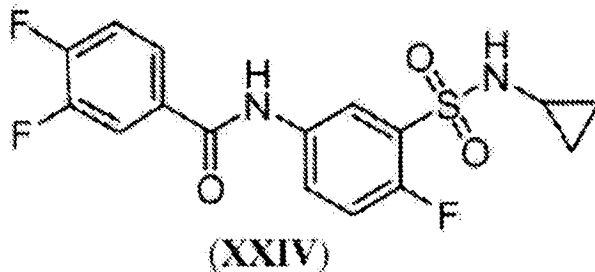
[0387]



[0388] 具有化学名称 3-(环丙烷亚磺酰氨基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺。

[0389] 出于说明在本文中命名以及提及本发明化合物所依的方式的目的，具有式 (XXIV) 的化合物：

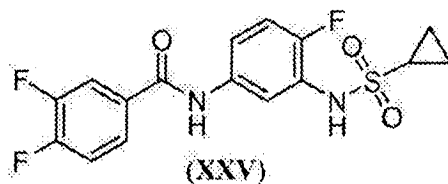
[0390]



[0391] 具有化学名称 N-(3-(N-环丙基氨磺酰基)-4-氟苯基)-3,4-二氟苯甲酰胺。

[0392] 出于说明在本文中命名以及提及本发明化合物所依的方式的目的,具有式 (XXV) 的化合物:

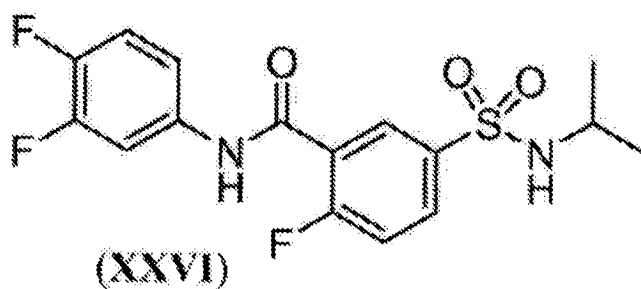
[0393]



[0394] 具有化学名称 N-(3-(环丙烷亚磺酰氨基)-4-氟苯基)-3,4-二氟苯甲酰胺。

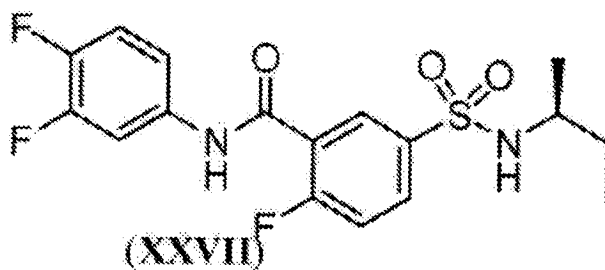
[0395] 出于本发明的目的,通过例如以下的外消旋式 (XXVI) 描绘的化合物:

[0396]



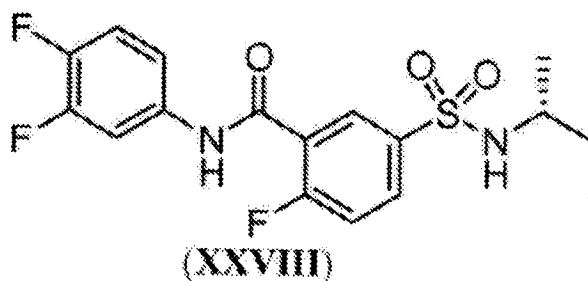
[0397] 将同样代表具有式 (XXVII):

[0398]



[0399] 或式 (XXVIII):

[0400]



[0401] 的两种对映异构体中的任一个或其混合物,或在其中存在第二手性中心的情况下,所有非对映异构体。

[0402] 在先前化合物的一些实施方案中,A 是 SO₂。

[0403] 在先前化合物的一些实施方案中,A 是 CO。

[0404] 在先前化合物的一些实施方案中, R¹是任选取代的 C₁₋₆直链烷基。

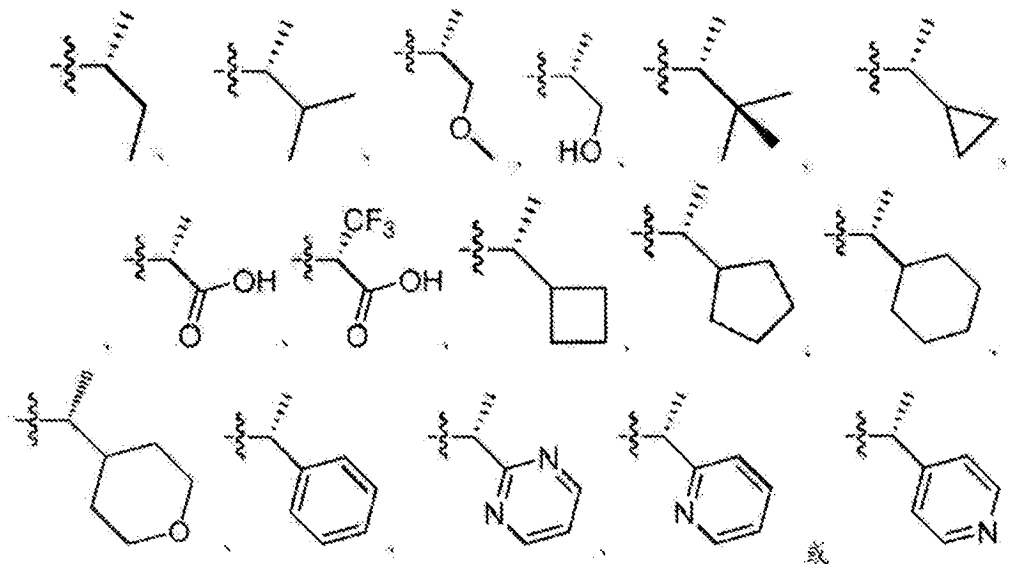
[0405] 在先前化合物的一些实施方案中, R¹是任选取代的 C₁₋₆支链烷基。

[0406] 在先前化合物的一些实施方案中, R¹是任选取代的 C₃₋₇ 环烷基

[0407] 在先前化合物的一些实施方案中, R¹是任选取代的芳基。

[0408] 在先前化合物的一些实施方案中, R¹是任选取代的苯甲基。烷基或苯甲基取代基可为手性的或无手性, 并且如果是手性的, 那么可为 S 或 R 构型。特别有吸引力的实施方案似乎包括其中 R¹主要具有 R 构型支链烷基的那些, 如

[0409]



[0410] 如本文所用,术语“主要 R 构型”包括其中在 R 异构体中在相应位置处,碳是纯的或增浓的那些化合物。在其它实施方案中,有用实施方案包括其中 R¹主要具有 S 构型支链烷基的那些。

[0411] 在先前化合物的一些实施方案中, R^2 是氢。

[0412] 在先前化合物的一些实施方案中, R²是任选取代的 C₁₋₆直链烷基。

[0413] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 3 个原子的任选取代的环。

[0414] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 4 个原子的任选取代的环。

[0415] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 5 个原子的任选取代的环。

[0416] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 6 个原子的任选取代的环。

[0417] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 7 个原子的任选取代的环。

[0418] 在先前化合物的一些实施方案中, R¹和 R²连同它们所结合的原子一起形成具有 6 个原子的任选取代的杂环。

[0419] 在先前化合物的一些实施方案中, R^1 和 R^2 连同它们所结合的原子一起形成具有 7

个原子的任选取代的杂环。

[0420] 在先前化合物的一些实施方案中, R^1 和 R^2 连同它们所结合的原子一起形成具有 8 个原子的任选取代的杂环。

[0421] 在先前化合物的一些实施方案中, R^1 和 R^2 连同它们所结合的原子一起形成具有 9 个原子的任选取代的杂环。

[0422] 在先前化合物的一些实施方案中, R^1 和 R^2 连同它们所结合的原子一起形成具有 10 个原子的任选取代的杂环。

[0423] 在先前化合物的一些实施方案中, R^3 是任选取代的芳基。

[0424] 在先前化合物的一些实施方案中, R^3 是任选取代的苯甲基。

[0425] 在先前化合物的一些实施方案中, R^3 是任选取代的烷基芳基。

[0426] 在先前化合物的一些实施方案中, R^3 是任选取代的杂芳基。

[0427] 在先前化合物的一些实施方案中, R^3 是任选取代的烷基杂芳基。

[0428] 在先前化合物的一些实施方案中, R^4 是氢。

[0429] 在先前化合物的一些实施方案中, R^4 是任选取代的 C_{1-6} 直链烷基。

[0430] 在先前化合物的一些实施方案中, R^5 是氢。

[0431] 在先前化合物的一些实施方案中, R^5 是卤素。

[0432] 在先前化合物的一些实施方案中, R^5 是任选取代的 C_{1-6} 直链烷基。

[0433] 在先前化合物的一些实施方案中, R^5 是任选取代的 C_{1-6} 支链烷基。

[0434] 在先前化合物的一些实施方案中, R^5 是任选取代的 C_{1-6} 卤代烷基。

[0435] 在先前化合物的一些实施方案中, R^5 是 OR^9 。

[0436] 在先前化合物的一些实施方案中, R^6 是氢。

[0437] 在先前化合物的一些实施方案中, R^6 是卤素。

[0438] 在先前化合物的一些实施方案中, R^6 是任选取代的 C_{1-6} 直链烷基。

[0439] 在先前化合物的一些实施方案中, R^6 是任选取代的 C_{1-6} 支链烷基。

[0440] 在先前化合物的一些实施方案中, R^6 是任选取代的 C_{1-6} 卤代烷基。

[0441] 在先前化合物的一些实施方案中, R^6 是 OR^9 。

[0442] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 5 个原子的任选取代的碳环或杂环。

[0443] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 6 个原子的任选取代的碳环或杂环。

[0444] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 5 个原子, 含有羰基的任选取代的碳环或杂环。

[0445] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 6 个原子, 含有羰基的任选取代的碳环或杂环。

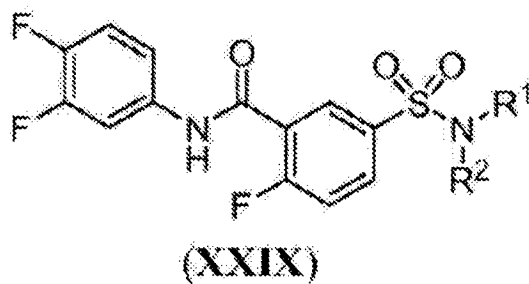
[0446] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 5 个原子, 含有两个羰基的任选取代的碳环或杂环。

[0447] 在先前化合物的一些实施方案中, R^4 和 R^6 连同它们所结合的原子一起形成具有 6 个原子, 含有两个羰基的任选取代的碳环或杂环。

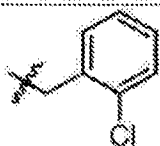
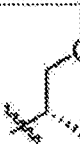
[0448] 在先前化合物的一些实施方案中, R^7 是氢。

- [0449] 在先前化合物的一些实施方案中, R^7 是卤素。
- [0450] 在先前化合物的一些实施方案中, R^7 是任选取代的 C_{1-6} 直链烷基。
- [0451] 在先前化合物的一些实施方案中, R^7 是任选取代的 C_{1-6} 支链烷基。
- [0452] 在先前化合物的一些实施方案中, R^7 是任选取代的 C_{1-6} 卤代烷基。
- [0453] 在先前化合物的一些实施方案中, R^7 是 OR^9 。
- [0454] 在先前化合物的一些实施方案中, R^8 是氢。
- [0455] 在先前化合物的一些实施方案中, R^8 是卤素。
- [0456] 在先前化合物的一些实施方案中, R^8 是任选取代的 C_{1-6} 直链烷基。
- [0457] 在先前化合物的一些实施方案中, R^8 是任选取代的 C_{1-6} 支链烷基。
- [0458] 在先前化合物的一些实施方案中, R^8 是任选取代的 C_{1-6} 卤代烷基。
- [0459] 在先前化合物的一些实施方案中, R^8 是 OR^9 。
- [0460] 在先前化合物的一些实施方案中, R^7 和 R^8 连同它们所结合的原子一起形成具有 5 个原子的任选取代的碳环或杂环。
- [0461] 在先前化合物的一些实施方案中, R^7 和 R^8 连同它们所结合的原子一起形成具有 6 个原子的任选取代的碳环或杂环。
- [0462] 在先前化合物的一些实施方案中, R^9 是氢。
- [0463] 在先前化合物的一些实施方案中, R^9 是任选取代的 C_{1-6} 直链烷基。
- [0464] 在先前化合物的一些实施方案中, R^9 是任选取代的 C_{1-6} 支链烷基。
- [0465] 在先前化合物的一些实施方案中, R^9 是任选取代的 C_{3-7} 环烷基。
- [0466] 在先前化合物的一些实施方案中, R^9 是任选取代的 C_{1-6} 卤代烷基。
- [0467] 在先前化合物的一些实施方案中, R^9 是任选取代的芳基。
- [0468] 在先前化合物的一些实施方案中, R^9 是任选取代的杂芳基。
- [0469] 在先前化合物的一些实施方案中, R^9 是任选取代的苯甲基。
- [0470] 在先前化合物的一些实施方案中, R^9 是任选取代的杂环基。
- [0471] 在先前化合物的一些实施方案中, R^{10} 是任选取代的芳基。
- [0472] 在先前化合物的一些实施方案中, R^{10} 是任选取代的杂芳基。
- [0473] 在先前化合物的一些实施方案中, n 是 0。
- [0474] 在先前化合物的一些实施方案中, n 是 1。
- [0475] 在先前化合物的一些实施方案中, y 是 0。
- [0476] 在先前化合物的一些实施方案中, y 是 1。
- [0477] 在先前化合物的一些实施方案中, y 是 2。
- [0478] 在先前化合物的一些实施方案中, z 是 0。
- [0479] 在先前化合物的一些实施方案中, z 是 1。
- [0480] 在先前化合物的一些实施方案中, f 是 0。
- [0481] 在先前化合物的一些实施方案中, f 是 1。
- [0482] 在先前化合物的一些实施方案中, g 是 0。
- [0483] 在先前化合物的一些实施方案中, g 是 1。
- [0484] 在先前化合物的一些实施方案中, h 是 0。
- [0485] 在先前化合物的一些实施方案中, h 是 1。

- [0486] 在先前化合物的一些实施方案中, R^{11} 是氢。
- [0487] 在先前化合物的一些实施方案中, R^{11} 是任选取代的 C_{1-6} 直链烷基。
- [0488] 在先前化合物的一些实施方案中, R^{11} 是任选取代的 C_{1-6} 支链烷基。
- [0489] 在先前化合物的一些实施方案中, R^{11} 是任选取代的 C_{3-7} 环烷基。
- [0490] 在先前化合物的一些实施方案中, k 是 0。
- [0491] 在先前化合物的一些实施方案中, k 是 1。
- [0492] 在先前化合物的一些实施方案中, j 是 0。
- [0493] 在先前化合物的一些实施方案中, j 是 1。
- [0494] 在先前化合物的一些实施方案中, r 是 0。
- [0495] 在先前化合物的一些实施方案中, r 是 1。
- [0496] 在先前化合物的一些实施方案中, t 是 0。
- [0497] 在先前化合物的一些实施方案中, t 是 1。
- [0498] 在一些实施方案中, R^{12} 是氢。
- [0499] 在先前化合物的一些实施方案中, R^{12} 是任选取代的 C_{1-6} 直链烷基。
- [0500] 在先前化合物的一些实施方案中, R^{12} 是任选取代的 C_{1-6} 支链烷基。
- [0501] 在先前化合物的一些实施方案中, R^{12} 是任选取代的 C_{3-7} 环烷基。
- [0502] 在先前化合物的一些实施方案中, R^{13} 是任选取代的芳基。
- [0503] 在先前化合物的一些实施方案中, R^{13} 是任选取代的苯甲基。
- [0504] 在先前化合物的一些实施方案中, R^{13} 是任选取代的烷基芳基。
- [0505] 在先前化合物的一些实施方案中, R^{13} 是任选取代的杂芳基。
- [0506] 在先前化合物的一些实施方案中, R^{13} 是任选取代的烷基杂芳基。
- [0507] 示例性实施方案包括具有式 (XXIX) 的化合物或其药学上可接受的盐形式:
- [0508]



- [0509] 其中 R^1 和 R^2 的非限制性实例在本文中在以下定义于表 1 中。
- [0510] 表 1: 式 (XXIX) 化合物的示例性实施方案:
- [0511]

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H
	H			H

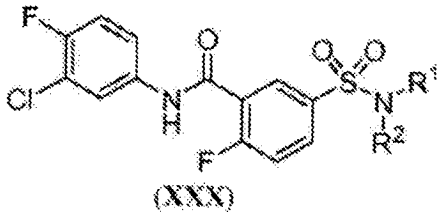
[0512]

	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₃ CH ₂ -	

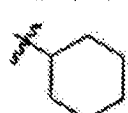
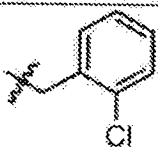
[0513]

	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

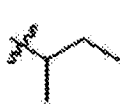
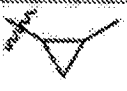
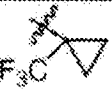
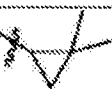
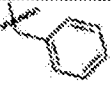
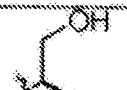
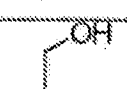
[0514] 示例性实施方案包括具有式 (XXX) 的化合物或其药学上可接受的盐形式：
[0515]



[0516] 其中 R¹和 R²的非限制性实例在本文中在以下定义于表 2 中。
[0517] 表 2 :式 (XXX) 化合物的示例性实施方案：
[0518]

R ¹	R ²		R ¹	R ²
	H			H
	H			H
	H			H
	H			H

[0519]

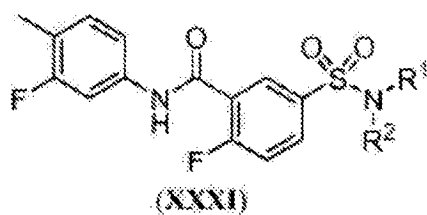
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₃ CH ₂ -	

[0520]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		

[0521] 示例性实施方案包括具有式 (XXXI) 的化合物或其药学上可接受的盐形式：

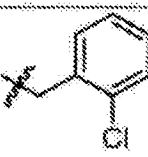
[0522]



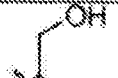
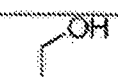
[0523] 其中 R¹和 R²的非限制性实例在本文中在以下定义于表 3 中。

[0524] 表 3 : 式 (XXXI) 化合物的示例性实施方案：

[0525]

R ¹	R ²		R ¹	R ²
	H			H
	H			H
	H			H
	H			H

[0526]

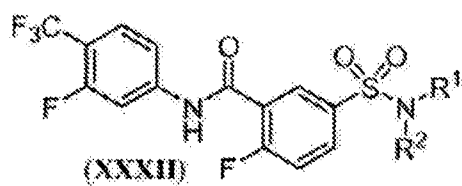
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

[0527]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

[0528] 示例性实施方案包括具有式 (XXXII) 的化合物或其药学上可接受的盐形式：

[0529]



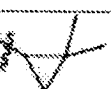
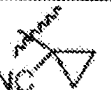
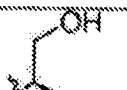
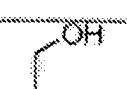
[0530] 其中 R^1 和 R^2 的非限制性实例在本文中在以下定义于表 4 中。

[0531] 表 4 : 式 (XXXII) 化合物的示例性实施方案：

[0532]

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

[0533]

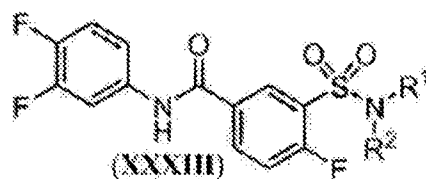
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

[0534]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

[0535] 示例性实施方案包括具有式 (XXXIII) 的化合物或其药学上可接受的盐形式：

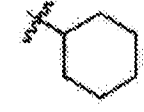
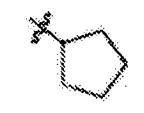
[0536]



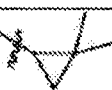
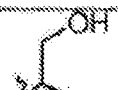
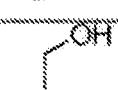
[0537] 其中 R^1 和 R^2 的非限制性实例在本文中在以下定义于表 5 中。

[0538] 表 5 : 式 (XXXIII) 化合物的示例性实施方案：

[0539]

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

[0540]

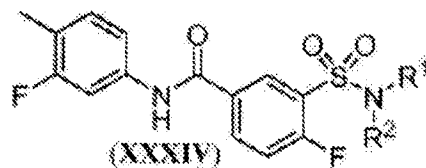
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₃ CH ₂ -	

[0541]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

[0542] 示例性实施方案包括具有式 (XXXIV) 的化合物或其药学上可接受的盐形式：

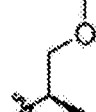
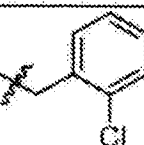
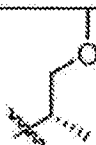
[0543]



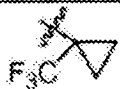
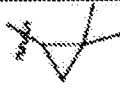
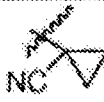
[0544] 其中 R^1 和 R^2 的非限制性实例在本文中在以下定义于表 6 中。

[0545] 表 6 : 式 (XXXIV) 化合物的示例性实施方案：

[0546]

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

[0547]

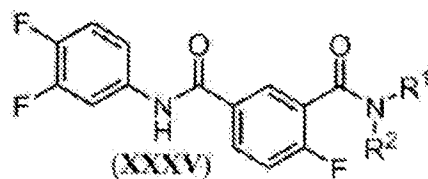
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₃ CH ₂ -	

[0548]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		

[0549] 示例性实施方案包括具有式 (XXXV) 的化合物或其药学上可接受的盐形式：

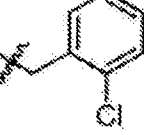
[0550]



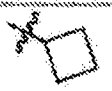
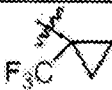
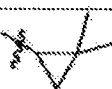
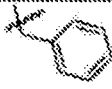
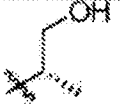
[0551] 其中 R^1 和 R^2 的非限制性实例在本文中在以下定义于表 7 中。

[0552] 表 7 : 式 (XXXV) 化合物的示例性实施方案：

[0553]

R^1	R^2		R^1	R^2
	H			H
	H			H
	H			H
	H			H

[0554]

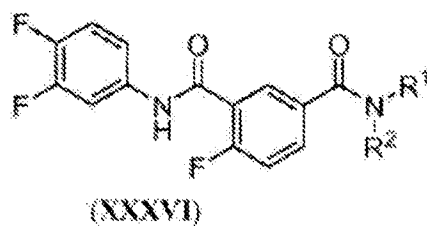
	H			H
	H			H
	H			H
	H			H
-CH ₃	H			H
-CH ₂ CH ₃	H			H
	H			H
	H			H
	H			H
	H			-CH ₂ CH ₃
	H		-CH ₂ CH ₂ -	
	H		-CH ₂ CH ₂ CH ₂ -	
	H		-CH ₂ (CH ₂) ₂ CH ₂ -	

[0555]

	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

[0556] 示例性实施方案包括具有式 (XXXVI) 的化合物或其药学上可接受的盐形式：

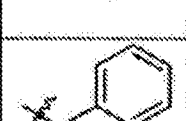
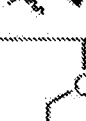
[0557]



[0558] 其中 R¹和 R²的非限制性实例在本文中在以下定义于表 8 中。

[0559] 表 8 : 式 (XXXVI) 化合物的示例性实施方案：

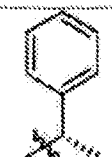
[0560]

R ¹	R ²		R ¹	R ²
	H			H
	H			H
	H			H

[0561]

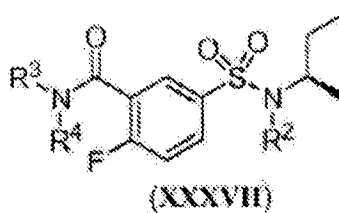
	H			H
	H			H
	H			H
	H			H
	H			H
$-\text{CH}_3$	H			H
$-\text{CH}_2\text{CH}_3$	H			H
	H			H
	H			H
	H			H
	H			$-\text{CH}_2\text{CH}_3$
	H		$-\text{CH}_2\text{CH}_2-$	
	H		$-\text{CH}_2\text{CH}_2\text{CH}_2-$	

[0562]

	H		$-\text{CH}_2(\text{CH}_2)_2\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$
	H		$-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$
	H		

[0563] 示例性实施方案包括具有式 (XXXVII) 的化合物或其药学上可接受的盐形式：

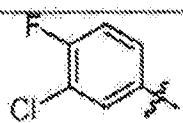
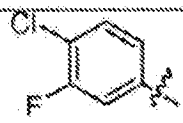
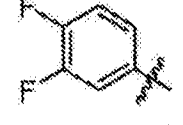
[0564]



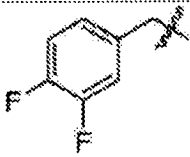
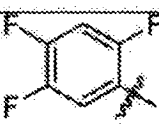
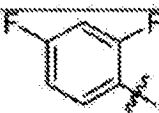
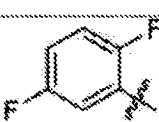
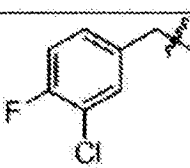
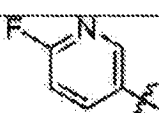
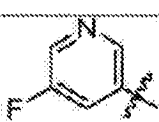
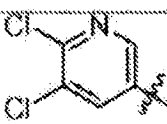
[0565] 其中 R^2 、 R^3 和 R^4 的非限制性实例在本文中在以下定义于表 9 中。

[0566] 表 9：式 (XXXVII) 化合物的示例性实施方案：

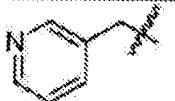
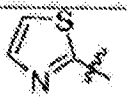
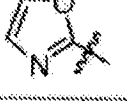
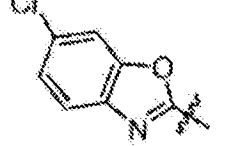
[0567]

R^2	R^3	R^4
H		H
H		H
H		H
H		CH_3

[0568]

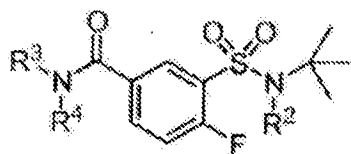
H		H
Me		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0569]

H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0570] 示例性实施方案包括具有式 (XXXVIII) 的化合物或其药学上可接受的盐形式：

[0571]

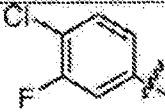
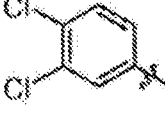
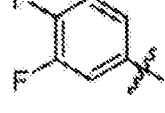
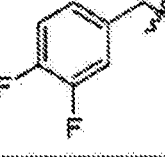
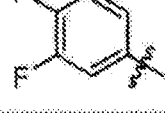
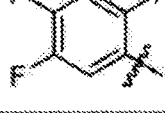
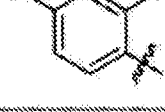
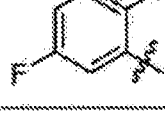
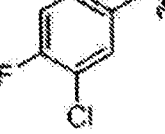


(XXXVIII)

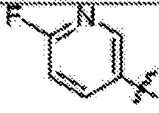
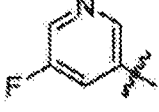
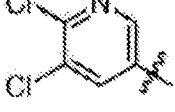
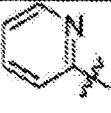
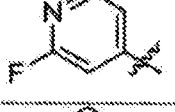
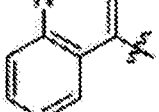
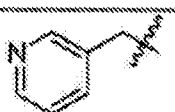
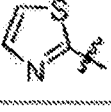
[0572] 其中 R^2 、 R^3 和 R^4 的非限制性实例在本文中在以下定义于表 10 中。

[0573] 表 10 : 式 (XXXVIII) 化合物的示例性实施方案：

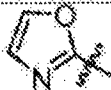
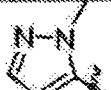
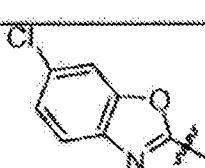
[0574]

R^2	R^3	R^2
H		H
H		H
H		H
H		CH ₃
H		H
Me		H
H		H
H		H
H		H
H		H

[0575]

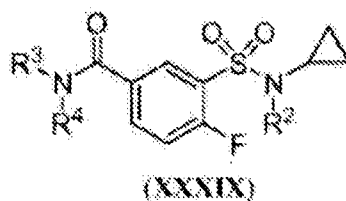
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0576]

H		H
H		H
H		H
H		H

[0577] 示例性实施方案包括具有式 (XXXIX) 的化合物或其药学上可接受的盐形式：

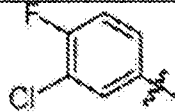
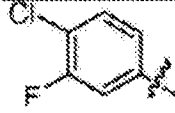
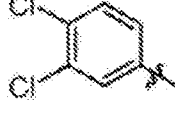
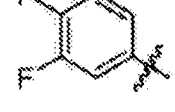
[0578]



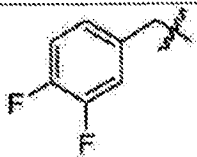
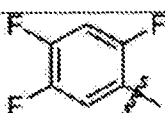
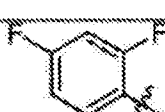
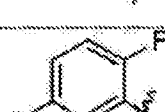
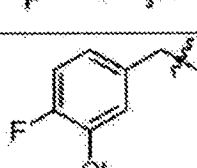
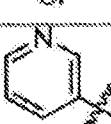
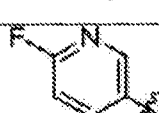
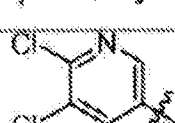
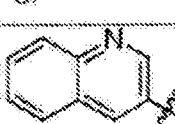
[0579] 其中 R²、R³ 和 R⁴ 的非限制性实例在本文中在以下定义于表 11 中。

[0580] 表 11 : 式 (XXXIX) 化合物的示例性实施方案：

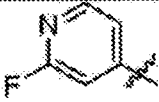
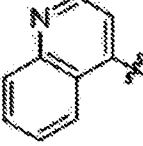
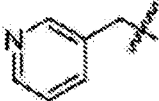
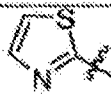
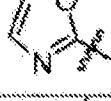
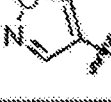
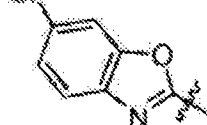
[0581]

R ²	R ³	R ⁴
H		H
H		H
H		H
H		CH ₃

[0582]

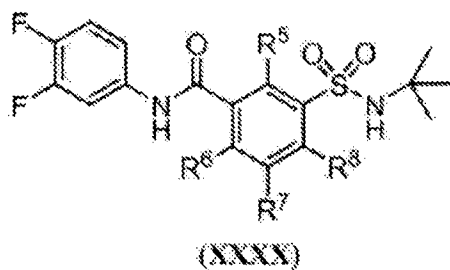
H		H
Me		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0583]

H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H
H		H

[0584] 示例性实施方案包括具有式 (XXXX) 的化合物或其药学上可接受的盐形式：

[0585]



[0586] 其中 R⁵、R⁶、R⁷和 R⁸的非限制性实例在本文中在以下定义于表 12 中。

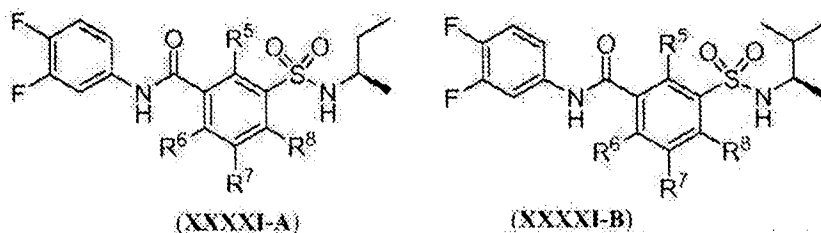
[0587] 表 12 :式 (XXXX) 化合物的示例性实施方案 :

[0588]

R ⁵	R ⁶	R ⁷	R ⁸
H	H	H	Me
H	H	H	OMe
H	H	H	Cl
H	F	H	F
H	H	F	F

[0589] 示例性实施方案包括具有式 (XXXXI-A 或 XXXXI-B) 的化合物或其药学上可接受的盐形式 :

[0590]



[0591] 其中 R⁵、R⁶、R⁷和 R⁸的非限制性实例在本文中在以下定义于表 13 中。

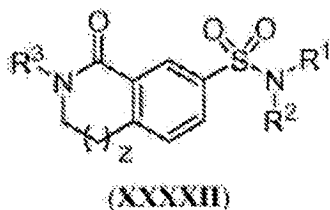
[0592] 表 13 :式 (XXXXI-A 或 XXXXI-B) 化合物的示例性实施方案 :

[0593]

R ⁵	R ⁶	R ⁷	R ⁸
H	Me	H	H
H	OMe	H	H
H	Cl	H	H
F	F	H	H
H	F	F	H
H	F	H	F

[0594] 示例性实施方案包括具有式 (XXXXII) 的化合物或其药学上可接受的盐形式 :

[0595]



[0596] 其中 R^1 、 R^2 、 R^3 和 z 的非限制性实例在本文中在以下定义于表 14 中。

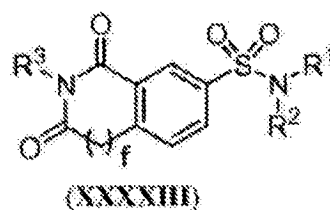
[0597] 表 14 : 式 (XXXXII) 化合物的示例性实施方案：

[0598]

z	R^1	R^2	R^3
0		H	
1		H	
0		H	
1		H	

[0599] 示例性实施方案包括具有式 (XXXXIII) 的化合物或其药学上可接受的盐形式：

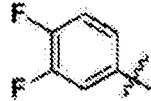
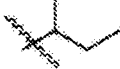
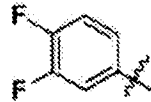
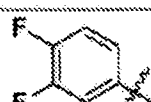
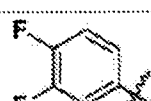
[0600]



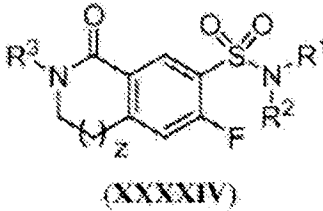
[0601] 其中 R^1 、 R^2 、 R^3 和 f 的非限制性实例在本文中在以下定义于表 15 中。

[0602] 表 15 : 式 (XXXXIII) 化合物的示例性实施方案：

[0603]

f	R ¹	R ²	R ³
0		H	
1		H	
0		H	
1		H	

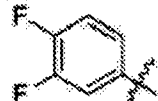
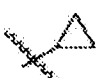
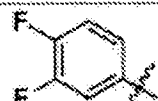
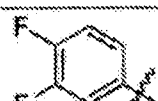
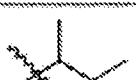
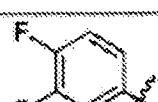
[0604] 示例性实施方案包括具有式 (XXXXIV) 的化合物或其药学上可接受的盐形式：
[0605]



[0606] 其中 R¹、R²、R³和 z 的非限制性实例在本文中在以下定义于表 16 中。
[0607] 表 16 :式 (XXXXIV) 化合物的示例性实施方案：
[0608]

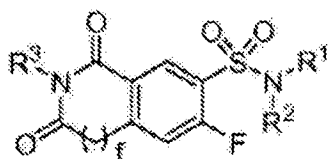
z	R ³	R ²	R ¹
---	----------------	----------------	----------------

[0609]

0		H	
1		H	
0		H	
1		H	

[0610] 示例性实施方案包括具有式 (XXXXV) 的化合物或其药学上可接受的盐形式：

[0611]



(XXXXV)

[0612] 其中 R^1 、 R^2 、 R^3 和 f 的非限制性实例在本文中在以下定义于表 17 中。

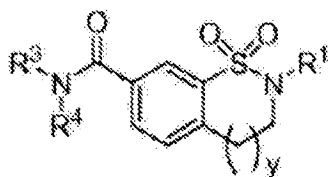
[0613] 表 17: 式 (XXXXV) 化合物的示例性实施方案:

[0614]

f	R^1	R^2	R^3
0		H	
1		H	
0		H	
1		H	

[0615] 示例性实施方案包括具有式 (XXXXVI) 的化合物或其药学上可接受的盐形式:

[0616]

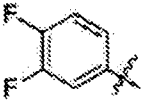
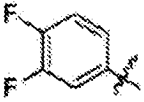
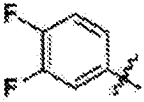


(XXXXVI)

[0617] 其中 R^1 、 R^3 、 R^4 和 y 的非限制性实例在本文中在以下定义于表 18 中。

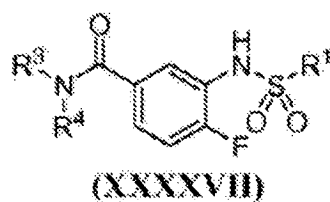
[0618] 表 18: 式 (XXXXVI) 化合物的示例性实施方案:

[0619]

y	R ¹	R ²	R ³
0			H
1			H
2			H

[0620] 示例性实施方案包括具有式 (XXXXVII) 的化合物或其药学上可接受的盐形式：

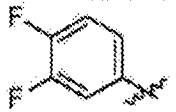
[0621]



[0622] 其中 R¹、R²和 R⁴的非限制性实例在本文中在以下定义于表 19 中。

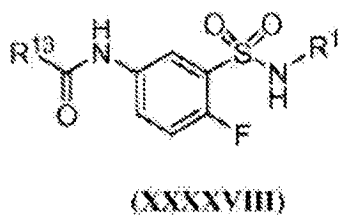
[0623] 表 19 :式 (XXXXVII) 化合物的示例性实施方案：

[0624]

R ¹	R ²	R ⁴
		H

[0625] 示例性实施方案包括具有式 (XXXXVIII) 的化合物或其药学上可接受的盐形式：

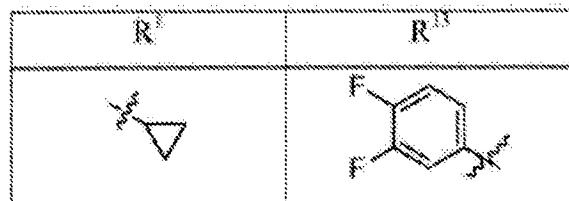
[0626]



[0627] 其中 R¹和 R¹³的非限制性实例在本文中在以下定义于表 19 中。

[0628] 表 20 :式 (XXXXVIII) 化合物的示例性实施方案：

[0629]



[0630] 在本文提供的所有实施方案中,适合任选取代基的实例不意图限制要求保护的发明的范围。本发明化合物可含有本文提供的任何取代基或取代基的组合。

[0631] 在本文中通过名称、结构或名称与结构两者列举的各化合物被视为作为物质组合物的个别实施方案。其它实施方案包括当与药学上可接受的赋形剂组合时,在本文中通过名称、结构或名称与结构两者列举的各化合物被视为作为药物组合物的一部分的个别实施方案。其它实施方案包括在本文中通过名称、结构或名称与结构两者列举的各化合物独自或作为药物组合物或列举的治疗方案的一部分用于治疗至少一种本文所述的病状的用途。其它实施方案包括通过向有需要的患者独自或作为药物组合物或列举的治疗方案的一部分施用药学上有效量的至少一种在本文中通过名称、结构或名称与结构两者列举的化合物来治疗患者的至少一种本文所述的病状的方法。

[0632] 本教义的化合物可根据本文概述的程序,自可商购获得的原料、文献中已知的化合物、或易于通过采用为本领域技术人员所知的标准合成方法和程序制备的中间体来制备。用于制备有机分子以及官能团转化和操作的的标准合成方法和程序可易于自相关科学文献或本领域中的标准教科书获得。应了解,当给出典型或优选工艺条件(即反应温度、时间、反应物的摩尔比、溶剂、压力等)时,除非另外陈述,否则也可使用其它工艺条件。最优反应条件可随使用的特定反应物或溶剂而变化,但所述条件可由本领域技术人员通过常规优化程序来确定。有机合成领域技术人员将认识到呈现的合成步骤的性质和顺序可出于优化本文所述的化合物的形成的目的而变化。

[0633] 本文所述的方法可根据本领域中已知的任何适合方法来监测。举例来说,产物形成可通过分光手段,如核磁共振光谱法(例如 ^1H 或 ^{13}C)、红外光谱法、分光光度测定法(例如紫外-可见)、质谱测定法;或通过色谱法,如高压液相色谱法(HPLC)、气相色谱法(GC)、胶凝渗透色谱法(GPC)或薄层色谱法(TLC)进行监测。

[0634] 制备化合物可涉及各种化学基团的保护和脱保护。对保护和脱保护的需要以及对适当保护基的选择可易于由本领域技术人员确定。保护基的化学性质可例如见于 Greene 等, *Protective Groups in Organic Synthesis*, 第 2 版 (Wiley&Sons, 1991) 中,所述书籍的整个公开内容出于所有目的以引用的方式并入本文。

[0635] 本文所述的反应或方法可在易于在由有机合成领域技术人员选择的适合溶剂中进行。适合溶剂通常大致上不与反应物、中间体和/或产物在进行反应所处的温度(即可在溶剂的冷冻温度至溶剂的沸腾温度的范围内的温度)下反应。给定反应可在一种溶剂或一种以上溶剂的混合物中进行。视特定反应步骤而定,可选择适于特定反应步骤的溶剂。

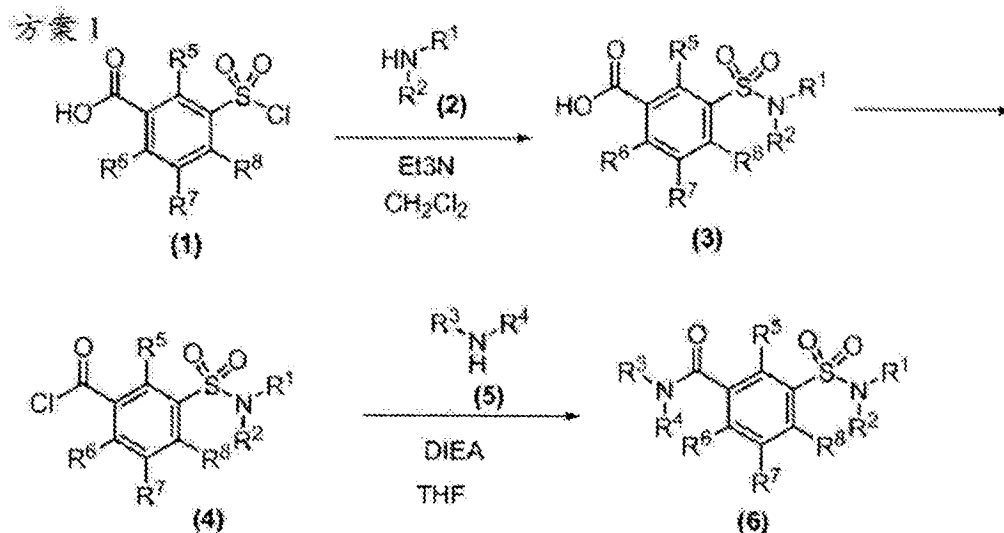
[0636] 这些教义的化合物可通过有机化学领域中已知的方法来制备。用于制备这些教义的化合物的试剂可商购获得或可通过文献中所述的标准程序来制备。举例来说,本发明化合物可根据一般性合成方案中说明的方法来制备:

[0637] 用于制备化合物的一般性合成方案。

[0638] 用于制备本发明的化合物的试剂可商购获得或可通过文献中所述的标准程序来制备。根据本发明, 所属种类的化合物可通过以下一个反应方案来产生。

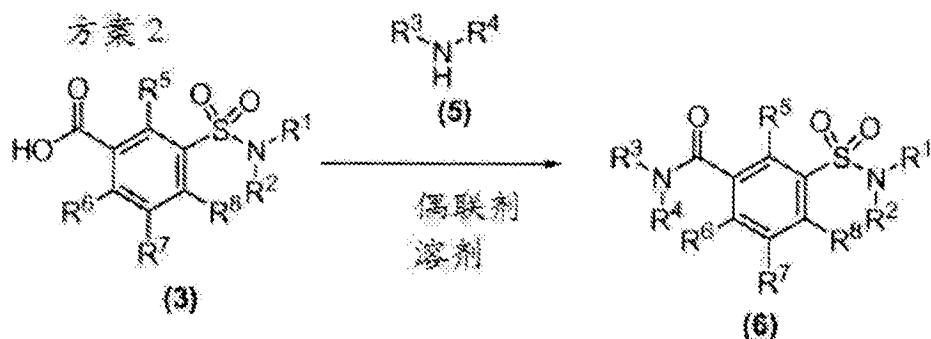
[0639] 式 (6) 化合物可根据方案 1-2 中概述的方法来制备。

[0640]



[0641] 因此, 使式 (1) 化合物 (已知化合物或通过已知方法制备的化合物) 与式 (2) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (3) 化合物。使式 (3) 化合物与亚硫酸氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (4) 化合物。或者, 使式 (3) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (4) 化合物。接着使式 (4) 化合物与式 (5) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (6) 化合物。

[0642]

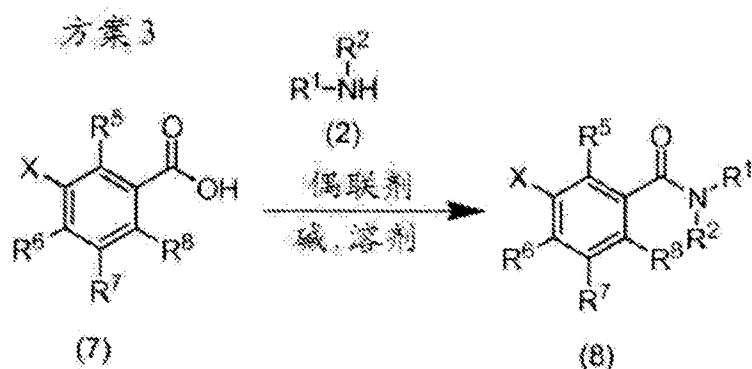


[0643] 或者, 使式 (3) 化合物与式 (5) 化合物 (已知化合物或通过已知方法制备的化合物) 在偶联剂 (如 1-乙基-3-(3-二甲基氨基丙基) 碳二亚胺、N,N'-二环己基碳二亚胺、0-苯并三唑-N,N',N'-四甲基-脲-六氟-磷酸盐、0-(7-氮杂苯并三

唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐、苯并三唑-1-基-氧基三吡咯烷基磷鎓六氟磷酸盐等)存在下,在有机溶剂(如四氢呋喃、1,4-二噁烷、二甲基甲酰胺、二氯甲烷、二氯乙烷、甲醇、乙醇等)中,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,任选在4-N,N-二甲基氨基吡啶存在下反应以提供式(6)化合物。

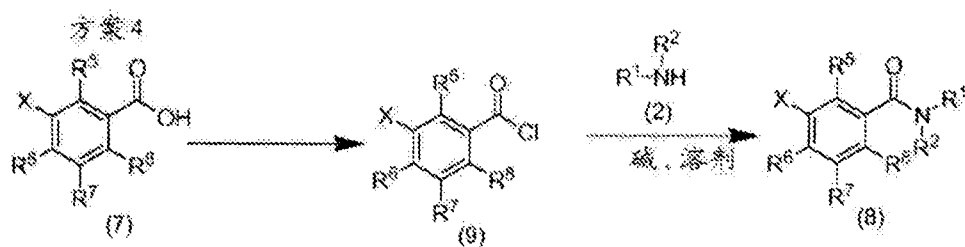
[0644] 式(10)化合物可根据方案3-5中概述的方法来制备。

[0645]



[0646] 使式(7)的经适合取代的化合物(已知化合物或通过已知方法制备的化合物)(其中X是卤素)与式(2)化合物(已知化合物或通过已知方法制备的化合物)在偶联剂(如1-乙基-3-(3-二甲基氨基丙基)碳二亚胺、N,N'-二环己基碳二亚胺、0-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐、0-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐、苯并三唑-1-基-氧基三吡咯烷基磷鎓六氟磷酸盐等)存在下,在有机溶剂(如四氢呋喃、1,4-二噁烷、二甲基甲酰胺、二氯甲烷、二氯乙烷、甲醇、乙醇等)中,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,任选在4-N,N-二甲基氨基吡啶存在下反应以提供式(8)化合物。

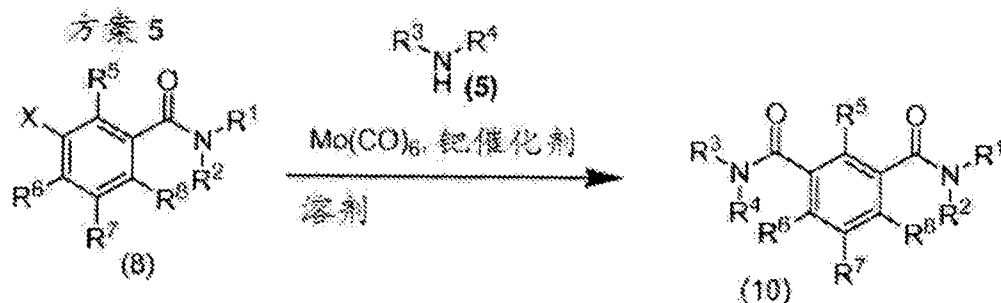
[0647]



[0648] 或者,使式(7)的经适合取代的化合物(已知化合物或通过已知方法制备的化合物)(其中X是卤素)与亚硫酰氯任选在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)存在下反应以提供式(9)化合物。或者,使式(7)化合物与草酰氯任选在二甲基甲酰胺存在下,任选在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中反应以提供式(9)化合物。接着使式(9)化合物与式(2)化合物(已知化合物或通过已知方法制备的化合物)任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,任选在4-N,N-二甲基氨基吡啶存在下,在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中反应以提供式(8)化合

物。

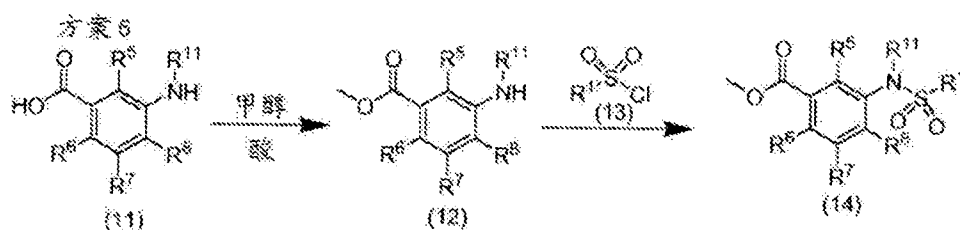
[0649]



[0650] 使式 (8) 化合物与式 (5) 化合物在六羰基钼存在下,在钼催化剂(如乙酸钼(II)、四(三苯基膦)钼(0)、二氯双(三苯基膦)钼(II)、钼/碳、双(乙腈)二氯钼(II)等)存在下,在 4,5-双(二苯基膦基)-9,9-二甲基氧杂蒽(Xantphos)存在下,在溶剂(如水、二甲基甲酰胺、二甲基乙酰胺、甲醇、乙醇、二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷等)中,任选在加热下,任选在微波辐射下,任选在惰性氛围(如氮气或氩气)中反应以提供式(10)化合物。

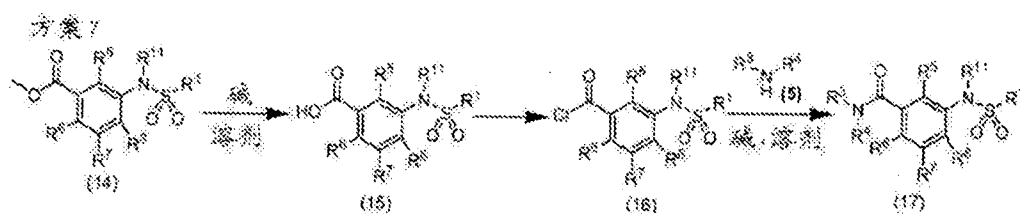
[0651] 式(17)化合物可根据方案 6-7 中概述的方法来制备。

[0652]



[0653] 使式 (11) 化合物(已知化合物或通过已知方法制备的化合物)与甲醇在酸(如盐酸、硫酸)存在下,任选在加热下反应以提供式 (12) 化合物。使式 (12) 化合物与式 (13) 化合物(已知化合物或通过已知方法制备的化合物)在碱(如吡啶、2,6-二甲基吡啶等)存在下,任选在二甲基氨基吡啶(DMAP)存在下,任选在溶剂(如二甲基甲酰胺、二甲基乙酰胺、二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷等)存在下,任选在加热下反应以提供式(14)化合物。

[0654]

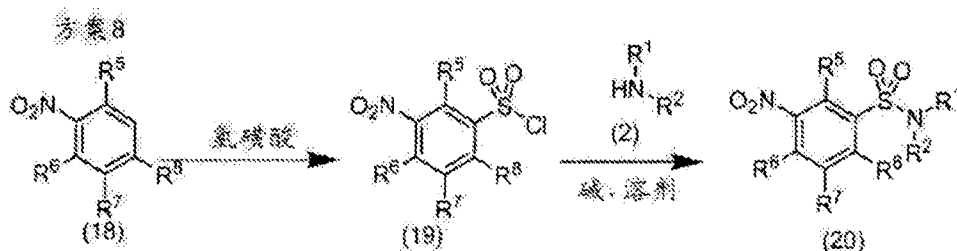


[0655] 使式 (14) 化合物与碱(如氢氧化锂、氢氧化钠、氢氧化钾、氢氧化铯、碳酸钾、碳酸钠等)在溶剂(如乙醇、甲醇、水、二甲基甲酰胺、二甲基乙酰胺、四氢呋喃、1,4-二噁烷等)中反应以提供式 (15) 化合物。接着使式 (15) 化合物与亚硫酰氯任选在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)存在下反应以提供式 (16) 化合物。或者,使式 (15) 化合物与草酰氯任选在二甲基甲酰胺存在下,任选在有机溶剂(如二

氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (16) 化合物。接着使式 (16) 化合物与式 (5) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 任选在 4-N, N- 二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (17) 化合物。

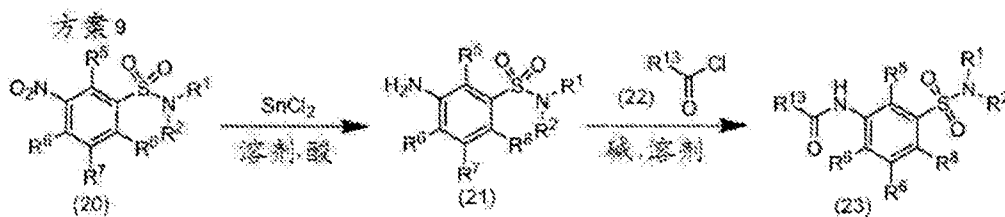
[0656] 式 (23) 化合物可根据方案 8-9 中概述的方法来制备。

[0657]



[0658] 使式 (18) 化合物 (已知化合物或通过已知方法制备的化合物) 与氯磺酸任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (19) 化合物。使式 (19) 化合物与式 (2) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (20) 化合物。

[0659]

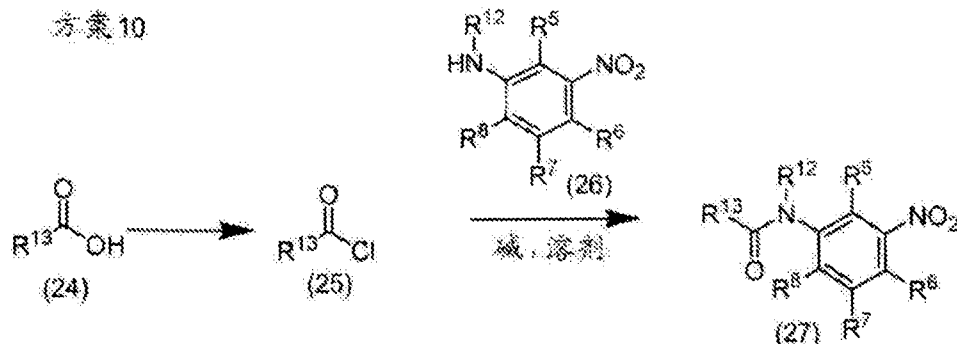


[0660] 接着使式 (20) 化合物与氯化锡在酸 (如盐酸、硫酸等) 存在下, 在有机溶剂 (如四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式化合物以提供式 (21) 化合物。接着使式 (21) 化合物与式 (22) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (23) 化合物。

[0661] 式 (30) 化合物可根据方案 10-11 中概述的方法来制备。

[0662]

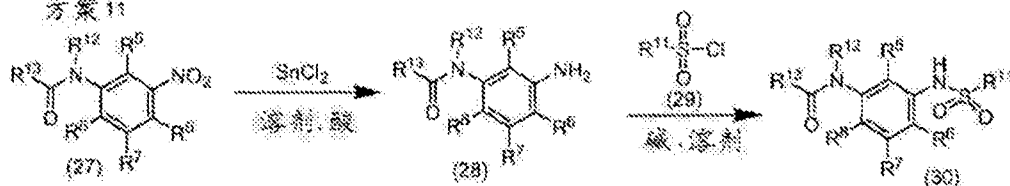
方案 10



[0663] 使式 (24) 化合物 (已知化合物或通过已知方法制备的化合物) 与亚硫酰氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (25) 化合物。或者, 使式 (24) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (25) 化合物。接着使式 (25) 化合物与式 (26) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (27) 化合物。

[0664]

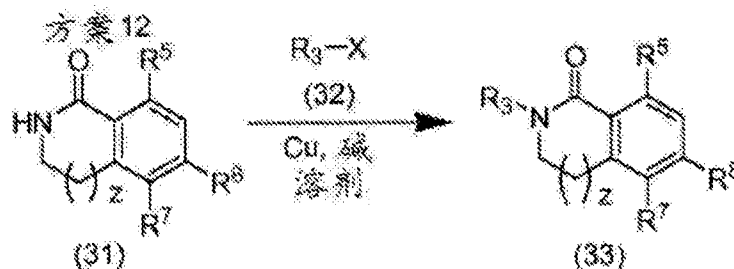
方案 11



[0665] 接着使式 (27) 化合物与氯化锡在酸 (如盐酸、硫酸等) 存在下, 在有机溶剂 (如四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式化合物以提供式 (28) 化合物。接着使式 (28) 化合物与式 (29) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (30) 化合物。

[0666] 式 (36) 化合物可根据方案 12-14 中概述的方法来制备。

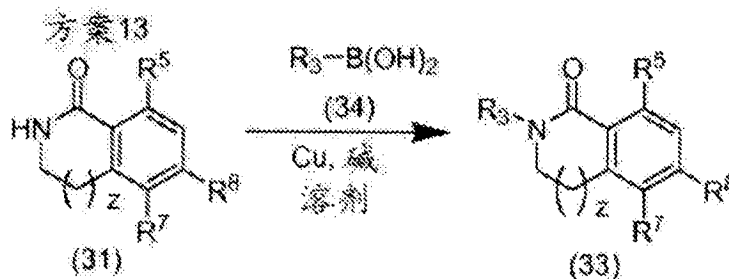
[0667]



[0668] 使式 (31) 化合物 (已知化合物或通过已知方法制备的化合物) 与式 (32) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 在铜盐 (如硫酸铜、碘化铜、

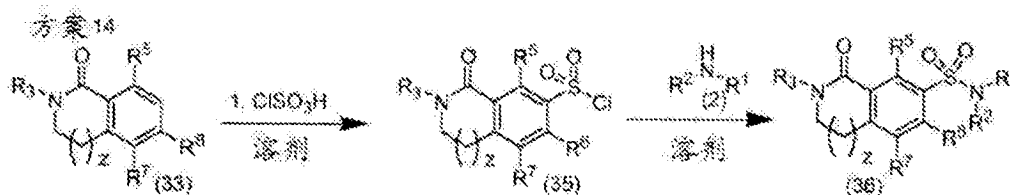
氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(33)化合物。

[0669]



[0670] 或者,使式(31)化合物(已知化合物或通过已知方法制备的化合物)与式(34)化合物(已知化合物或通过已知方法制备的化合物)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(33)化合物。

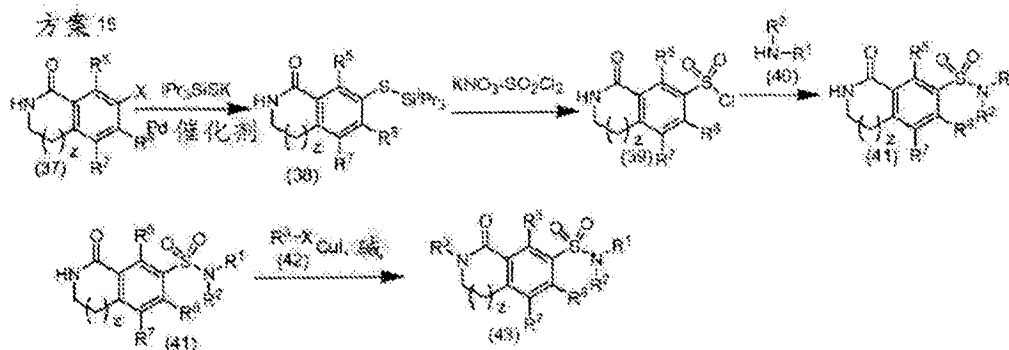
[0671]



[0672] 使式(33)化合物与氯磺酸任选在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)存在下反应以提供式(35)化合物。使式(35)化合物与式(2)化合物(已知化合物或通过已知方法制备的化合物)在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(36)化合物。

[0673] 式(43)化合物可根据方案 15 中概述的方法来制备。

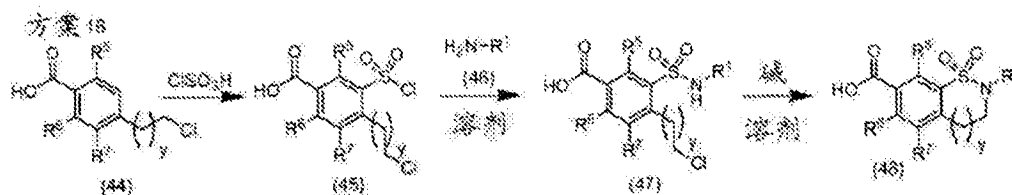
[0674]



[0675] 使式 (37) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 与三异丙基-硅烷硫醇钾盐在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯/碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 在溶剂 (如二甲基甲酰胺、二甲基乙酰胺、二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷等) 中, 任选在加热下, 任选在微波辐射下, 任选在惰性氛围 (如氮气或氩气) 中反应以提供式 (38) 化合物。接着使式 (38) 化合物与 $\text{KNO}_3\text{-SO}_2\text{Cl}_2$ 在溶剂 (如二甲基甲酰胺、二甲基乙酰胺、二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、甲醇、乙醇等) 中反应以提供式 (39) 化合物。使式 (39) 化合物与式 (40) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (41) 化合物。接着使式 (41) 化合物与式 (42) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯/碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (43) 化合物。

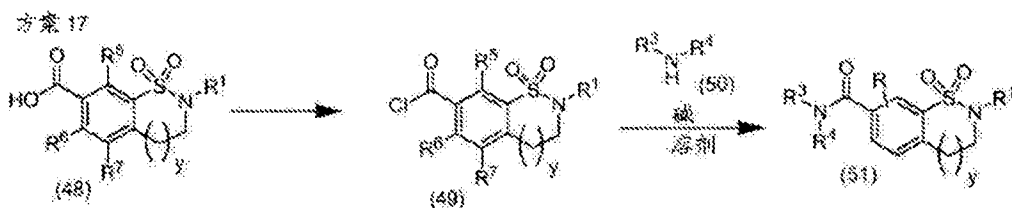
[0676] 式 (51) 化合物可根据方案 16-18 中概述的方法来制备。

[0677]



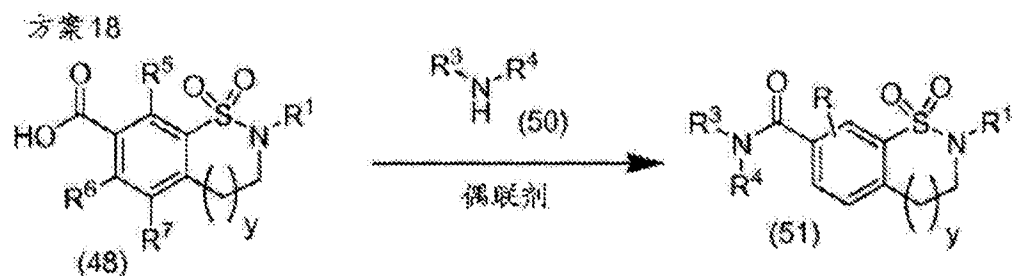
[0678] 使式 (44) 化合物 (已知化合物或通过已知方法制备的化合物) 与氯磺酸任选在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (45) 化合物。接着使式 (45) 化合物与式 (46) 化合物 (已知化合物或通过已知方法制备的化合物) 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (47) 化合物。接着使式 (47) 化合物与碱 (如氢氧化钠、氢氧化锂、氢氧化钾、碳酸钠、碳酸钾、碳酸锂等) 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺、甲醇、乙醇等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (48) 化合物。

[0679]



[0680] 使式 (48) 化合物与亚硫酰氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (49) 化合物。或者, 使式 (48) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (49) 化合物。接着使式 (49) 化合物与式 (50) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (51) 化合物。

[0681]

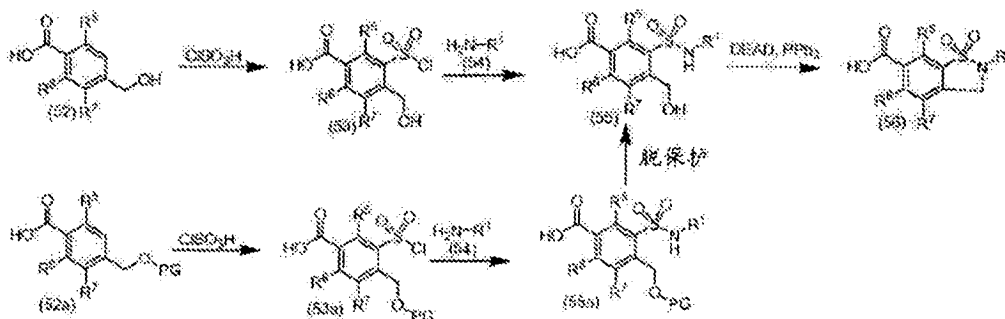


[0682] 或者, 使式 (48) 化合物与式 (50) 化合物 (已知化合物或通过已知方法制备的化合物) 在偶联剂 (如 1-乙基-3-(3-二甲基氨基丙基) 碳二亚胺、N,N'-二环己基碳二亚胺、O-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐、O-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐、苯并三唑-1-基-氧基三吡咯烷基磷鎓六氟磷酸盐等) 存在下, 在有机溶剂 (如四氢呋喃、1,4-二噁烷、二甲基甲酰胺、二氯甲烷、二氯乙烷、甲醇、乙醇等) 中, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下反应以提供式 (51) 化合物。

[0683] 式 (58) 化合物可根据方案 19-20 中概述的方法来制备。

[0684]

方案 18

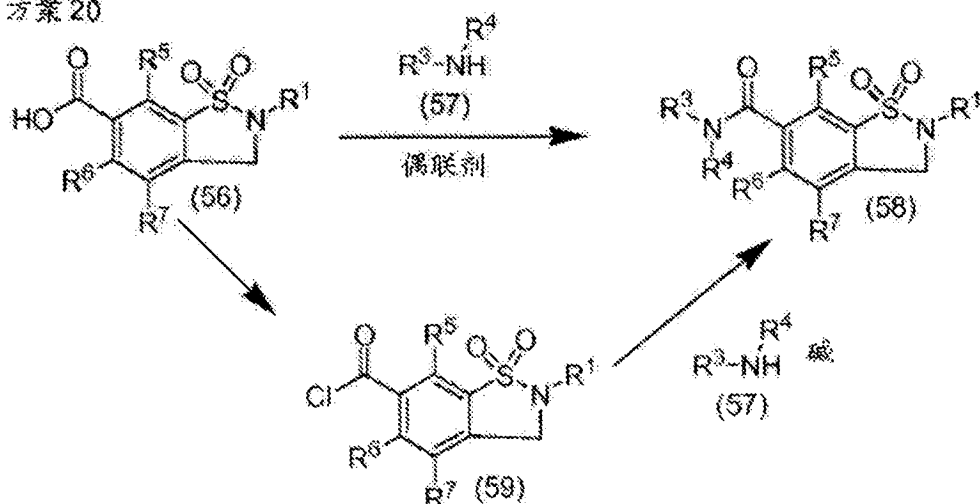


[0685] 使式 (52) 化合物 (已知化合物或通过已知方法制备的化合物) 与氯磺酸任选在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (53) 化合物。接着使式 (53) 化合物与式 (54) 化合物 (已知化合物或通过已知方法制备的化合物) 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (55) 化合物。接着使式 (55) 化合物与偶氮二甲酸二乙酯 (DEAD) 在三苯基膦存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (56) 化合物。

[0686] 或者, 使式 (52a) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 PG 是保护基, 如叔丁基二甲基硅烷基醚、甲基醚、叔丁基醚、苯甲基醚、 β -甲氧基乙氧基甲基醚、乙酰基、苯甲酰基、苯甲氧甲酰基、叔丁基氧基羰基、9-苄基甲基氧基羰基等) 与氯磺酸任选在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (53a) 化合物。接着使式 (53a) 化合物与式 (54) 化合物 (已知化合物或通过已知方法制备的化合物) 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (55a) 化合物。接着通过与酸 (如三氟乙酸、盐酸等) 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、甲醇、乙醇、1,4-二噁烷、二甲基甲酰胺等) 中反应来将式 (55a) 化合物脱保护以提供式 (55) 化合物。或者, 接着通过与氢气在催化剂 (如钯/碳、氧化铂等) 存在下在适合溶剂 (如甲醇、乙醇、四氢呋喃等) 中反应来将式 (55a) 化合物脱保护以提供式 (55) 化合物。或者, 接着通过与碱 (如氢氧化钠、氢氧化钾、氢氧化锂等) 在溶剂 (如甲醇、乙醇、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应来将式 (55a) 化合物脱保护以提供式 (55) 化合物。或者, 接着通过与碱 (如哌啶) 在溶剂 (如甲醇、乙醇、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应来将式 (55a) 化合物脱保护以提供式 (55) 化合物。接着使式 (55) 化合物与偶氮二甲酸二乙酯 (DEAD) 在三苯基膦存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (56) 化合物。

[0687]

方案 20

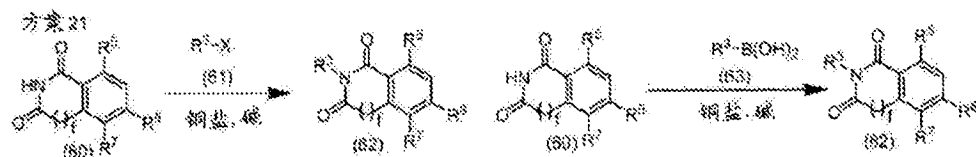


[0688] 使式 (56) 化合物与式 (57) 化合物 (已知化合物或由已知方法制备的化合物) 在偶联剂 (如 1-乙基-3-(3-二甲基氨基丙基) 碳二亚胺、N,N'-二环己基碳二亚胺、0-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐、0-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐、苯并三唑-1-基-氧基三吡咯烷基磷鎓六氟磷酸盐等) 存在下, 在有机溶剂 (如四氢呋喃、1,4-二噁烷、二甲基甲酰胺、二氯甲烷、二氯乙烷、甲醇、乙醇等) 中, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下反应以提供式 (58) 化合物。

[0689] 或者, 使式 (56) 化合物与亚硫酰氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (59) 化合物。或者, 使式 (56) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (59) 化合物。接着使式 (59) 化合物与式 (57) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (58) 化合物。

[0690] 式 (66) 化合物可根据方案 21-22 中概述的方法来制备。

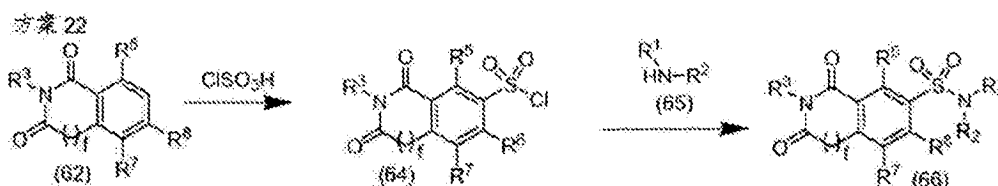
[0691]



[0692] 使式 (60) 化合物 (已知化合物或通过已知方法制备的化合物) 与式 (61) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四(三苯基膦)钯 (0)、二氯双(三苯基膦)钯 (II)、钯/碳、双(乙腈)二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四

氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(62)化合物。或者,使式(30)化合物(已知化合物或通过已知方法制备的化合物)与式(63)化合物(已知化合物或通过已知方法制备的化合物)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(62)化合物。

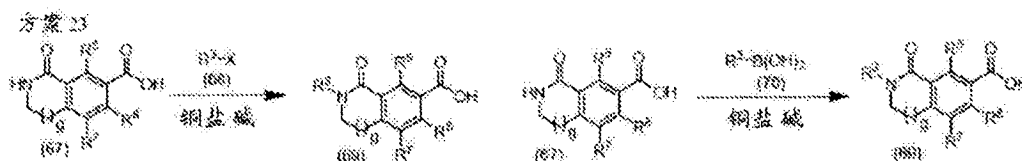
[0693]



[0694] 使式(62)化合物(已知化合物或通过已知方法制备的化合物)与氯磺酸任选在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)存在下反应以提供式(64)化合物。使式(64)化合物与式(65)化合物(已知化合物或通过已知方法制备的化合物)在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)存在下反应以提供式(66)化合物。

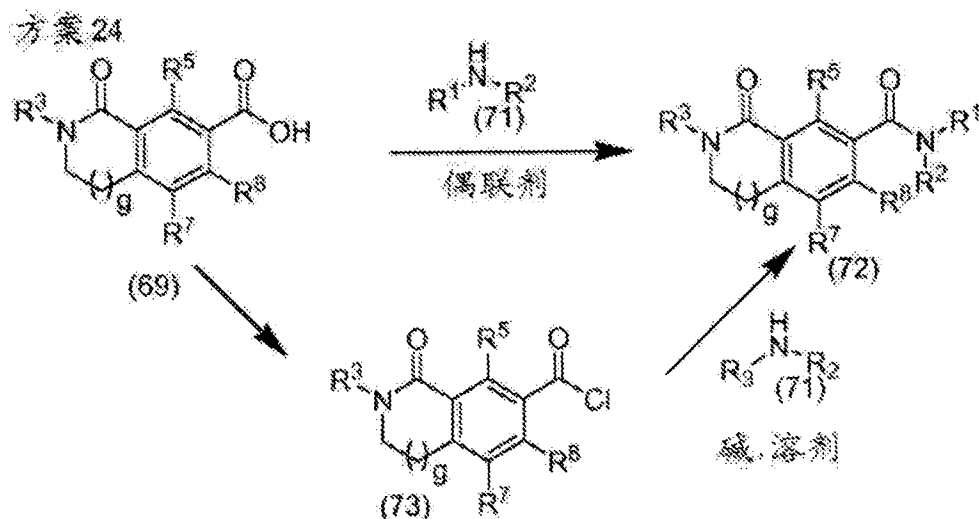
[0695] 式(71)化合物可根据方案23-24中概述的方法来制备。

[0696]



[0697] 使式(67)化合物(已知化合物或通过已知方法制备的化合物)与式(68)化合物(已知化合物或通过已知方法制备的化合物)(其中X是卤素)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(69)化合物。或者,使式(67)化合物(已知化合物或通过已知方法制备的化合物)与式(70)化合物(已知化合物或通过已知方法制备的化合物)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(69)化合物。

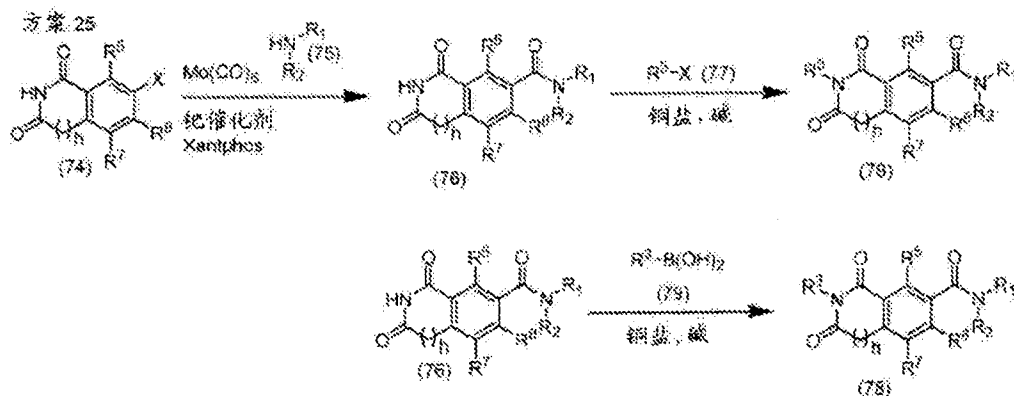
[0698]



[0699] 使式 (69) 化合物与式 (71) 化合物 (已知化合物或通过已知方法制备的化合物) 在偶联剂 (如 1-乙基-3-(3-二甲基氨基丙基) 碳二亚胺、N,N'-二环己基碳二亚胺、0-苯并三唑-N,N,N',N'-四甲基-脲-六氟-磷酸盐、0-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐、苯并三唑-1-基-氧基-三-(二甲基氨基)-磷鎓六氟磷酸盐、苯并三唑-1-基-氧基三吡咯烷基磷鎓六氟磷酸盐等) 存在下, 在有机溶剂 (如四氢呋喃、1,4-二噁烷、二甲基甲酰胺、二氯甲烷、二氯乙烷、甲醇、乙醇等) 中, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下反应以提供式 (72) 化合物。或者, 使式 (69) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (73) 化合物。或者, 使式 (69) 化合物与亚硫酰氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (73) 化合物。接着使式 (73) 化合物与式 (71) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等) 存在下, 任选在 4-N,N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (72) 化合物。

[0700] 式 (78) 化合物可根据方案 25 中概述的方法来制备。

[0701]

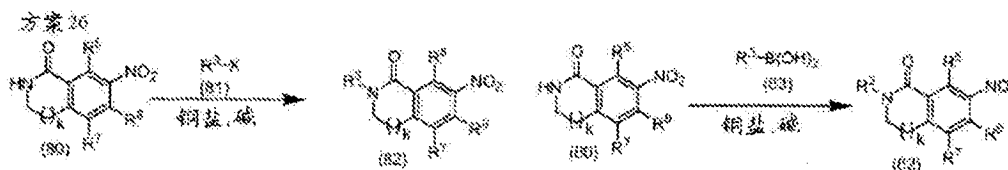


[0702] 使式 (74) 化合物与式 (75) 化合物在六羰基钼存在下, 在钯催化剂 (如乙酸钯

(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,在4,5-双(二苯基膦基)-9,9-二甲基氧杂蒽(Xantphos)存在下,在溶剂(如水、二甲基甲酰胺、二甲基乙酰胺、甲醇、乙醇、二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷等)中,任选在加热下,任选在微波辐射下,任选在惰性氛围(如氮气或氩气)中反应以提供式(76)化合物。使式(76)化合物与式(77)化合物(已知化合物或通过已知方法制备的化合物)(其中X是卤素)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(78)化合物。或者,使式(76)化合物与式(79)化合物(已知化合物或通过已知方法制备的化合物)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(78)化合物。

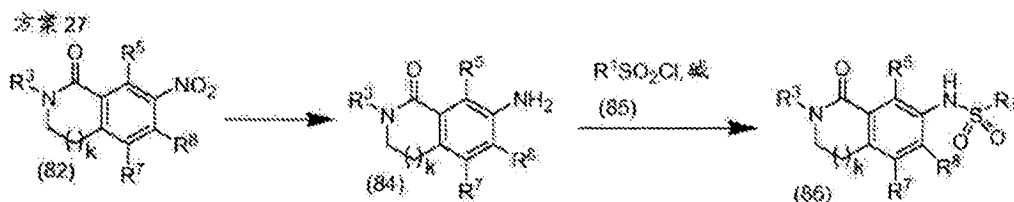
[0703] 式(86)化合物可根据方案26-27中概述的方法来制备。

[0704]



[0705] 使式(80)化合物与式(81)化合物(已知化合物或通过已知方法制备的化合物)(其中X是卤素)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(82)化合物。或者,使式(80)化合物与式(83)化合物(已知化合物或通过已知方法制备的化合物)在铜盐(如硫酸铜、碘化铜、氯化铜、乙酸铜等)存在下,任选在钯催化剂(如乙酸钯(II)、四(三苯基膦)钯(0)、二氯双(三苯基膦)钯(II)、钯/碳、双(乙腈)二氯钯(II)等)存在下,任选在碱(如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等)存在下,在溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等)中,任选在加热下,任选在微波辐射下反应以提供式(82)化合物。

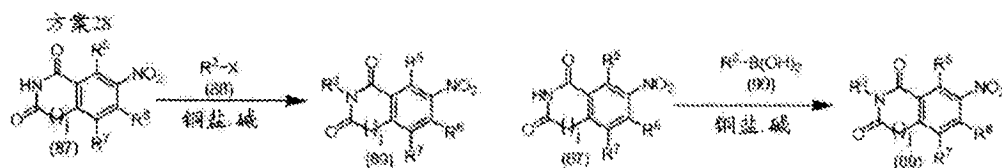
[0706]



[0707] 接着使式 (82) 化合物与氯化锡在酸 (如盐酸、硫酸等) 存在下, 在有机溶剂 (如四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (84) 化合物。或者, 使式 (82) 化合物与氢气在钯催化剂 (如钯 / 碳、乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在乙酸存在下, 任选在溶剂 (如甲醇、乙醇、四氢呋喃、1, 4- 二噁烷等) 中反应以提供式 (84) 化合物。接着使式 (84) 化合物与式 (85) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (86) 化合物。

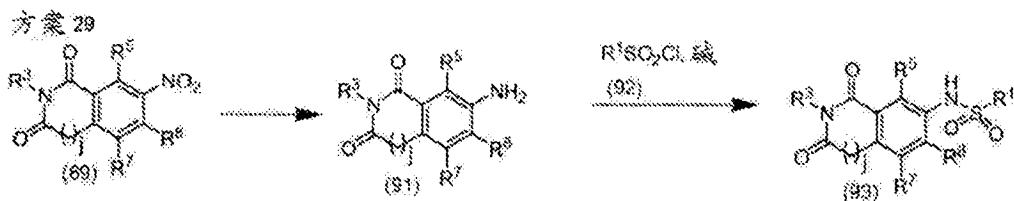
[0708] 式 (93) 化合物可根据方案 28-29 中概述的方法来制备。

[0709]



[0710] 使式 (87) 化合物与式 (88) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (89) 化合物。或者, 使式 (87) 化合物与式 (90) 化合物 (已知化合物或通过已知方法制备的化合物) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (89) 化合物。

[0711]

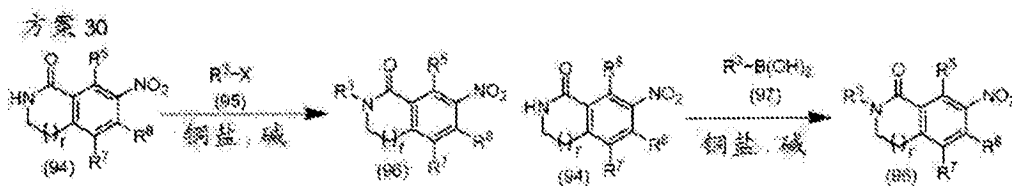


[0712] 接着使式 (89) 化合物与氯化锡在酸 (如盐酸、硫酸等) 存在下, 在有机溶剂 (如四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等) 中反应以提供式 (91) 化合物。或者, 使式 (89)

化合物与氢气在钯催化剂（如钯/碳、乙酸钯 (II)、四（三苯基膦）钯 (0)、二氯双（三苯基膦）钯 (II)、钯/碳、双（乙腈）二氯钯 (II) 等）存在下，任选在乙酸存在下，任选在溶剂（如甲醇、乙醇、四氢呋喃、1,4-二噁烷等）中反应以提供式 (91) 化合物。接着使式 (91) 化合物与式 (92) 化合物（已知化合物或通过已知方法制备的化合物）在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式 (93) 化合物。

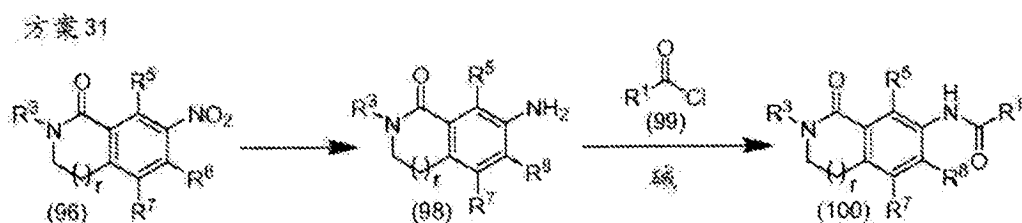
[0713] 式 (100) 化合物可根据方案 30-31 中概述的方法来制备。

[0714]



[0715] 使式 (94) 化合物与式 (95) 化合物（已知化合物或通过已知方法制备的化合物）（其中 X 是卤素）在铜盐（如硫酸铜、碘化铜、氯化铜、乙酸铜等）存在下，任选在钯催化剂（如乙酸钯 (II)、四（三苯基膦）钯 (0)、二氯双（三苯基膦）钯 (II)、钯/碳、双（乙腈）二氯钯 (II) 等）存在下，任选在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，在溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中，任选在加热下，任选在微波辐射下反应以提供式 (96) 化合物。或者，使式 (94) 化合物与式 (97) 化合物（已知化合物或通过已知方法制备的化合物）在铜盐（如硫酸铜、碘化铜、氯化铜、乙酸铜等）存在下，任选在钯催化剂（如乙酸钯 (II)、四（三苯基膦）钯 (0)、二氯双（三苯基膦）钯 (II)、钯/碳、双（乙腈）二氯钯 (II) 等）存在下，任选在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，在溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中，任选在加热下，任选在微波辐射下反应以提供式 (96) 化合物。

[0716]

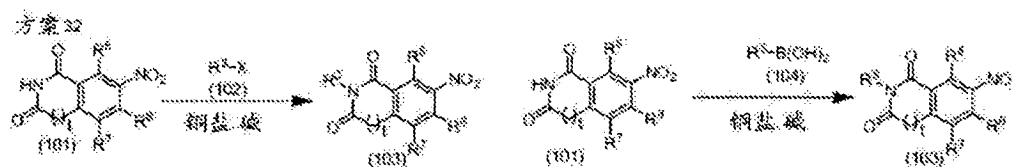


[0717] 接着使式 (96) 化合物与氯化锡在酸（如盐酸、硫酸等）存在下，在有机溶剂（如四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式化合物以提供式 (98) 化合物。或者，使式 (96) 化合物与氢气在钯催化剂（如钯/碳、乙酸钯 (II)、四（三苯基膦）钯 (0)、二氯双（三苯基膦）钯 (II)、钯/碳、双（乙腈）二氯钯 (II) 等）存在下，任选在乙酸存在下，任选在溶剂（如甲醇、乙醇、四氢呋喃、1,4-二噁烷等）中反应以提供式 (98) 化合物。接着使式 (98) 化合物与式 (99) 化合物（已知化合物或通过已知方法制备的化合物）在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式化合物以提供式 (100) 化

合物。

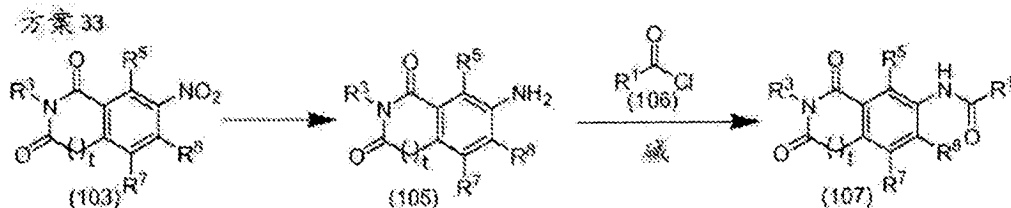
[0718] 式 (107) 化合物可根据方案 32-33 中概述的方法来制备。

[0719]



[0720] 使式 (101) 化合物与式 (102) 化合物 (已知化合物或通过已知方法制备的化合物) (其中 X 是卤素) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6-二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (103) 化合物。或者, 使式 (101) 化合物与式 (104) 化合物 (已知化合物或通过已知方法制备的化合物) 在铜盐 (如硫酸铜、碘化铜、氯化铜、乙酸铜等) 存在下, 任选在钯催化剂 (如乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6-二甲基吡啶等) 存在下, 在溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中, 任选在加热下, 任选在微波辐射下反应以提供式 (103) 化合物。

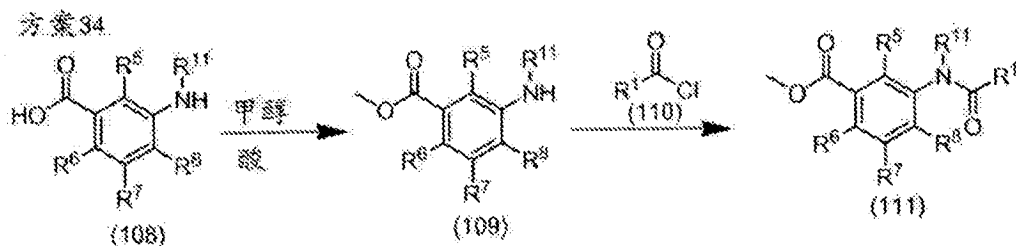
[0721]



[0722] 接着使式 (103) 化合物与氯化锡在酸 (如盐酸、硫酸等) 存在下, 在有机溶剂 (如四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (105) 化合物。或者, 使式 (103) 化合物与氢气在钯催化剂 (如钯 / 碳、乙酸钯 (II)、四 (三苯基膦) 钯 (0)、二氯双 (三苯基膦) 钯 (II)、钯 / 碳、双 (乙腈) 二氯钯 (II) 等) 存在下, 任选在乙酸存在下, 任选在溶剂 (如甲醇、乙醇、四氢呋喃、1, 4-二噁烷等) 中反应以提供式化合物以提供式 (105) 化合物。接着使式 (105) 化合物与式 (106) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6-二甲基吡啶等) 存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中反应以提供式化合物以提供式 (107) 化合物。

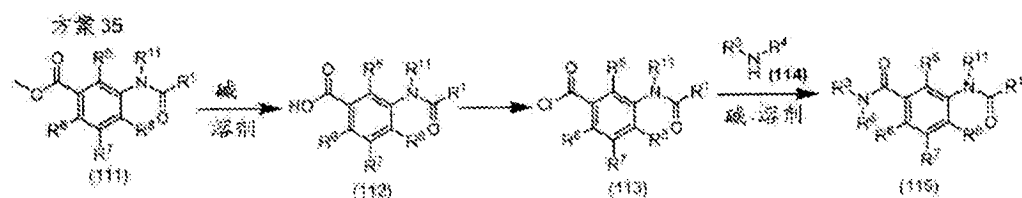
[0723] 式 (115) 化合物可根据方案 34-35 中概述的方法来制备。

[0724]



[0725] 使式 (108) 化合物 (已知化合物或通过已知方法制备的化合物) 与甲醇在酸 (如盐酸、硫酸) 存在下, 任选在加热下反应以提供式 (109) 化合物。使式 (109) 化合物与式 (110) 化合物 (已知化合物或通过已知方法制备的化合物) 在碱 (如吡啶、2, 6-二甲基吡啶等) 存在下, 任选在二甲基氨基吡啶 (DMAP) 存在下, 任选在溶剂 (如二甲基甲酰胺、二甲基乙酰胺、二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷等) 存在下, 任选在加热下反应以提供式 (111) 化合物。

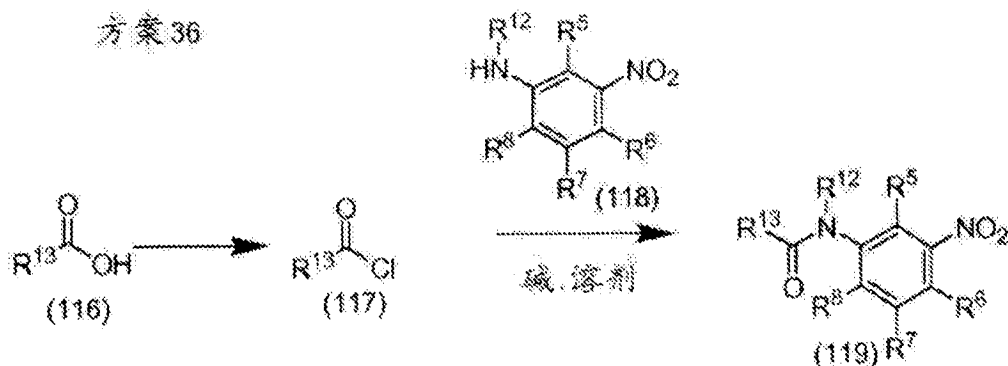
[0726]



[0727] 使式 (111) 化合物与碱 (如氢氧化锂、氢氧化钠、氢氧化钾、氢氧化铯、碳酸钾、碳酸钠等) 在溶剂 (如乙醇、甲醇、水、二甲基甲酰胺、二甲基乙酰胺、四氢呋喃、1, 4-二噁烷等) 中反应以提供式 (112) 化合物。接着使式 (112) 化合物与亚硫酰氯任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 存在下反应以提供式 (113) 化合物。或者, 使式 (112) 化合物与草酰氯任选在二甲基甲酰胺存在下, 任选在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (113) 化合物。接着使式 (113) 化合物与式 (114) 化合物 (已知化合物或通过已知方法制备的化合物) 任选在碱 (如三乙胺、二异丙基乙胺、吡啶、2, 6-二甲基吡啶等) 存在下, 任选在 4-N, N-二甲基氨基吡啶存在下, 在有机溶剂 (如二氯甲烷、二氯乙烷、四氢呋喃、1, 4-二噁烷、二甲基甲酰胺等) 中反应以提供式 (115) 化合物。

[0728] 式 (122) 化合物可根据方案 36-37 中概述的方法来制备。

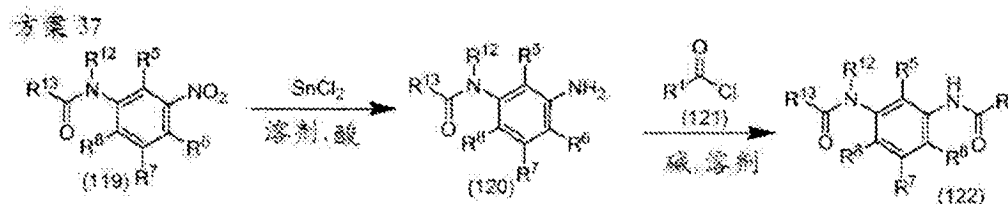
[0729]



[0730] 使式 (116) 化合物 (已知化合物或通过已知方法制备的化合物) 与亚硫酰氯任选

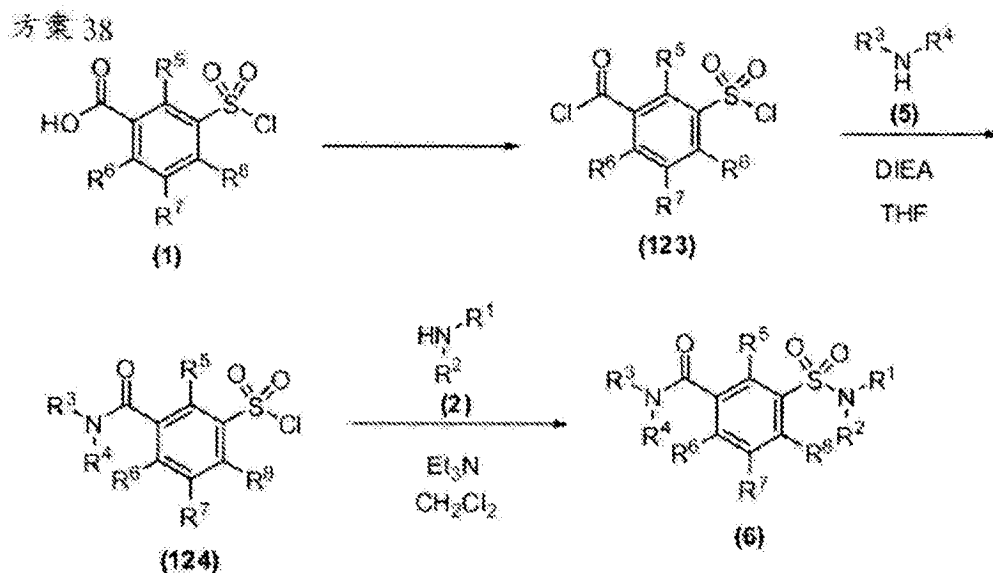
在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）存在下反应以提供式 (117) 化合物。或者，使式 (116) 化合物与草酰氯任选在二甲基甲酰胺存在下，任选在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式 (117) 化合物。接着使式 (117) 化合物与式 (118) 化合物（已知化合物或通过已知方法制备的化合物）任选在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，任选在 4-N,N-二甲基氨基吡啶存在下，在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式 (119) 化合物。

[0731]



[0732] 接着使式 (119) 化合物与氯化锡在酸（如盐酸、硫酸等）存在下，在有机溶剂（如四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式化合物以提供式 (120) 化合物。接着使式 (120) 化合物与式 (121) 化合物（已知化合物或通过已知方法制备的化合物）任选在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在下，任选在 4-N,N-二甲基氨基吡啶存在下，在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式 (122) 化合物。

[0733]



[0734] 或者，使式 (1) 化合物（已知化合物或通过已知方法制备的化合物）与亚硫酰氯任选在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）存在下反应以提供式 (123) 化合物。或者，使式 (1) 化合物与草酰氯任选在二甲基甲酰胺存在下，任选在有机溶剂（如二氯甲烷、二氯乙烷、四氢呋喃、1,4-二噁烷、二甲基甲酰胺等）中反应以提供式 (123) 化合物。接着使式 (123) 化合物与式 (5) 化合物（已知化合物或通过已知方法制备的化合物）任选在碱（如三乙胺、二异丙基乙胺、吡啶、2,6-二甲基吡啶等）存在

下,任选在 4-N, N- 二甲基氨基吡啶存在下,在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等)中反应以提供式 (124) 化合物。接着使式 (124) 化合物与式 (2) 化合物(已知化合物或通过已知方法制备的化合物)任选在碱(如三乙胺、二异丙基乙胺、吡啶、2, 6- 二甲基吡啶等)存在下,任选在 4-N, N- 二甲基氨基吡啶存在下,在有机溶剂(如二氯甲烷、二氯乙烷、四氢呋喃、1, 4- 二噁烷、二甲基甲酰胺等)中反应以提供式 (6) 化合物。

[0735] 制剂和治疗方法

[0736] 本发明也涉及包含本发明化合物的组合物或制剂。一般来说,本发明的组合物包含有效量的一种或多种有效用于治疗病毒性感染,尤其乙型肝炎病毒(HBV)感染和相关病状的根据本发明的本公开的化合物及其盐;以及一种或多种药学上可接受的赋形剂。

[0737] 出于本发明的目的,术语“赋形剂”和“载体”在本发明的整篇描述中可互换使用,并且所述术语在本文中定义为“用于实施配制安全且有效药物组合物的成分”。

[0738] 配制者将了解,赋形剂主要用于递送安全、稳定以及功能性药物的作用,从而不仅充当用于递送的总体媒介物的一部分,而且也充当用于达成由接受者有效吸收活性成分的手段。赋形剂可作为惰性填充剂简单和直接地发挥作用,或如本文所用的赋形剂可为 pH 稳定化系统或包衣的一部分以确保向胃安全递送成分。配制者也可利用本发明化合物具有改进的细胞效价、药物动力学性质以及改进的口服生物利用度的事实。

[0739] 本教义也提供包括至少一种本文所述的化合物以及一种或多种药学上可接受的载体、赋形剂或稀释剂的药物组合物。所述载体的实例为本领域技术人员所熟知,并且可根据可接受的药物程序制备,所述程序例如像 Remington's Pharmaceutical Sciences, 第 17 版, Alfonso R. Gennaro 编, Mack Publishing Company, Easton, PA (1985) 中所述的那些,所述书籍的整个公开内容出于所有目的以引用的方式并入本文。如本文所用,“药学上可接受”是指某一物质就毒理学观点来看可为在药物应用中使用所接受,并且不会不利地与活性成分相互作用。因此,药学上可接受的载体是可与制剂中的其它成分相容,并且在生物学上可接受的那些。补充性活性成分也可并入药物组合物中。

[0740] 本教义的化合物可经口服或经胃肠外单纯或与常规药物载体组合施用。适合的固体载体可包括一种或多种也可充当调味剂、润滑剂、增溶剂、助悬剂、填充剂、助流剂、压制助剂、粘合剂或片剂崩解剂或囊封材料的物质。所述化合物可以常规方式,例如以与用于已知抗病毒剂的方式类似的方式配制。含有本文公开的化合物的口服制剂可包括任何常规使用的口服形式,包括片剂、胶囊、经颊形式、锭剂、糖锭和口服液体、混悬液或溶液。在粉剂中,载体可为微细固体,其是与微细化合物的掺合物。在片剂中,可以适合比例使本文公开的化合物与具有必要压制性质的载体混合,并且以所需形状和尺寸加以压制。粉剂和片剂可含有多达 99% 的化合物。

[0741] 胶囊可含有一种或多种本文公开的化合物与惰性填充剂和/或稀释剂如药学上可接受的淀粉(例如玉米、马铃薯或木薯淀粉)、糖、人工甜味剂、粉状纤维素(例如结晶和微晶纤维素)、面粉、明胶、树胶等的混合物。

[0742] 有用的片剂制剂可通过常规压制、湿法制粒或干法制粒方法来制备,并且利用药学上可接受的稀释剂、粘合剂、润滑剂、崩解剂、表面改性剂(包括表面活性剂)、助悬剂或稳定剂,包括但不限于硬脂酸镁、硬脂酸、月桂基硫酸钠、滑石、糖、乳糖、糊精、淀粉、明胶、

纤维素、甲基纤维素、微晶纤维素、羧甲基纤维素钠、羧甲基纤维素钙、聚乙烯吡咯烷、海藻酸、阿拉伯胶、黄原胶、柠檬酸钠、复合硅酸盐、碳酸钙、甘氨酸、蔗糖、山梨糖醇、磷酸二钙、硫酸钙、乳糖、高岭土、甘露糖醇、氯化钠、低熔点蜡和离子交换树脂。表面改性剂包括非离子和阴离子表面改性剂。表面改性剂的代表性实例包括但不限于泊洛沙姆 188(poloxamer 188)、苯扎氯铵、硬脂酸钙、鲸蜡硬脂醇、聚西托醇乳化蜡、脱水山梨醇酯、胶体二氧化硅、磷酸盐、十二烷基磺酸钠、硅酸铝镁和三乙醇胺。本文口服制剂可利用标准延迟或定时释放制剂来改变化合物的吸收。口服制剂也可由施用以含根据需要含有适当增溶剂或乳化剂的水或果汁形式本文公开的化合物组成。

[0743] 液体载体可用于制备溶液、混悬液、乳液、糖浆、酏剂,并且用于吸入递送。可将本教义的化合物溶解或混悬于药学上可接受的液体载体,如水、有机溶剂、或两者的混合物、或药学上可接受的油或脂肪中。液体载体可含有其它适合药物添加剂,如增溶剂、乳化剂、缓冲剂、防腐剂、甜味剂、调味剂、助悬剂、增稠剂、着色剂、粘度调控剂、稳定剂和渗透调控剂。供口服和胃肠外施用的液体载体的实例包括但不限于水(特别是含有如本文所述的添加剂,例如纤维素衍生物,如羧基甲基纤维素钠溶液)、醇(包括一元醇和多元醇,例如二醇)和它们的衍生物、以及油(例如分馏椰子油和花生油)。对于胃肠外施用,载体可为油性酯,如油酸乙酯和肉豆蔻酸异丙酯。无菌液体载体用于供胃肠外施用的无菌液体形式组合物中。用于加压组合物的液体载体可为卤素化烃或其它药学上可接受的推进剂。

[0744] 为无菌溶液或混悬液的液体药物组合物可通过例如肌肉内、腹膜内或皮下注射来利用。无菌溶液也可静脉内施用。供口服施用的组合物可呈液体或固体形式。

[0745] 优选地,药物组合物呈单位剂型,例如呈片剂、胶囊、粉剂、溶液、混悬剂、乳剂、颗粒剂或栓剂形式。在所述形式中,药物组合物可再分成含有适量化合物的单位剂量。单位剂型可为包装组合物,例如含有液体的包装粉剂、小瓶、安瓿、预填充注射器或囊剂。或者,单位剂型可为胶囊或片剂自身,或它可为适当数目的呈包装形式的任何所述组合物。所述单位剂型可含有约 1mg/kg 化合物至约 500mg/kg 化合物,并且可以单次剂量或以两次或更多次剂量给予。所述剂量可以用于将化合物引导至接受者的血流中的任何方式,包括口服、通过植入物、经胃肠外(包括静脉内、腹膜内和皮下注射)、经直肠、经阴道和经皮施用。

[0746] 当施用以治疗或抑制特定疾病状态或病症时,应了解,有效剂量可视所用特定化合物、施用模式和所治疗的病状的严重性、以及与所治疗的个体相关的各种身体因素而变化。在治疗应用中,本教义的化合物可以足以治愈或至少部分改善疾病和它的并发症的症状的量向已罹患所述疾病的患者提供。待用于治疗特定个体的剂量通常必须由主治医师主观确定。涉及的变量包括特定病状和它的状态以及患者的身材、年龄和应答模式。

[0747] 在一些情况下,可合乎需要的是使用装置直接向患者的气道施用化合物,所述装置如但不限于剂量计量吸入器、呼吸操纵的吸入器、多剂量干粉剂吸入器、泵、挤压触动的雾化喷雾剂分配器、气雾剂分配器和气雾剂雾化器。对于通过鼻内或支气管内吸入进行的施用,可将本教义的化合物配制成液体组合物、固体组合物或气雾剂组合物。通过说明方式,液体组合物可包括一种或多种溶解、部分溶解、或混悬于一种或多种药学上可接受的溶剂中的本教义的化合物,并且可例如通过泵或挤压触动的雾化喷雾剂分配器来施用。溶剂可例如为等张盐水或抑菌水。通过说明方式,固体组合物可为包括一种或多种与乳糖或可为支气管内使用所接受的其它惰性粉末混杂的本教义的化合物的粉末制剂,并且可例如通

过气雾剂分配器或破坏或刺穿包覆固体组合物的胶囊,并且递送固体组合物以达成吸入的装置来施用。通过说明方式,气雾剂组合物可包括一种或多种本教义的化合物、推进剂、表面活性剂和共溶剂,并且可例如通过计量装置来施用。推进剂可为氯氟烃(CFC)、氢氟烷(HFA)或在生理上和在环境上可接受的其它推进剂。

[0748] 本文所述的化合物可经胃肠外或经腹膜内施用。这些化合物或其药学上可接受的盐、水合物或酯的溶液或混悬液可于适当地与如羟基-丙基纤维素的表面活性剂混合的水中制备。分散液也可于甘油、液体聚乙二醇及其于油中的混合物中制备。在一般储存和使用条件下,这些制剂通常含有防腐剂以抑制微生物生长。

[0749] 适于注射的药物形式可包括无菌水溶液或分散液以及用于临时制备无菌可注射溶液或分散液的无菌粉剂。在一些实施方案中,所述形式可无菌,并且它的粘度允许它流过注射器。所述形式优选在制造和储存条件下是稳定的,并且可防止如细菌和真菌的微生物的污染作用。载体可为溶剂或分散介质,其含有例如水、乙醇、多元醇(例如甘油、丙二醇和液体聚乙二醇)、其适合混合物以及植物油。

[0750] 本文所述的化合物可经皮施用,即跨越身体表面以及身体通道的内衬(包括上皮和粘膜组织)施用。所述施用可使用本教义的化合物,包括其药学上可接受的盐、水合物或酯以洗剂、乳膏剂、泡沫剂、贴片、混悬剂、溶液和栓剂(直肠和阴道)形式来进行。

[0751] 经皮施用可通过使用含有如本文公开的化合物的化合物以及可对所述化合物呈惰性、可对皮肤无毒并且可允许递送所述化合物以经由皮肤全身性吸收至血流中的载体的经皮贴片来达成。载体可采用许多形式,如乳膏剂和软膏剂、糊剂、凝胶剂和闭塞性装置。乳膏剂和软膏剂可为水包油或油包水型粘性液体或半固体乳液。由分散在石油或亲水性石油中的含有所述化合物的吸收性粉末组成的糊剂也可适合的。多种闭塞性装置可用于将所述化合物释放至血流中,如覆盖含有化合物,具有或不具有载体的贮存器的半透膜,或含有所述化合物的基质。其它闭塞性装置在文献中是已知的。

[0752] 本文所述的化合物可以常规栓剂形式经直肠或经阴道施用。栓剂制剂可由包括可可脂(添加或不添加蜡以改变栓剂的熔点)和甘油的传统材料制得。也可使用水溶性栓剂基质,如具有各种分子量的聚乙二醇。

[0753] 脂质制剂或纳米胶囊可用于在体外或在体内将本教义的化合物引入宿主细胞中。脂质制剂和纳米胶囊可通过本领域中已知的方法来制备。

[0754] 为增加本教义的化合物的有效性,可合乎需要的是将化合物与有效治疗靶疾病的其它药剂组合。举例来说,有效治疗靶疾病的其它活性化合物(即其它活性成分或药剂)可与本教义的化合物一起施用。其它药剂可与本文公开的化合物同时或不同时施用。

[0755] 本教义的化合物可适用于治疗或抑制例如人受试者的哺乳动物的病理性病状或病症。因此,本教义提供通过向哺乳动物(包括人患者)提供本教义的化合物(包括其药学上可接受的盐)或包括一种或多种与药学上可接受的载体组合或联合的本教义的化合物的药物组合物来治疗或抑制病理性病状或病症的方法。本教义的化合物可单独或其它治疗有效化合物或疗法组合施用以治疗或抑制病理性疾患或病症。

[0756] 根据本发明的组合物的非限制性实例包括约0.001mg至约1000mg一种或多种本发明化合物以及一种或多种赋形剂;约0.01mg至约100mg一种或多种根据本发明的化合物以及一种或多种赋形剂;和约0.1mg至约10mg一种或多种根据本发明的化合物以及一种或

多种赋形剂。

[0757] 在任何以上方法中,本发明的化合物或药学上可接受的盐可以单一疗法或与一种或多种其它治疗剂组合施用。在某些实施方案中,其它治疗剂可包括 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、文献描述的衣壳装配调节剂、5 逆转录酶抑制剂、TLR 激动剂或具有不同或未知机理的药剂或其组合。

[0758] 其它治疗剂选自免疫调节剂或免疫刺激剂疗法,其包括属于干扰素类别的生物药剂,如干扰素 α 2a 或 2b 或修饰的干扰素,如聚乙二醇化干扰素 α 2a、 α 2b、 λ ;或 TLR 调节剂,如 TLR-7 激动剂或 TLR-9 激动剂;或阻断病毒进入或成熟或靶向 HBV 聚合酶的抗病毒剂,如核苷或核苷酸或非核苷或核苷酸聚合酶抑制剂;以及具有不同或未知机理的药剂,包括破坏为 HBV 复制或持续所需的其它必需病毒蛋白质或宿主蛋白质的功能的药剂。

[0759] 逆转录酶抑制剂可包括以下的至少一个:齐多夫定 (Zidovudine)、地达诺新 (Didanosine)、扎西他滨 (Zalcitabine)、ddA、司他夫定 (Stavudine)、拉米夫定 (Lamivudine)、阿巴卡韦 (Abacavir)、恩曲他滨 (Emtricitabine)、恩替卡韦、阿立他滨 (Apricitabine)、阿韦拉平 (Atevirapine)、利巴韦林 (ribavirin)、阿昔洛韦 (acyclovir)、泛昔洛韦 (famciclovir)、伐昔洛韦 (valacyclovir)、更昔洛韦 (ganciclovir)、缙更昔洛韦 (valganciclovir)、替诺福韦、阿德福韦 (Adefovir)、PMPA、昔多福韦 (cidofovir)、依法韦仑 (Efavirenz)、奈韦拉平 (Nevirapine)、德拉韦定 (Delavirdine) 或依曲韦林 (Etravirine)。

[0760] 组合疗法 TLR-7 激动剂可为 SM360320 (9- 苯甲基 -8- 羟基 -2- (2- 甲氧基乙氧基) 腺嘌呤) 或 AZD 8848 ([3-([3-(6- 氨基 -2- 丁氧基 -8- 氧代 -7, 8- 二氢 -9H- 嘌呤 -9- 基) 丙基] [3-(4- 吗啉基) 丙基] 氨基) 甲基) 苯基] 乙酸甲酯)。

[0761] 在这些组合疗法的一些实施方案中,共同配制本发明的化合物或药学上可接受的盐和其它治疗剂。在其它实施方案中,共同施用化合物和其它治疗剂。在其它实施方案中,分开配制或施用本发明的化合物或药学上可接受的盐和其它治疗剂。

[0762] 在组合疗法的其它实施方案中,施用本发明的化合物或药学上可接受的盐允许相较于单独施用至少一种为在有需要的个体中在防治性治疗 HBV 感染方面获得类似结果所需的其它治疗剂,以较低剂量或频率施用其它治疗剂。

[0763] 在组合疗法的其它实施方案中,在施用治疗有效量的本发明的化合物或药学上可接受的盐之前,已知个体为选自由以下组成的组的化合物所难以治疗的:HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同衣壳装配调节剂、具有不同或未知机理的抗病毒化合物或其组合。

[0764] 在方法的其它实施方案中,相较于施用 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同衣壳装配调节剂、具有不同或未知机理的抗病毒化合物或其组合,施用本发明的化合物或药学上可接受的盐在更大程度上降低个体中的病毒载量。

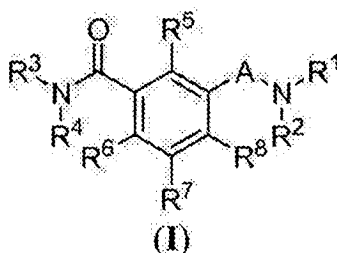
[0765] 在其它实施方案中,施用本发明的化合物或药学上可接受的盐比施用 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同衣壳装配调节剂、具有不同或未知机理的抗病毒化合物或其组合导致更低的病毒突变和 / 或病毒抗性发生率。

[0766] 以下实施方案清单意图补充而非替换或取代先前描述。

[0767] 实施方案 1. 一种包含式 (I) 的结构化合物或其对映异构体、非对映异构体或药

学上接受的盐、水合物或溶剂合物；

[0768]



[0769] 包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中：

[0770] A 选自由 SO_2 和 CO 组成的组；

[0771] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基组成的组； R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基- C_{1-6} -烷氧化物、 $-\text{SO}_2-\text{C}_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基；

[0772] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组； R^2 也可或者或另外任选包括任选取代的 C_{3-7} 环烷基或任选取代的杂环；或

[0773] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环（包括双环或金刚烷基结构）；并且

[0774] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组；在一些实施方案中， R^3 也可包括任选取代的 C_{1-6} 直链烷基；

[0775] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组；

[0776] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^5 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$ ；

[0777] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$ ；或

[0778] R^4 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；并且

[0779] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$ ；

[0780] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $\text{N}(\text{R}^9)_2$ ；或

[0781] R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的碳环或杂环；并且

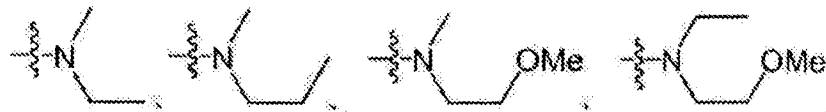
[0782] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组； R^9 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；

[0783] 条件是当 A 是 SO_2 ， R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环；并

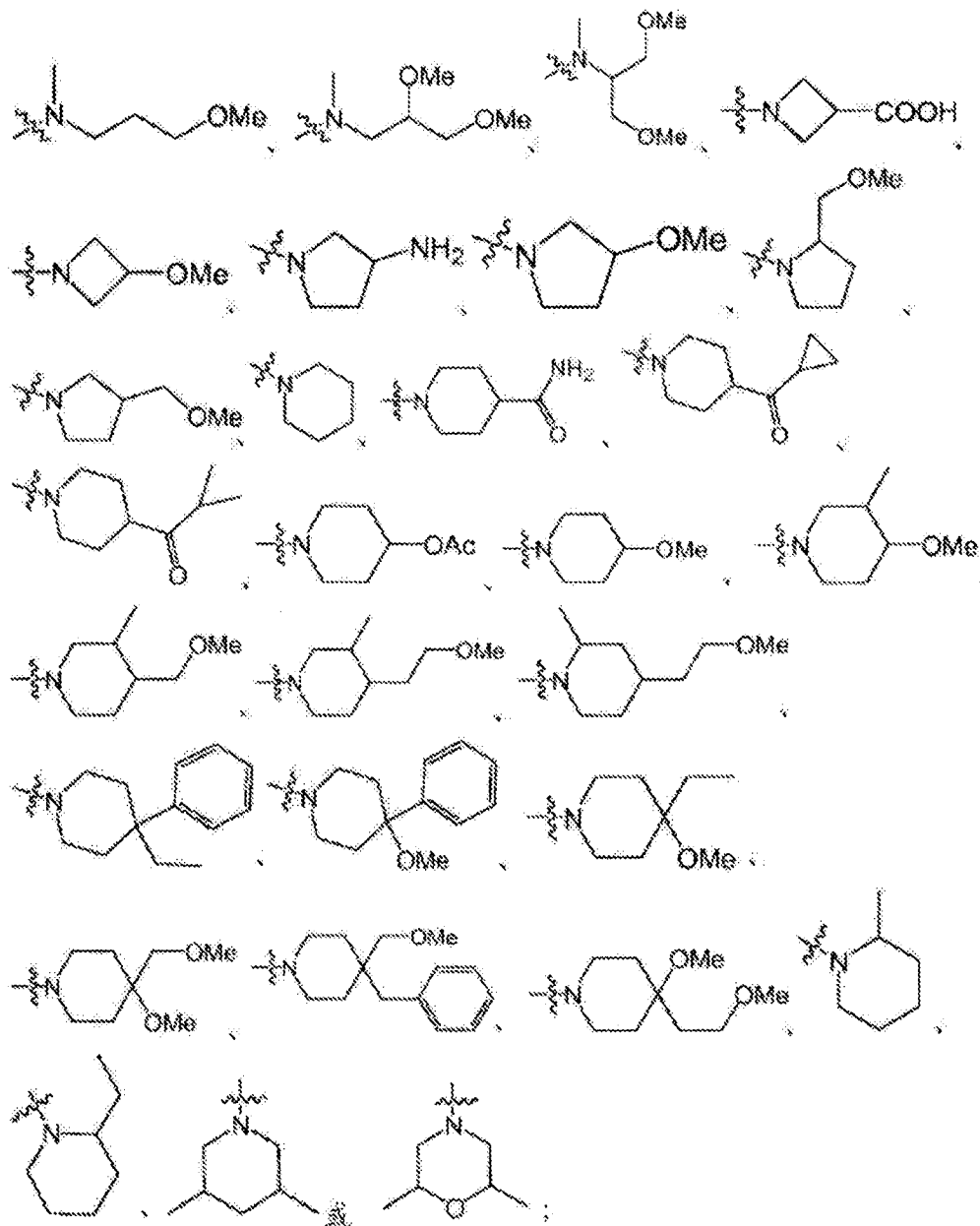
且 R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环时, 那么以下 (a) 至 (d) 都不适用:

[0784] (a) R^3 是任选取代的苯基, 并且 R^1 或 R^2 单独地或当一起时含有羟基, 或

[0785] (b) R^3 是任选取代的烷基或苯基, 并且 $N(R^1)(R^3)$ 是任选取代的哌嗪或



[0786]

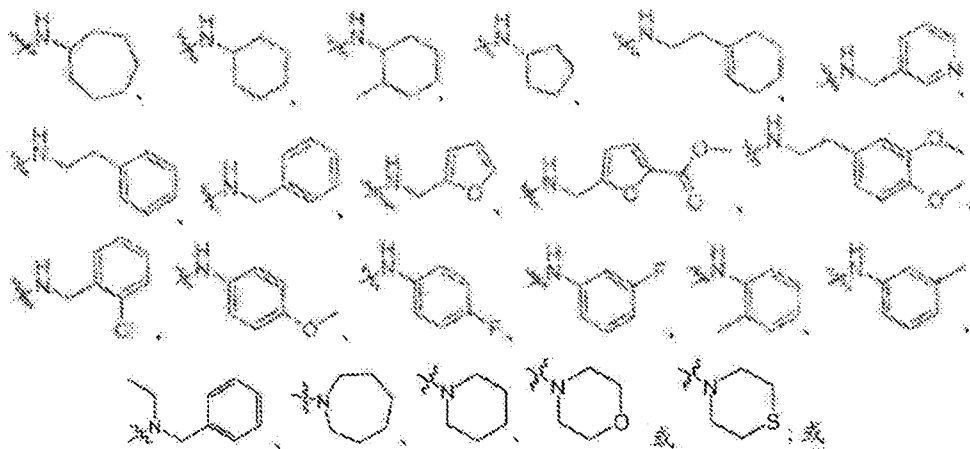


[0787] (c) R^3 是任选取代的烷基、芳基或烷芳基, 并且 $N(R^1)(R^2)$ 是

[0788]



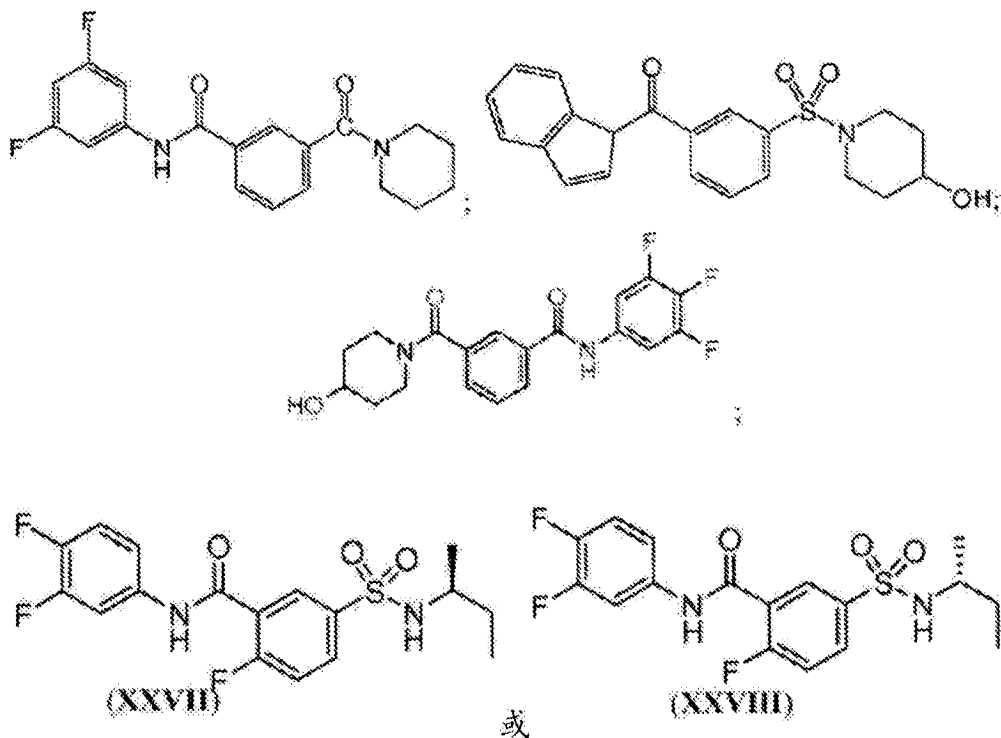
[0789]



[0790] (d) R³或 R⁴是未被取代或被单取代的芳基、或未被取代或被单取代的芳烷基、或未被取代或被单取代的杂芳基,并且 R¹和 R²连同它们所结合的原子一起形成具有 6 至 12 个原子的任选取代的杂环结构;或

[0791] 条件是化合物不是 3-[[(二环丙基甲基) 氨基] 磺酰基]-N-(4-异丙氧基苯基) 苯甲酰胺; 或 3-[[(2-(1H-苯并咪唑-2-基) 丙基) 氨基] 磺酰基]-N-(4-异丙氧基苯基) 苯甲酰胺; 或 3-[(环己基氨基) 磺酰基]-N-(4-异丙基苯基) 苯甲酰胺; 或 3-(苯胺基磺酰基)-N-(4-异丙基苯基) 苯甲酰胺; 或 5-[[(3-[[(4-甲氧基苯基) 氨基] 羰基] 苯基) 磺酰基] 氨基] 戊酸; 或 3-[(叔丁基氨基) 磺酰基]-N-(4-甲氧基苯基) 苯甲酰胺; 或 (3S)-1-[(3-[(5-异丙氧基吡啶-2-基) 氨基] 羰基] 苯基) 磺酰基] 哌啶-3-甲酰胺; 或 (3R)-1-[(3-[(5-异丙氧基吡啶-2-基) 氨基] 羰基] 苯基) 磺酰基] 哌啶-3-甲酰胺; 或 3-(哌啶-1-基磺酰基)-N-[(1S)-1,2,3,4-四氢萘-1-基] 苯甲酰胺; 或 N-(5-溴-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺; 或 N-(3-甲氧基-5-苯基吡啶-2-基)-3-(吡咯烷-1-基磺酰基) 苯甲酰胺; 或 N-(3-甲氧基-5-苯氧基吡啶-2-基)-3-(吡咯烷-1-基磺酰基) 苯甲酰胺; 或 N-[3-甲氧基-5-(苯硫基) 吡啶-2-基]-3-(吡咯烷-1-基磺酰基) 苯甲酰胺; 或 N-(5-乙基-3-甲氧基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺; 或 N-(3-甲氧基-5-乙烯基吡啶-2-基)-3-(哌啶-1-基磺酰基) 苯甲酰胺; 或

[0792]



[0793] 式(I)化合物的一些实施方案也排除当A是SO₂;R⁴和R⁶连同它们所结合的原子一起不形成任选取代的环;并且R²和R⁸连同它们所结合的原子一起不形成任选取代的环,R³是任选取代的烷基、芳基或烷芳基,并且N(R¹)(R²)是任选取代的哌啶时的那些化合物。

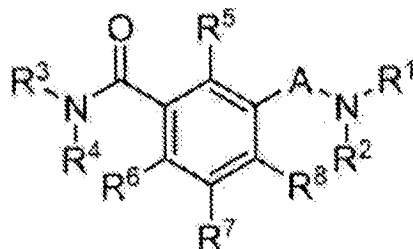
[0794] 实施方案2. 所述式(I)化合物,其中:

[0795] R⁴和R⁶连同它们所结合的原子一起不形成任选取代的环;并且

[0796] R²和R⁸连同它们所结合的原子一起不形成任选取代的环;

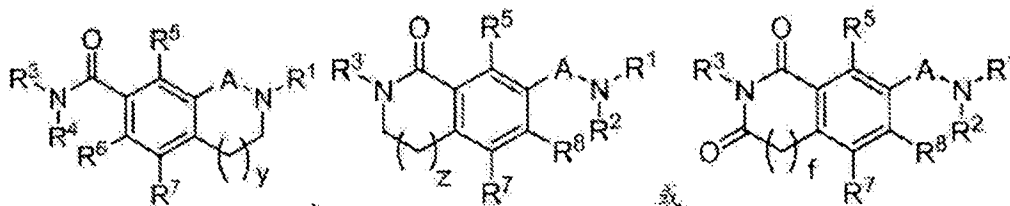
[0797] 由此提供具有下式的化合物:

[0798]



[0799] 实施方案3. 如实施方案1所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,所述化合物包含以下结构之一:

[0800]



[0801] 其中,视情况:

[0802] R^4 和 R^6 连同它们所结合的原子一起不形成任选取代的环;并且

[0803] R^2 和 R^8 连同它们所结合的原子一起不形成任选取代的环;并且

[0804] 其中 z 和 f 独立地是0或1,并且 y 独立地是0、1或2。

[0805] 实施方案4. 如实施方案1至3中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中A是 SO_2 。

[0806] 实施方案5. 如实施方案1至3中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中A是CO。

[0807] 实施方案6. 如实施方案1至5中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

[0808] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基、任选取代的烷基杂芳基和任选取代的 C_{1-6} 直链烷基组成的组;并且

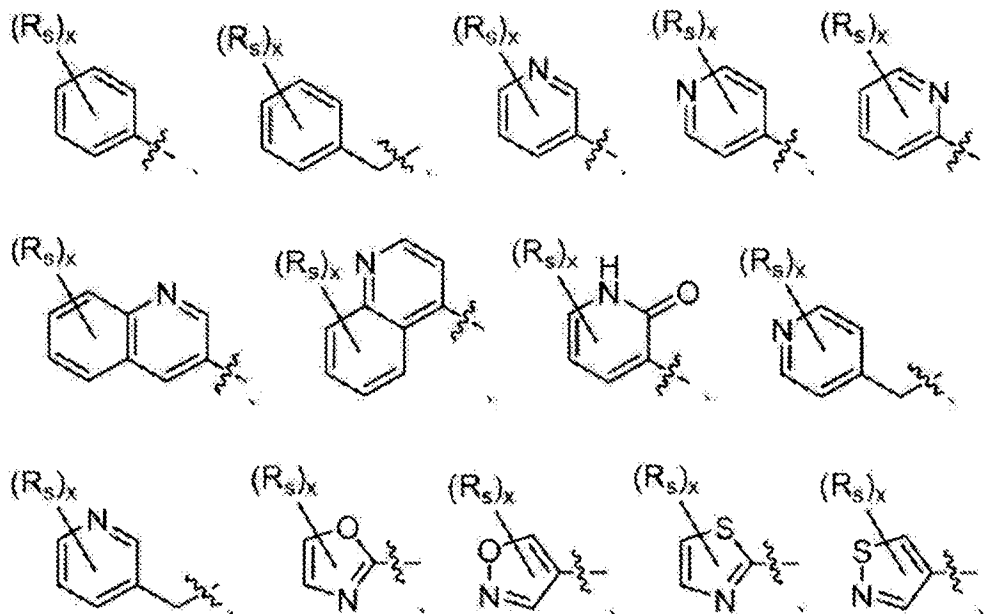
[0809] 当存在时, R^4 是氢。

[0810] 实施方案7. 如实施方案6所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

[0811] R^3 选自由任选取代的苯基、任选取代的苯甲基、任选取代的苯并异噻唑基、任选取代的苯并噻唑基、任选取代的呋喃基、任选取代的咪唑基、任选取代的吡啶基、任选取代的吡啶-2-酮-基、任选取代的吡啶基、任选取代的吡咯基、任选取代的喹啉基、任选取代的噻唑基、任选取代的噻吩基和任选取代的甲基吡啶基组成的组。

[0812] 实施方案8. 如实施方案7所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中 R^3 是

[0813]



[0814]



[0815] 其中

[0816] R_s 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化 C_{1-6} 烷基（例如 $-CH_3$ 、 $-CH_2F$ 、 $-CF_2H$ 、 $-CF_3$ ）、 $-O-(C_{1-6}烷基)$ ，或当两个 R_s 一起形成稠环部分或杂环部分时；并且

[0817] x 是 0、1、2 或 3；并且

[0818] 当存在时， R^1 是氢。

[0819] 应了解，指示符  指示当化合价允许时，取代基可存在于任何可用环成员上

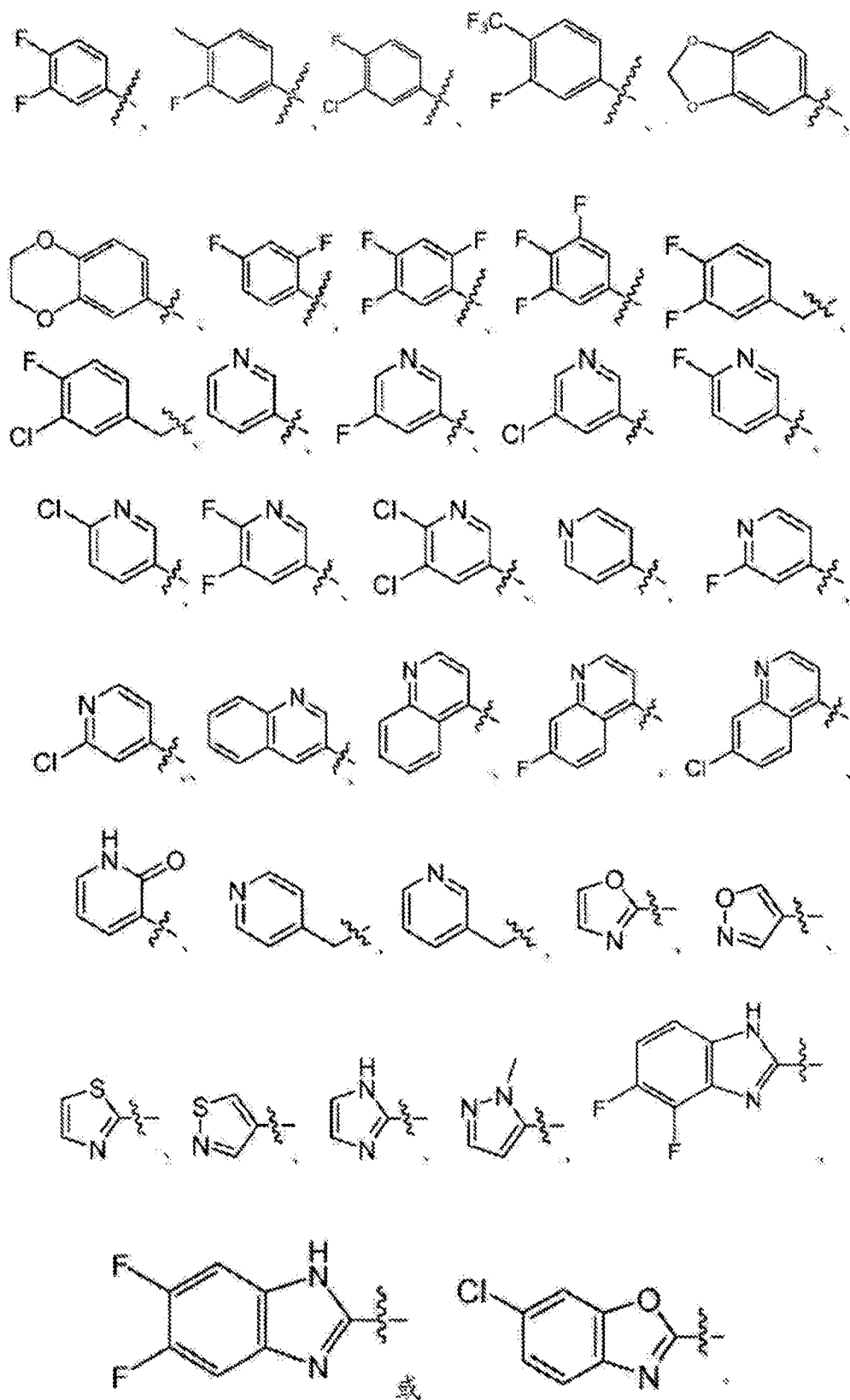
（包括在氮上进行烷基取代）。对于稠合双环系统，相同指示符暗示当化合价允许时，取代基可存在于任一环的环成员上。

[0820] 实施方案 9. 如实施方案 1 至 7 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其中 R^3 的任选取代包括至少一个卤代或 C_{1-6} 烷基。

[0821] 实施方案 10. 如实施方案 8 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物，其中 R^3 的所述任选取代包括至少一个卤代。

[0822] 实施方案 11. 如实施方案 1 至 9 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 R^3 是

[0823]

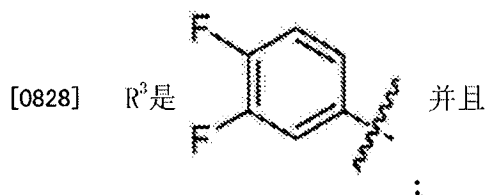


[0824] 实施方案 12. 如实施方案 1 至 10 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

[0825] R^5 和 R^7 在每次出现时都各自独立地是H或F;并且

[0826] R^6 和 R^8 在每次出现时都各自独立地是氢、氯代、氟代或 C_{1-3} 烷基或 C_{1-3} 烷氧基。

[0827] 实施方案 13. 如实施方案 1 至 11 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中



[0829] 当存在时, R^4 是氢。

[0830] 实施方案 14. 如实施方案 1 至 12 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

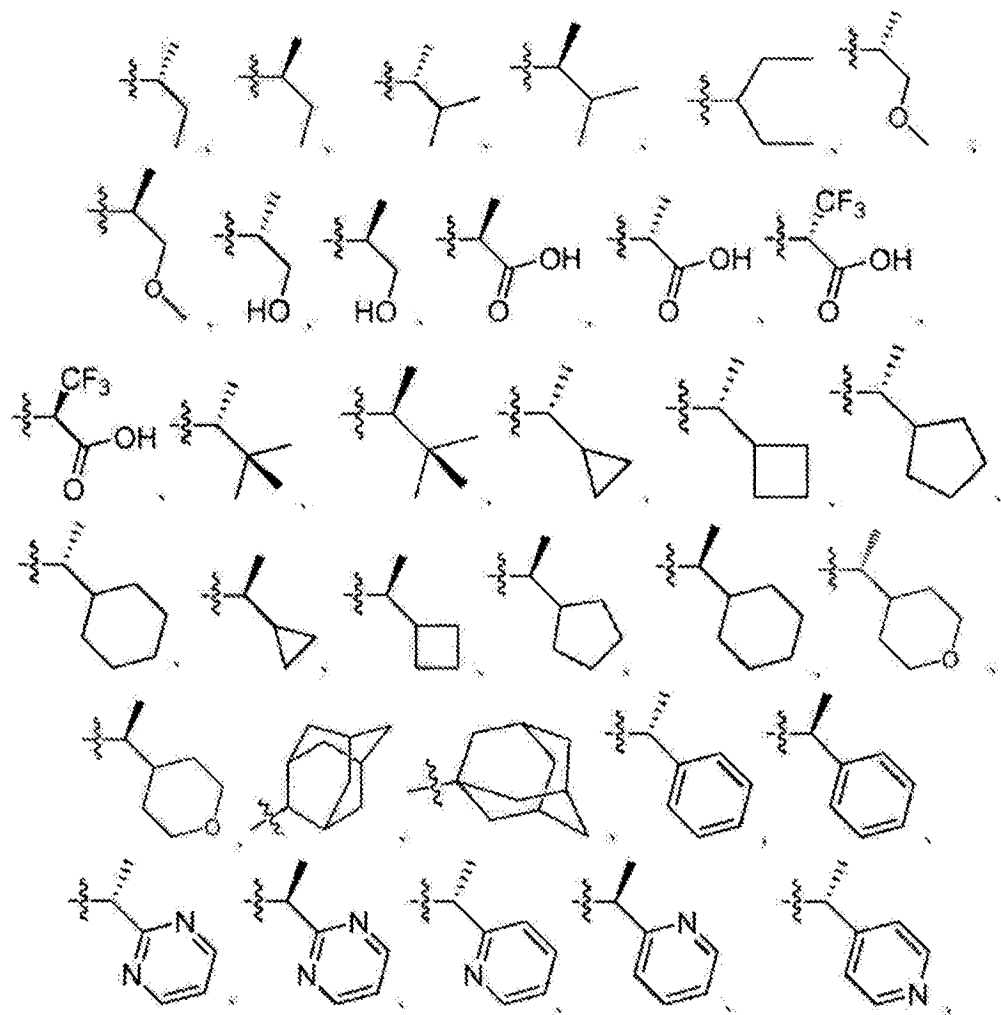
[0831] R^5 、 R^7 和 R^8 各自是H;并且

[0832] R^6 是氢、氯代、氟代或甲氧基。

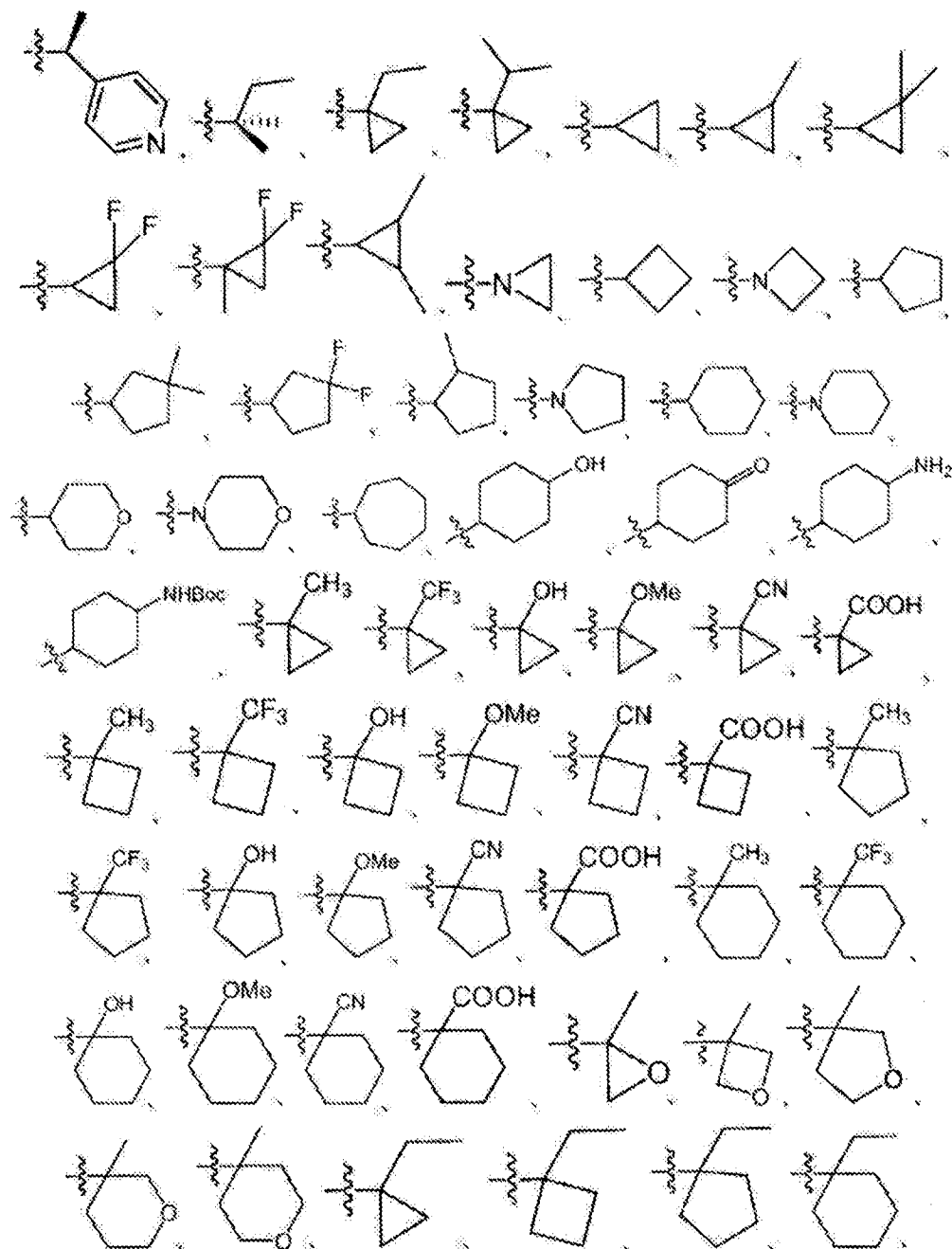
[0833] 实施方案 15. 如实施方案 1 至 13 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中,

[0834] R^1 是甲基、甲胺(或其经保护的类似物)、甲氧基、乙基、乙胺(或其经保护的类似物)、乙氧基、正丙基、丙胺(或其经保护的类似物)、正丙氧基、异丙基、异丙胺(或其经保护的类似物)、异丙氧基、正丁基、正丁胺(或其经保护的类似物)、正丁氧基、仲丁基、仲丁胺(或其经保护的类似物)、仲丁氧基、叔丁基、叔丁胺(或其经保护的类似物)、叔丁氧基、乙烯基、任选取代的苯基、任选取代的苯甲基、任选取代的苯并异噁唑基、任选取代的苯并噁唑基、任选取代的呋喃基、任选取代的咪唑基、任选取代的吡啶基、任选取代的异噁唑基、任选取代的异噻唑基、任选取代的噁唑基、任选取代的吡唑基、任选取代的吡啶-2-酮-基、任选取代的吡啶基、任选取代的吡咯基、任选取代的喹啉基、任选取代的噻唑基、任选取代的噻吩基和任选取代的甲基吡啶基、

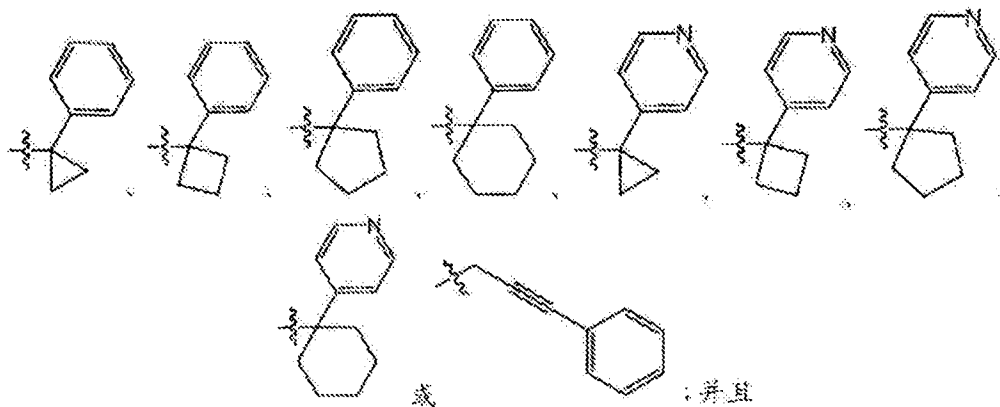
[0835]



[0836]



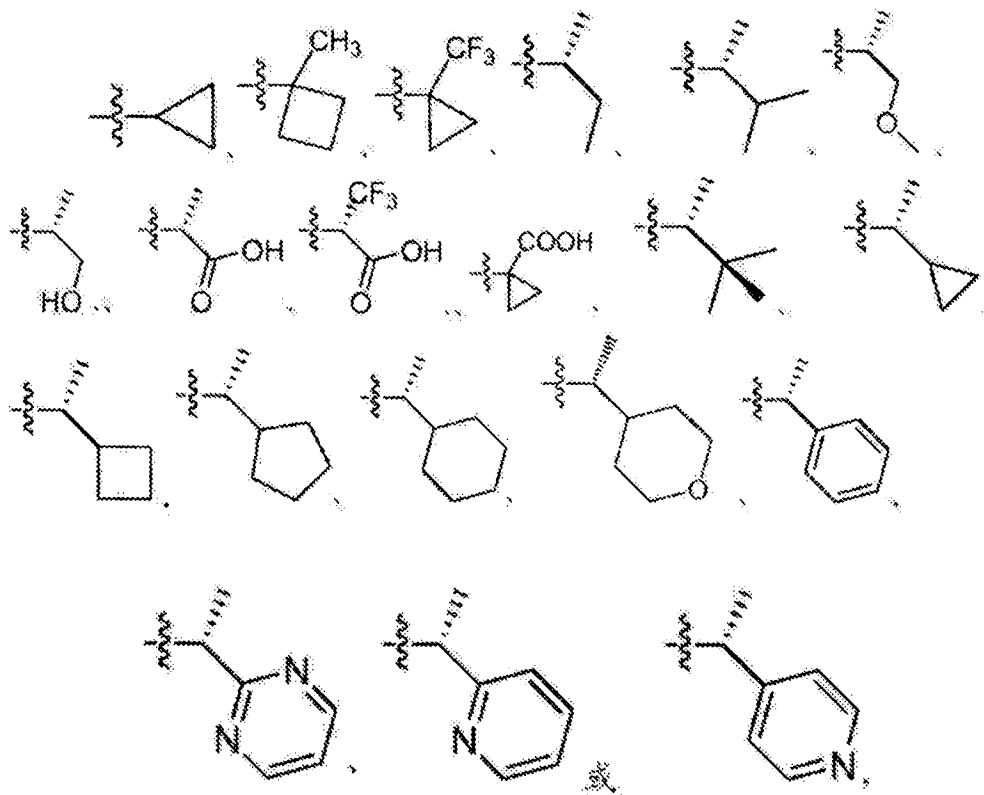
[0837]



[0838] 当存在时, R^2 是 H。

[0839] 实施方案 16. 如实施方案 1 至 14 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、盐或水合物, 其中 R^1 是异丙基、叔丁基、

[0840]



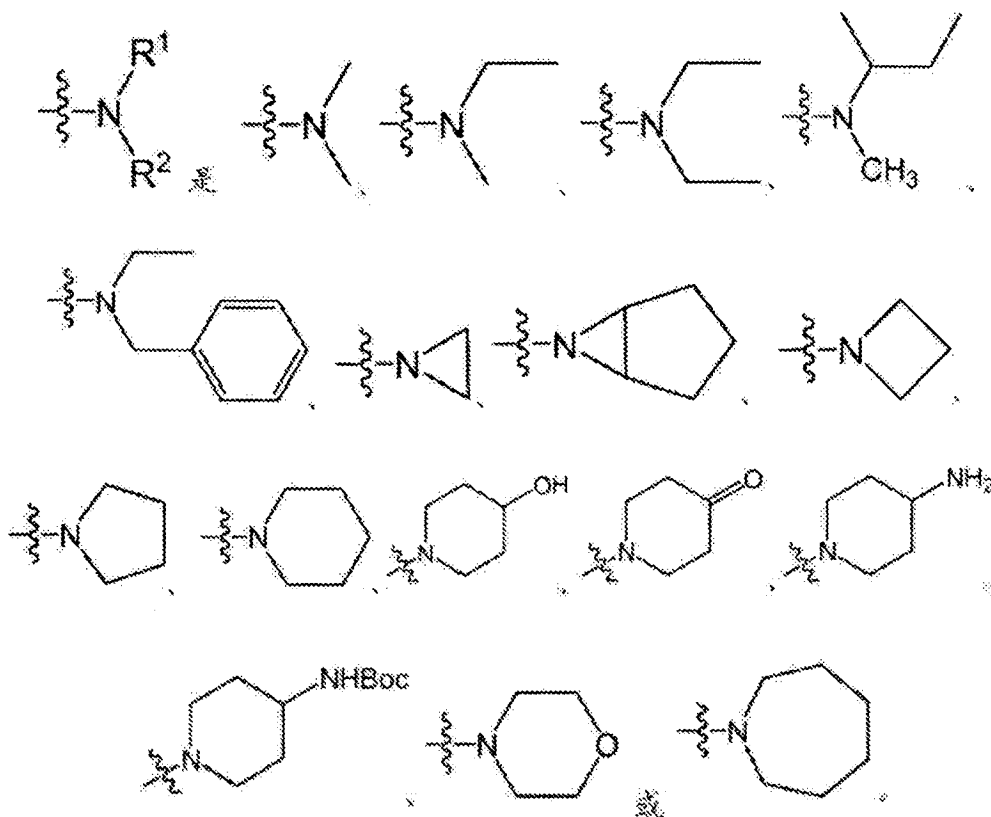
[0841] 并且当存在时, R^2 是 H。

[0842] 实施方案 17. 如实施方案 1 至 15 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 条件是所述 $-N(R^1)(R^2)$ 部分不含有羟基。

[0843] 实施方案 18. 如实施方案 1 至 15 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 条件是 R^1 不是环戊烷。

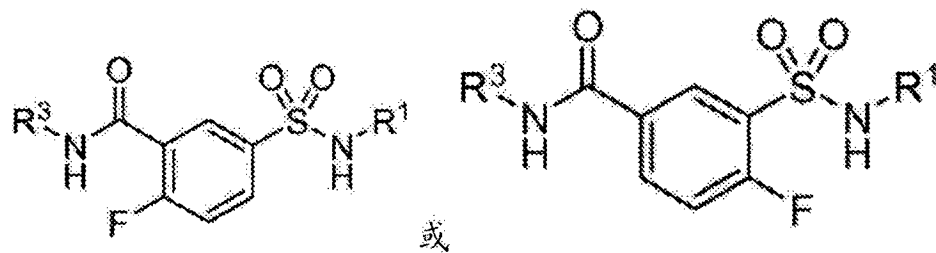
[0844] 实施方案 19. 如实施方案 1 至 15 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

[0845]



[0846] 实施方案 20. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其包含结构

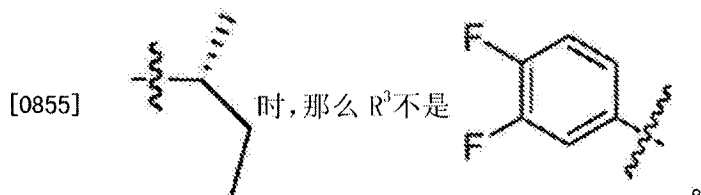
[0847]

[0848] 其中 R¹ 是

[0849]

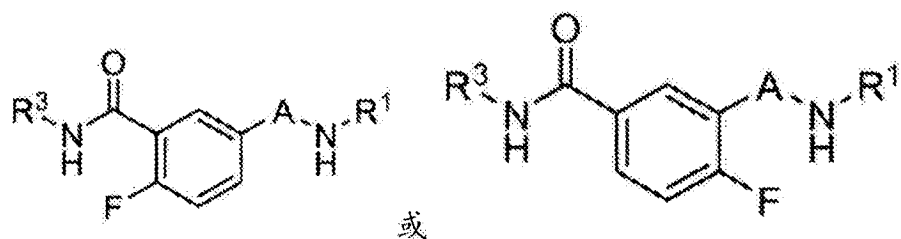
并且 x 是 0、1、2 或 3

[0854] 条件是当 R^1 是



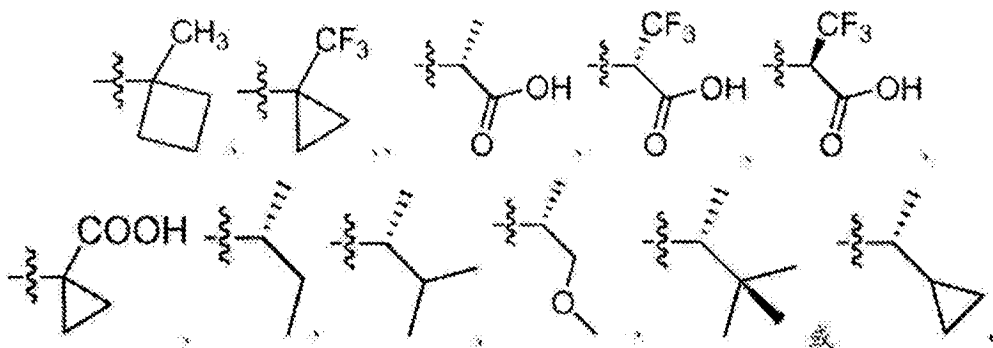
[0856] 实施方案 21. 如实施方案 20 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其包含结构

[0857]



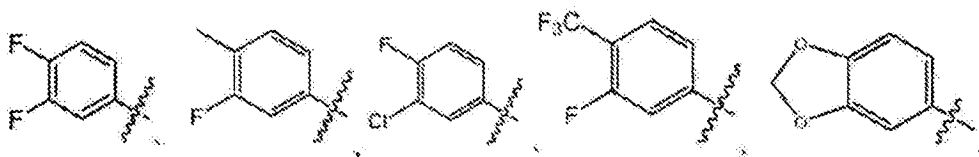
[0858] 其中 R^1 是异丙基、叔丁基、

[0859]

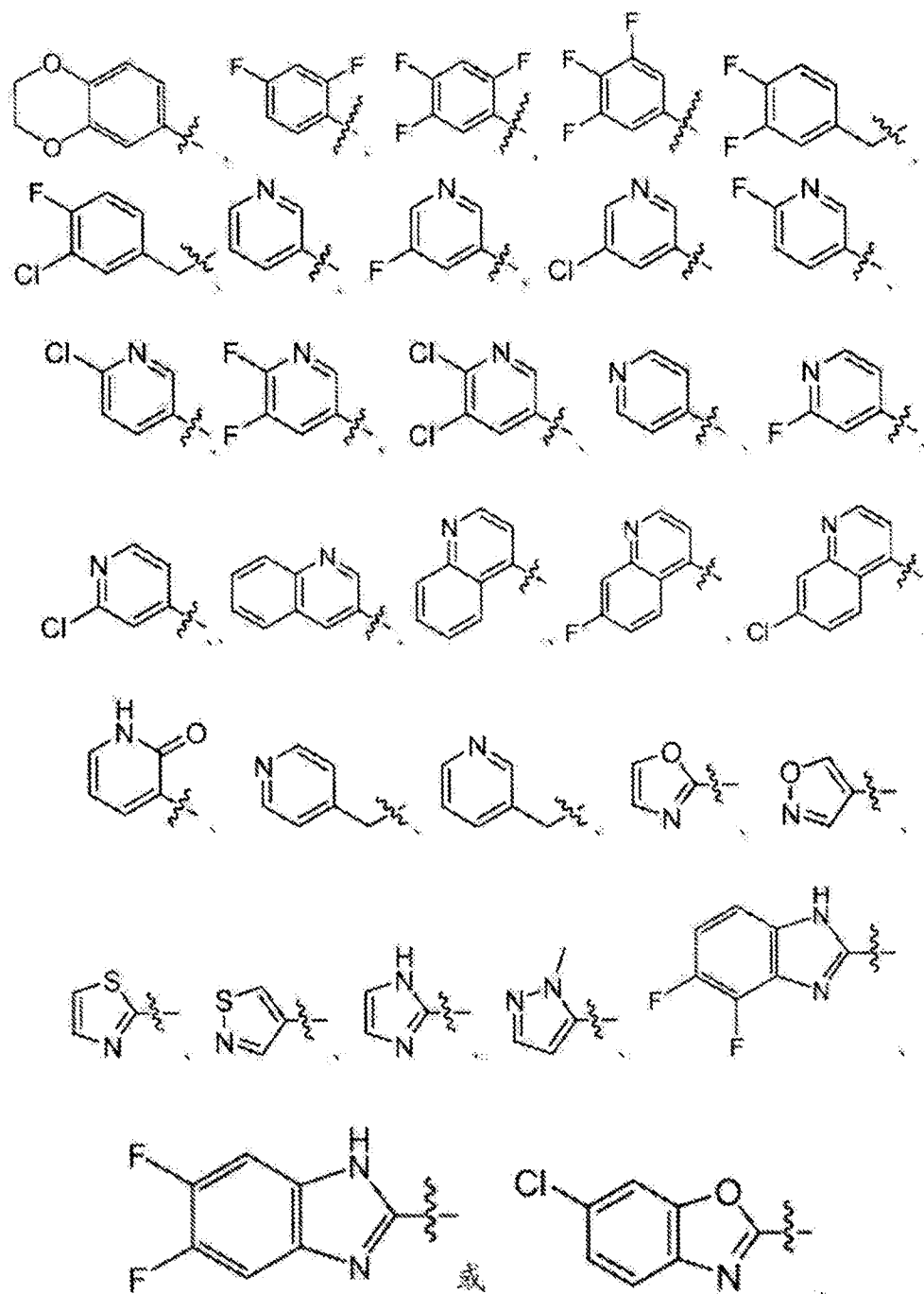


[0860] 并且 R^3 是

[0861]

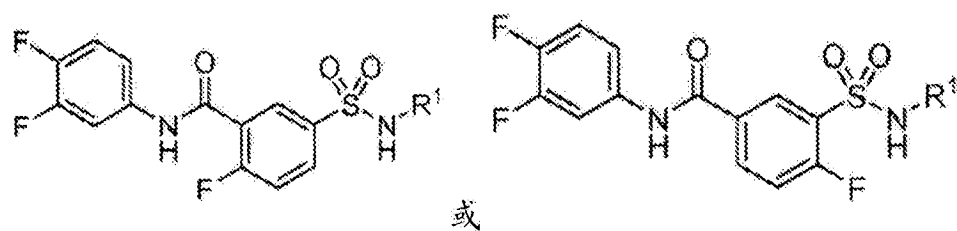


[0862]



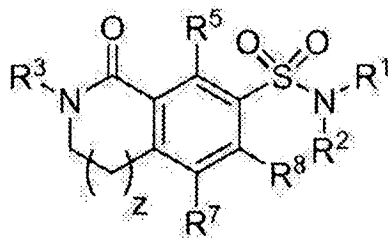
[0863] 实施方案 22. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其包含结构

[0864]



体、非对映异构体或药学上接受的盐、水合物或溶剂合物,所述化合物包含结构:

[0877]

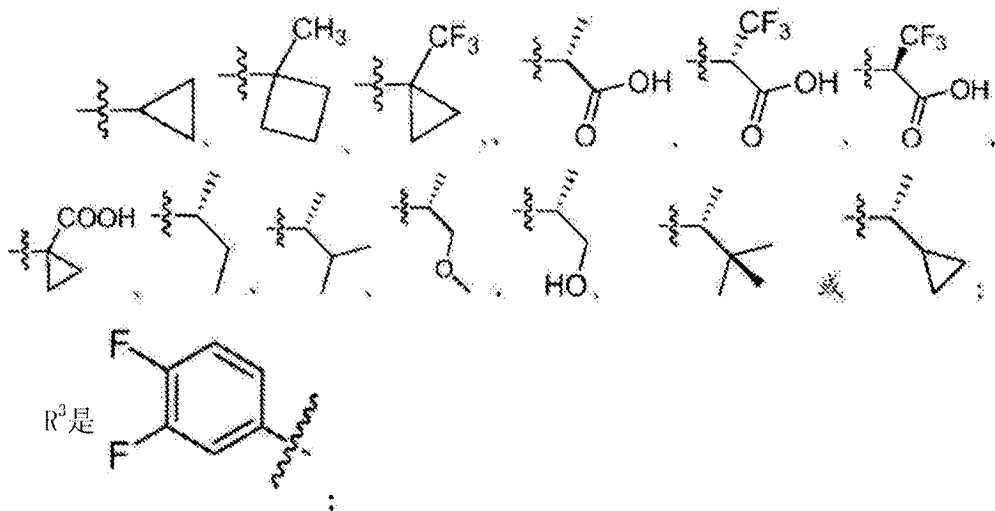


[0878] 其中 z 是 0 或 1。

[0879] 实施方案 26. 如实施方案 24 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

[0880] R^1 是异丙基、叔丁基、

[0881]



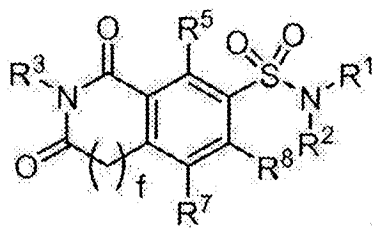
[0882] R^3 是

[0883] R^5 和 R^7 是 H; 并且

[0884] R^8 是 H 或 F。

[0885] 实施方案 27. 如实施方案 2、以及实施方案 5 至 18 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,所述化合物包含结构:

[0886]

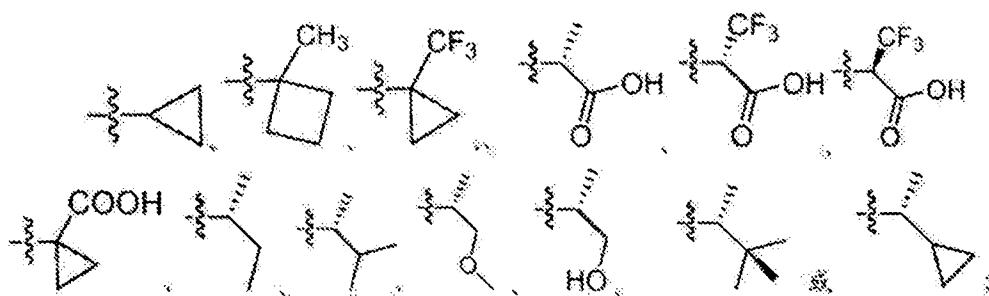
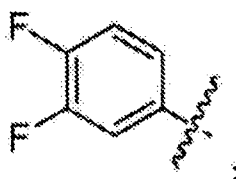


[0887] 其中 f 是 0 或 1。

[0888] 实施方案 28. 如实施方案 26 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物,其中

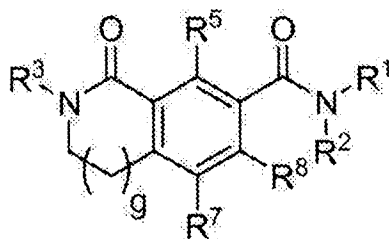
[0889] R^1 是异丙基、叔丁基、

[0890]

[0891] R^2 是 H;[0892] R^3 是[0893] R^5 和 R^7 是 H; 并且[0894] R^8 是 H 或 F。

[0895] 实施方案 29. 如实施方案 3、或实施方案 6 至 19 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含结构:

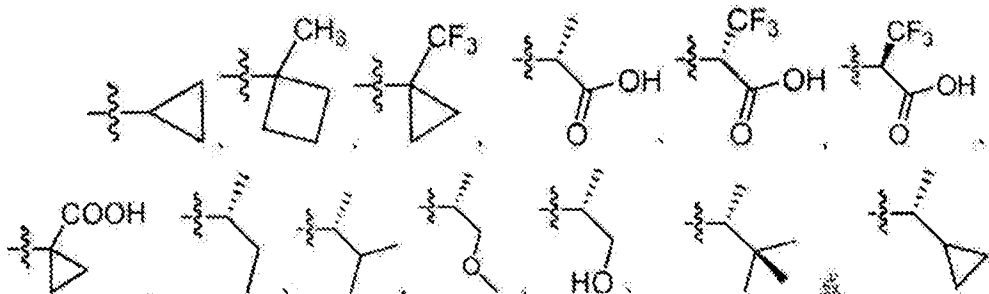
[0896]

[0897] 其中 g 是 0 或 1。

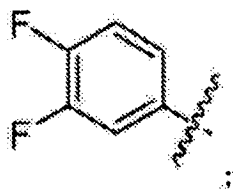
[0898] 实施方案 30. 如实施方案 29 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

[0899] R^1 是异丙基、叔丁基、

[0900]

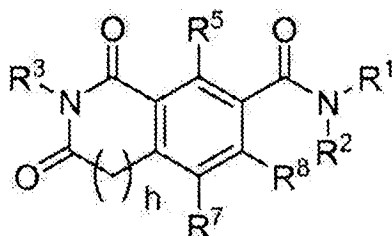
[0901] R^2 是 H;

[0902]

 R^3 是[0903] R^5 和 R^7 是 H; 并且[0904] R^8 是 H 或 F。

[0905] 实施方案 31. 如实施方案 3、或实施方案 6 至 19 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含结构:

[0906]

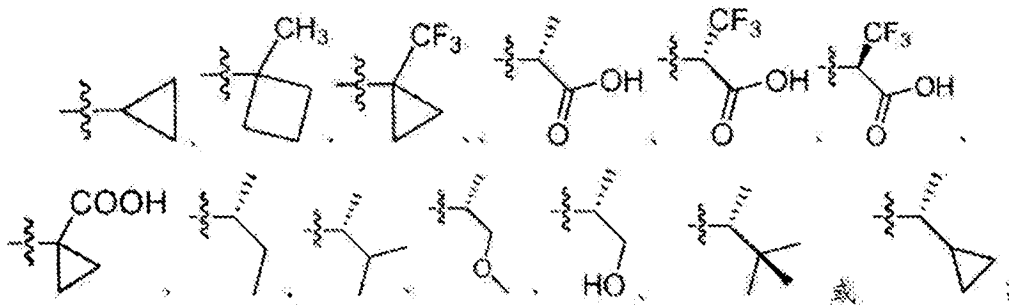
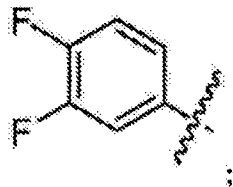


[0907] 其中 h 是 0 或 1。

[0908] 实施方案 32. 如实施方案 31 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 其中

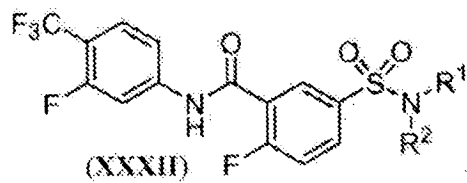
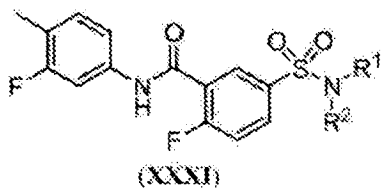
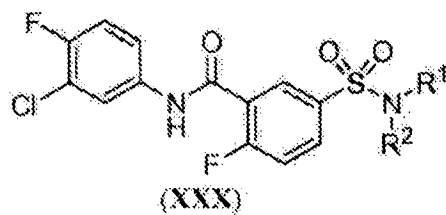
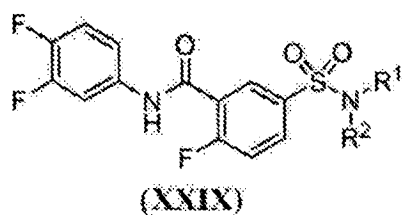
[0909] R^1 是异丙基、叔丁基、

[0910]

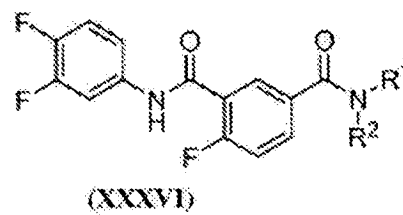
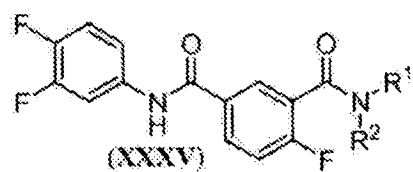
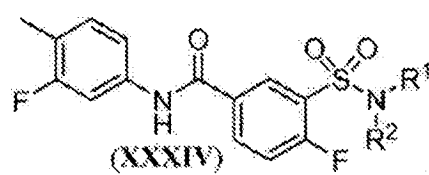
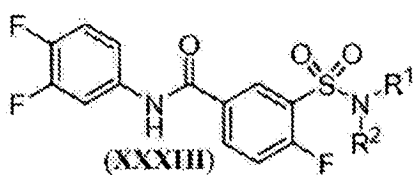
[0911] R^2 是 H;[0912] R^3 是[0913] R^5 和 R^7 是 H; 并且[0914] R^8 是 H 或 F。

[0915] 实施方案 33. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐、水合物或溶剂合物, 所述化合物包含以下任一结构:

[0916]

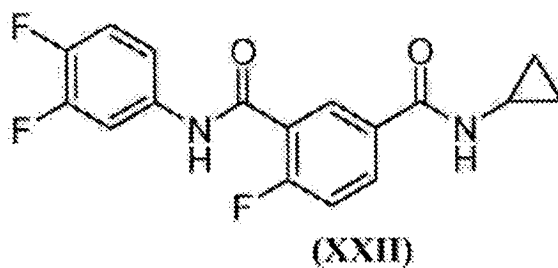


[0917]



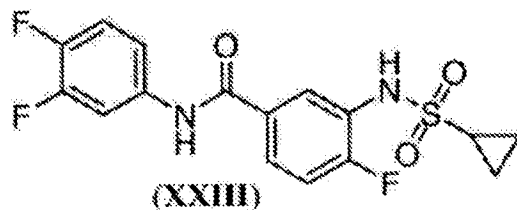
[0918] 实施方案 34. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含式 (XXII) 的结构:

[0919]



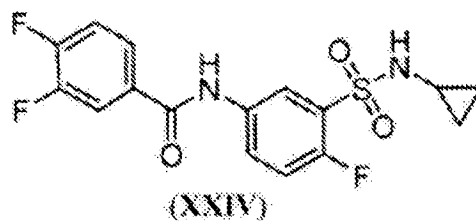
[0920] 实施方案 35. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含式 (XXIII) 的结构:

[0921]



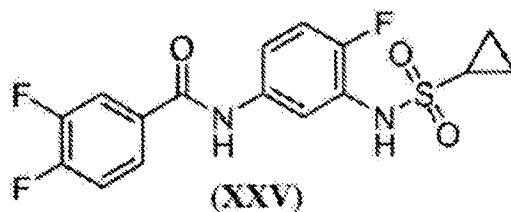
[0922] 实施方案 36. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含式 (XXIV) 的结构:

[0923]



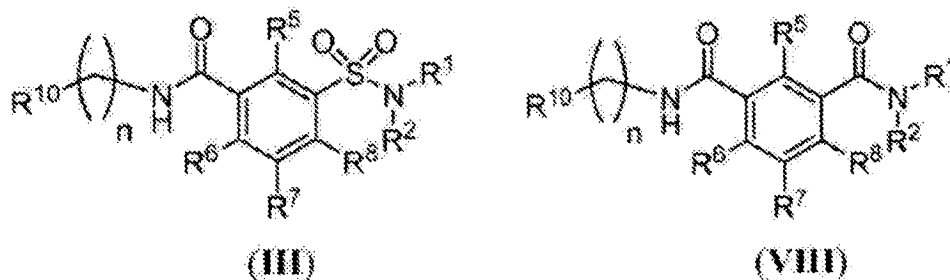
[0924] 实施方案 37. 如实施方案 1 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含式 (XXV) 的结构:

[0925]



[0926] 实施方案 38. 一种包含式 (III) 或式 (VIII) 的结构的化合物或其对映异构体、非对映异构体或药学上接受的盐:

[0927]



[0928] 其中:

[0929] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基; R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_2 烯基、任选取代的 C_2 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基- C_{1-6} 烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基组成的组;

[0930] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组; R^2 也可或者或另外任选包括任

选取代的 C_{3-7} 环烷基或任选取代的杂环 ; 或

[0931] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环 (包括双环或金刚烷基结构) ; 并且

[0932] R^3 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组 ; R^3 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0933] R^4 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组 ; R^4 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0934] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组 ; R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0935] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组 ; R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$; 或

[0936] R^7 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的环 ; 并且

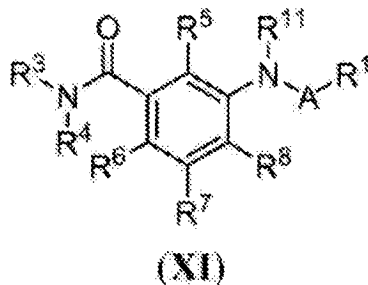
[0937] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基和任选取代的 C_{1-6} 卤代烷基组成的组 ; R^9 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基 ;

[0938] R^{10} 选自由任选取代的芳基和任选取代的杂芳基组成的组 ; 并且

[0939] n 是 0 或 1。

[0940] 实施方案 39. 一种包含式 (XI) 的结构化合物或其对映异构体、非对映异构体或药学上接受的盐 :

[0941]



[0942] 其中 :

[0943] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基 ; R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-C_{1-6}-$ 烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基组成的组 ;

[0944] R^3 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基、任选取代的烷基杂芳基和任选取代的 C_{1-6} 直链烷基组成的组 ;

[0945] R^4 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组 ;

[0946] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组 ; R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$;

[0947] R^6 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；或

[0948] R^4 和 R^6 连同它们所结合的原子一起形成具有 5 至 6 个原子、任选含有羰基、任选含有两个羰基的任选取代的碳环或杂环；

[0949] R^7 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基、 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[0950] R^8 选自自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

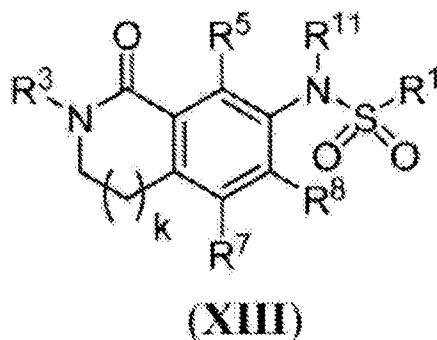
[0951] R^9 在每次出现时都独立地选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基和任选取代的 C_{1-6} 卤代烷基组成的组； R^9 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；并且

[0952] R^{11} 选自自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组。

[0953] 实施方案 40. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 A 是 SO_2 。

[0954] 实施方案 41. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，所述化合物包含式 (XIII) 的结构：

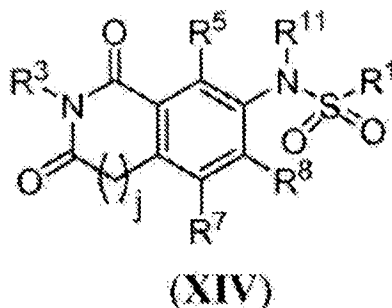
[0955]



[0956] 其中 k 是 0 或 1。

[0957] 实施方案 42. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，所述化合物包含式 (XIV) 的结构，

[0958]

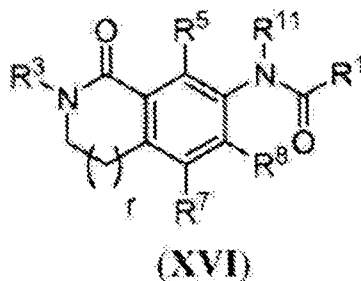


[0959] 其中 j 是 0 或 1。

[0960] 实施方案 43. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中 A 是羰基、CO。

[0961] 实施方案 44. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 (XVI) 的结构:

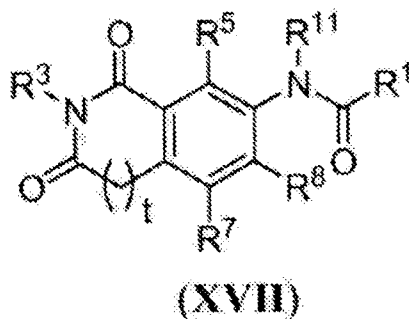
[0962]



[0963] 其中 r 是 0 或 1。

[0964] 实施方案 45. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 (XVII) 的结构,

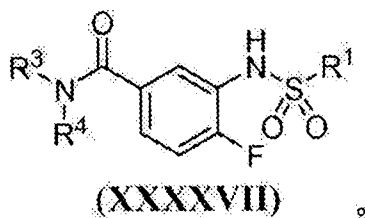
[0965]



[0966] 其中 t 是 0 或 1。

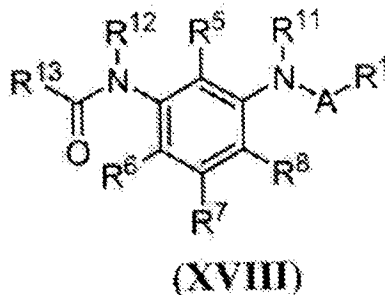
[0967] 实施方案 46. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含式 XXXXVII 的结构:

[0968]



[0969] 实施方案 47. 如实施方案 39 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 所述化合物包含结构

[0970]



[0982] 其中：

[0983] A 选自由 SO₂ 和 CO 组成的组；

[0984] R¹ 选自由任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基、任选取代的 C₃₋₇ 环烷基、任选取代的芳基和任选取代的苯甲基；R¹ 也可或者或另外任选包括任选取代的 C₁₋₆ 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C₂₋₈ 烯基、任选取代的 C₂₋₈ 炔基、任选取代的 C₁₋₆ 烷氧基、任选取代的胺、任选取代的脞、任选取代的羧基胺、任选取代的羧基 -C₁₋₆- 烷氧化物、-SO₂-C₁₋₆ 烷基、任选取代的杂环或任选取代的杂芳基组成的组；

[0985] R⁵ 选自由氢、卤素、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基、任选取代的 C₁₋₆ 卤代烷基和 OR⁹ 组成的组；R⁵ 也可或者或另外任选包括氰基或 N(R⁹)₂；

[0986] R⁶ 选自由氢、卤素、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基、任选取代的 C₁₋₆ 卤代烷基和 OR⁹ 组成的组；R⁶ 也可或者或另外任选包括氰基或 N(R⁹)₂；

[0987] R⁷ 选自由氢、卤素、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基、任选取代的 C₁₋₆ 卤代烷基和 OR⁹ 组成的组；R⁷ 也可或者或另外任选包括氰基或 N(R⁹)₂；

[0988] R⁸ 选自由氢、卤素、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基、任选取代的 C₁₋₆ 卤代烷基和 OR⁹ 组成的组；R⁸ 也可或者或另外任选包括氰基或 N(R⁹)₂；或

[0989] R⁹ 在每次出现时都独立地选自由氢、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基和任选取代的 C₃₋₇ 环烷基和任选取代的 C₁₋₆ 卤代烷基组成的组；R⁹ 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；并且

[0990] R¹² 选自由氢、任选取代的 C₁₋₆ 直链烷基、任选取代的 C₁₋₆ 支链烷基和任选取代的 C₃₋₇ 环烷基组成的组；并且

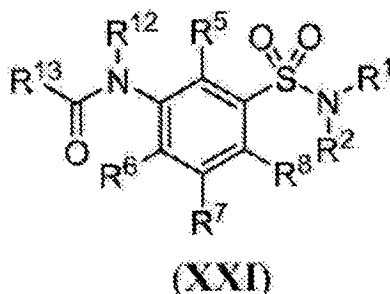
[0991] R¹³ 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

[0992] 实施方案 50. 如实施方案 49 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 A 是 SO₂。

[0993] 实施方案 51. 如实施方案 49 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，其中 A 是羰基、CO。

[0994] 实施方案 52. 一种包含式 (XXI) 的结构化合物或其对映异构体、非对映异构体或药学上接受的盐：

[0995]



[0996] 其中：

[0997] R^1 选自由任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{3-7} 环烷基、任选取代的芳基和任选取代的苯甲基； R^1 也可或者或另外任选包括任选取代的 C_{1-6} 卤代烷基、任选取代的 3-7 元环杂烷基、任选取代的 C_{2-8} 烯基、任选取代的 C_{2-8} 炔基、任选取代的 C_{1-6} 烷氧基、任选取代的胺、任选取代的脒、任选取代的羧基胺、任选取代的羧基 $-C_{1-6}-$ 烷氧化物、 $-SO_2-C_{1-6}$ 烷基、任选取代的杂环或任选取代的杂芳基组成的组；

[0998] R^2 选自由氢和任选取代的 C_{1-6} 直链烷基组成的组； R^2 也可或者或另外任选包括任选取代的 C_{3-7} 环烷基或任选取代的杂环；或

[0999] R^1 和 R^2 连同它们所结合的原子一起形成具有 3 至 10 个原子的任选取代的杂环（包括双环或金刚烷基结构）；

[1000] R^5 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^5 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[1001] R^6 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^6 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[1002] R^7 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^7 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；

[1003] R^8 选自由氢、卤素、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基、任选取代的 C_{1-6} 卤代烷基和 OR^9 组成的组； R^8 也可或者或另外任选包括氰基或 $N(R^9)_2$ ；或

[1004] R^2 和 R^8 连同它们所结合的原子一起形成具有 5 至 6 个原子的任选取代的环；

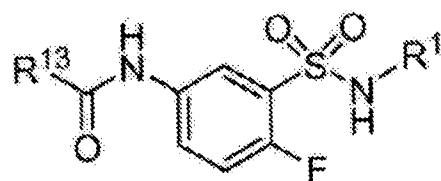
[1005] R^9 在每次出现时都独立地选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组； R^9 也可或者或另外在每次出现时都任选独立地包括任选取代的芳基、任选取代的苯甲基、任选取代的杂环基或任选取代的杂芳基；

[1006] R^{12} 选自由氢、任选取代的 C_{1-6} 直链烷基、任选取代的 C_{1-6} 支链烷基和任选取代的 C_{3-7} 环烷基组成的组；并且

[1007] R^{13} 选自由任选取代的芳基、任选取代的苯甲基、任选取代的烷基芳基、任选取代的杂芳基和任选取代的烷基杂芳基组成的组。

[1008] 实施方案 53. 如实施方案 52 所述的化合物、对映异构体、非对映异构体或药学上接受的盐，所述化合物包含式 XXXVIII 的结构：

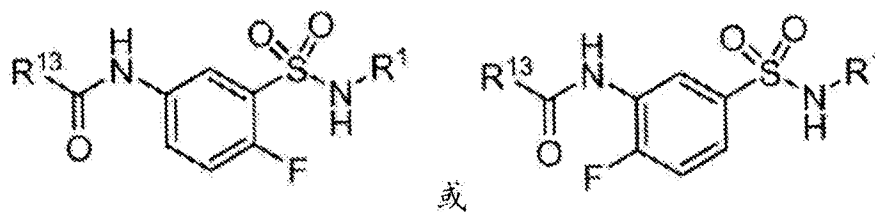
[1009]



(XXXXVIII)

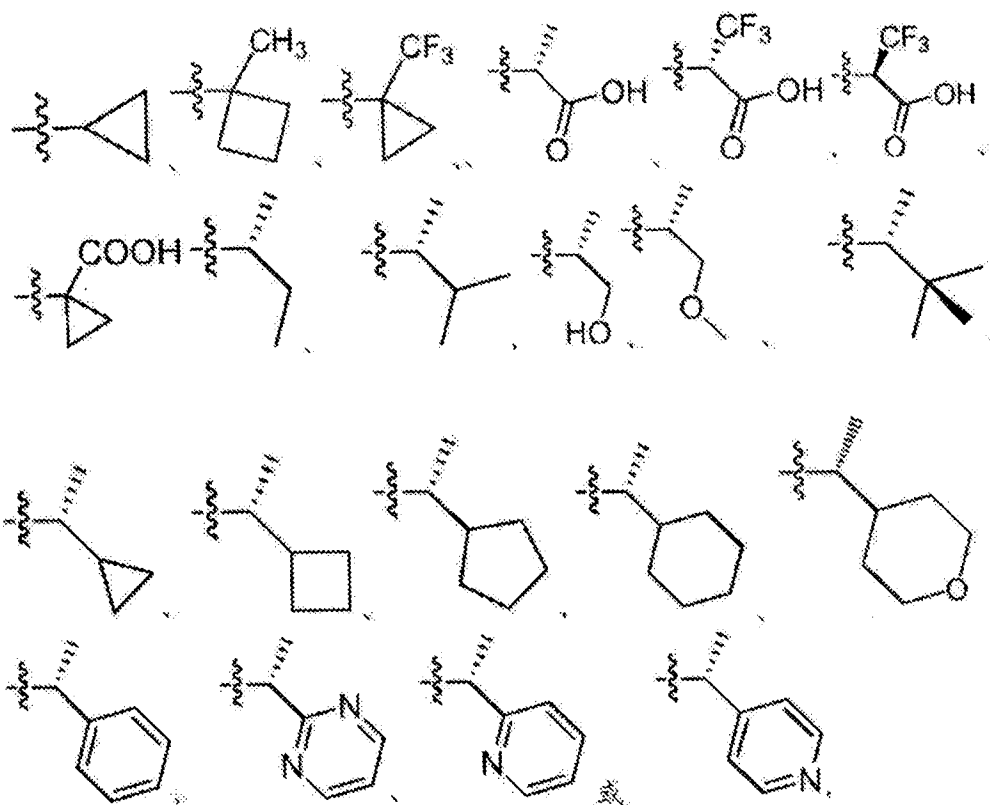
[1010] 实施方案 54. 如实施方案 53 所述的化合物、对映异构体、非对映异构体或药学上接受的盐,所述化合物包含结构

[1011]



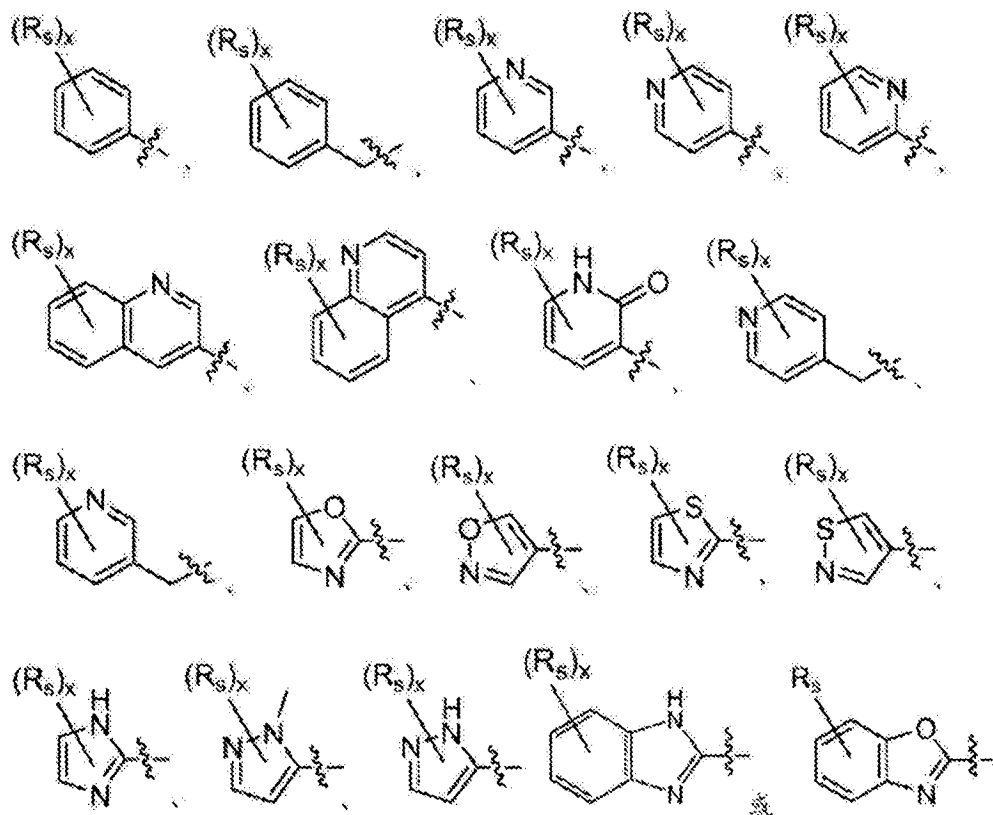
[1012] 其中 R¹是异丙基、叔丁基、

[1013]



[1014] R¹³是

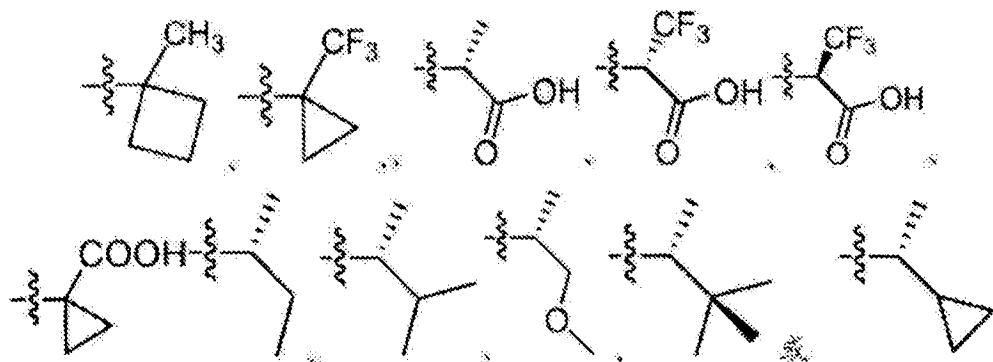
[1015]



[1016] R_5 在每次出现时都独立地是溴代、氯代、氟代、氰基、羟基、任选氟化 C_{1-6} 烷基（例如 $-CH_3$ 、 $-CH_2F$ 、 $-CF_2H$ 、 $-CF_3$ ）、 $-O-(C_{1-6}烷基)$ ，或当两个 R_5 一起形成稠环部分或杂环部分时；并且 x 是 0、1、2 或 3。

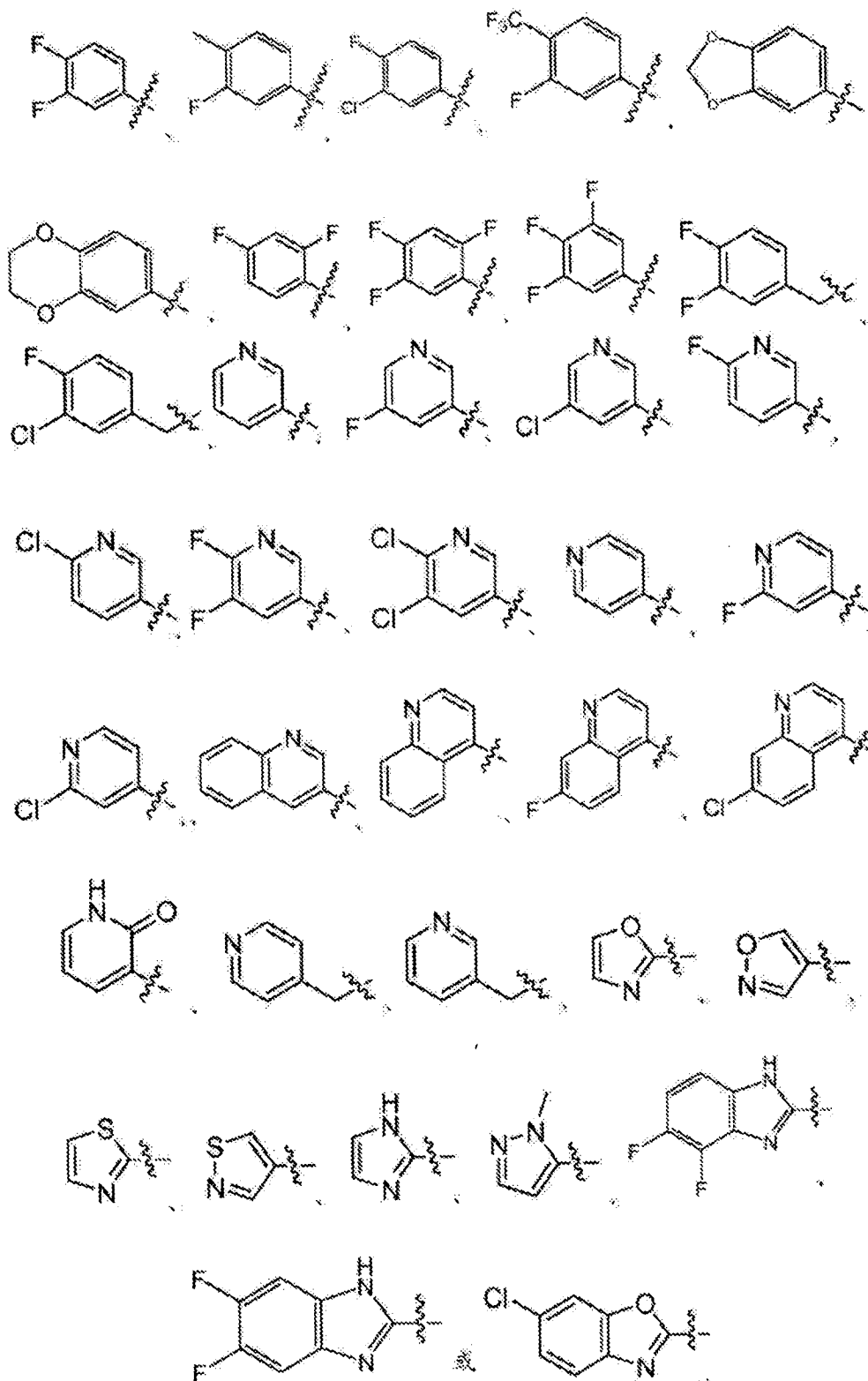
[1017] 实施方案 55. 如实施方案 54 所述的化合物、对映异构体、非对映异构体或药学上接受的盐, 其中 R¹是

[1018]



[1019] 并且 R^{13} 是

[1020]



[1021] 实施方案 56. 一种药物组合物, 其包含如实施方案 1 至 55 中任一项所述的化合物或本说明书内所述的任何化合物以及药学上可接受的赋形剂。

[1022] 实施方案 57. 一种治疗涉及前基因组 RNA 衣壳化的疾病的方法, 所述方法包括向需要所述治疗的患者施用有效量的至少一种如实施方案 1 至 55 中任一项所述的化合物或

如实施方案 56 所述的组合物。

[1023] 实施方案 58. 如实施方案 57 所述的方法, 其中所述涉及前基因组 RNA 衣壳化的疾病是乙型肝炎病毒感染。

[1024] 实施方案 59. 一种治疗乙型肝炎病毒性感染的方法, 所述方法包括向需要所述治疗的患者施用有效量的至少一种如要求保护的实施方案 1 至 55 中任一项所述的化合物或本说明书中所述的任何个别化合物或如实施方案 56 所述的组合物。

[1025] 实施方案 60. 如实施方案 59 所述的方法, 其中所述治疗控制或改善与肝病相关的病状, 包括肝硬化和肝细胞癌。

[1026] 实施方案 61. 一种阻遏病毒复制、形态发生、或复制与形态发生两者的方法, 其包括向有需要的患者施用如实施方案 1 至 55 中任一项所述的化合物、对映异构体、非对映异构体或药学上接受的盐或如实施方案 56 所述的组合物。

[1027] 实施方案 62. 如实施方案 57 至 61 中任一项所述的方法, 其中所述化合物或药学上可接受的盐是与一种或多种其它治疗剂组合施用。

[1028] 实施方案 63. 如实施方案 62 所述的方法, 其中所述其它治疗剂包括 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、文献描述的衣壳装配调节剂、5 逆转录酶抑制剂、TLR 激动剂或具有不同或未知机理的药剂或其组合。

[1029] 实施方案 64. 如实施方案 62 所述的方法, 其中所述其它治疗剂包括免疫调节剂或免疫刺激剂疗法, 其包括属于干扰素类别的生物药剂, 如干扰素 α 2a 或 2b 或修饰的干扰素, 如聚乙二醇化干扰素 α 2a、 α 2b、 λ ; 或 TLR 调节剂, 如 TLR-7 激动剂或 TLR-9 激动剂; 或阻断病毒进入或成熟或靶向 HBV 聚合酶的抗病毒剂, 如核苷或核苷酸或非核苷或核苷酸聚合酶抑制剂; 以及具有不同或未知机理的药剂, 包括破坏为 HBV 复制或持续所需的其它必需病毒蛋白质或宿主蛋白质的功能的药剂。

[1030] 实施方案 65. 如实施方案 62 所述的方法, 其中所述逆转录酶抑制剂包括以下至少一个: 齐多夫定、地达诺新、扎西他滨、ddA、司他夫定、拉米夫定、阿巴卡韦、恩曲他滨、恩替卡韦、阿立他滨、阿韦拉平、利巴韦林、阿昔洛韦、泛昔洛韦、伐昔洛韦、更昔洛韦、缬更昔洛韦、替诺福韦、阿德福韦、PMPA、昔多福韦、依法韦仑、奈韦拉平、德拉韦定或依曲韦林。

[1031] 实施方案 66. 如实施方案 62 所述的方法, 其中所述 TLR 激动剂包括 SM360320 (9- 苯甲基 -8- 羟基 -2-(2- 甲氧基乙氧基) 腺嘌呤) 或 AZD8848 ([3-([3-(6- 氨基 -2- 丁氧基 -8- 氧代 -7, 8- 二氢 -9H- 嘌呤 -9- 基) 丙基][3-(4- 吗啉基) 丙基] 氨基} 甲基) 苯基] 乙酸甲酯)。

[1032] 实施方案 67. 如实施方案 60 至 66 中任一项所述的方法, 其中共同配制、共同施用、或共同配制且共同施用所述化合物或其药学上可接受的盐和所述其它治疗剂。

[1033] 实施方案 68. 如实施方案 60 至 64 中任一项所述的方法, 其中分开配制、分开施用、或分开配制且分开施用所述化合物或其药学上可接受的盐和所述其它治疗剂。

[1034] 实施方案 69. 如实施方案 57 至 68 中任一项所述的方法, 其中施用本发明的所述化合物或药学上可接受的盐允许相较于单独施用所述至少一种为在有需要的个体中在防治性治疗 HBV 感染方面达成类似结果所需的其它治疗剂, 以较低剂量或频率施用所述其它治疗剂。

[1035] 实施方案 70. 如实施方案 57 至 69 中任一项所述的方法, 其中, 在施用所述治疗有

效量的所述化合物或药学上可接受的盐之前,已知所述患者为 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同衣壳装配调节剂、具有不同或未知机理的抗病毒化合物或其组合所难以治疗的。

[1036] 实施方案 71. 如实施方案 57 至 70 中任一项所述的方法,其中相较于施用 HBV 聚合酶抑制剂、干扰素、病毒进入抑制剂、病毒成熟抑制剂、不同衣壳装配调节剂、具有不同或未知机理的抗病毒化合物或其组合,施用化合物或药学上可接受的盐在更大程度上降低所述个体中的病毒载量。

实施例

[1037] 提供以下实施例以说明本公开内描述的一些概念。尽管各实施例被视为提供组合物、制备和使用方法的特定个别实施方案,但无实施例应被视为限制本文所述的更一般性实施方案。

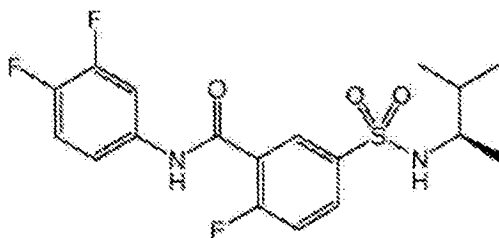
[1038] 在以下实施例中,已努力确保关于所用数值(例如量、温度等)的准确性,但应考虑一些实验误差和偏差。除非另外指示,否则温度是以℃计,压力是在大气压下或接近大气压。

[1039] 以下实施例提供用于制备本公开的代表性化合物的非限制性方法。熟练从业者将了解如何替换为本领域技术人员所知的适当试剂、原料和纯化方法以制备本发明的其它化合物。

[1040] 在 300MHz INOVA VARIAN 光谱仪上记录 ^1H NMR 光谱。化学位移值以 ppm 给出,并且被称为 TMS(四甲基硅烷)的内标。如下指示峰型:b,宽峰;s,单峰;d,双重峰;t,三重峰;q,四重峰;qint,五重峰;m,多重峰;dd,双二重峰;以及 dt,双三重峰。偶合常数(J)是以赫兹(Hz)报告。在 1200Agilent LC-MS 光谱仪(ES-API,正性)上获得质谱。经 100-200 目硅胶进行硅胶柱色谱法,并且洗脱剂是乙酸乙酯和己烷的混合物或甲醇和二氯甲烷的混合物。在配备有 Agilent, ZORBAX SB-C18 柱和 210nm 下的 UV 检测的 Agilent 1100HPLC 仪器上运行分析型 HPLC。

[1041] 实施例 1:一般性程序 A

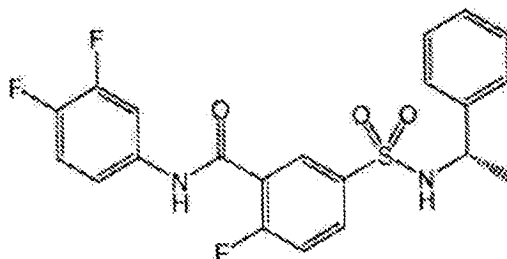
[1042]



[1043] (R)-N-(3,4-二氟苯基)-2-氟-5-((R)-2-((S)-2-甲基丁烷-2-基)氨基磺酰基)苯甲酰胺:向 5-氯磺酰基-2-氟苯甲酸(150mg,0.62mmol)于 THF(3mL)中的 0℃溶液中添加 NEt_3 (125mg,1.24mmol)和 (R)-(-)-2-氨基-3-甲基丁烷(54mg,0.62mmol)。使反应物升温至 20℃,并且搅拌 20 分钟。浓缩混合物,并且将残余物分配于 EtOAc(20mL)与 1N HCl(5mL)之间。有机层用 2N HCl(5mL)、水(5mL)和盐水(1mL)洗涤,干燥(Na_2SO_4)并浓缩。物质不经进一步纯化即使用。

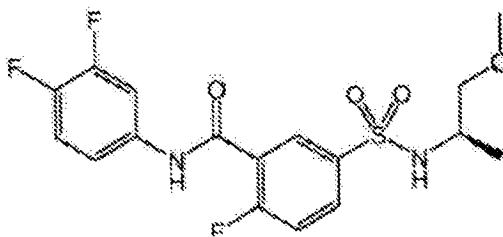
[1044] 向来自先前步骤的物质中添加亚硫酸氯 (2mL), 并在回流下加热该混合物 2 小时。浓缩混合物, 并且用 THF (1mL) 处理残余物。添加该溶液至 NEt_3 (144mg, 1.43mmol) 和 3, 4-二氟苯胺 (60mg, 0.48mmol) 于 THF (3mL) 中的 0℃ 溶液中。使反应物升温至 20℃, 并且搅拌 16 小时。浓缩混合物, 并且将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (10mL)、水 (10mL)、稀 NaHCO_3 (10mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (20–50% EtOAc/ 己烷) 纯化以产生呈灰白色固体状的所需产物 (44mg, 18% (历经 3 步))。MS: $\text{M}+\text{H}^+$ 401。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 8.23–8.20 (m, 1H), 8.07–8.04 (m, 1H), 7.85–7.77 (m, 1H), 7.47–7.35 (m, 2H), 7.26 (q, $J = 9.0\text{Hz}$, 1H), 3.15–3.12 (m, 1H), 1.65–1.59 (m, 1H), 0.90–0.82 (m, 6H)。

[1045]



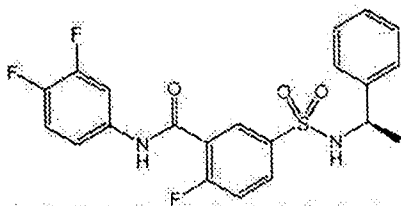
[1046] (S)-N-(3, 4-二氟苯基)-2-氟-5-(N-(1-苯基乙基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 A, 使用 (S)-(+)-1-甲基-苯甲胺 (75mg, 0.62mmol) 以产生呈灰白色固体状的所需产物 (106mg, 39% (历经 3 步))。MS: $\text{M}+\text{H}^+$ 435。 ^1H NMR (300MHz, CDCl_3): δ 8.41 (dd, $J = 2.6, 7.6\text{Hz}$, 1H), 8.25 (d, $J = 14.0\text{Hz}$, 1H), 7.78–7.71 (m, 2H), 7.20–7.05 (m, 9H), 5.11 (d, $J = 7.3\text{Hz}$, 1H), 4.56 (dq, $J = 6.7, 7.0\text{Hz}$, 1H), 1.47 (d, $J = 6.7\text{Hz}$, 3H)。

[1047]



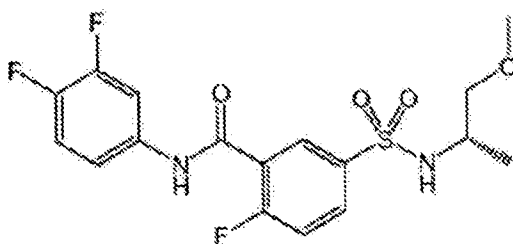
[1048] (R)-N-(3, 4-二氟苯基)-2-氟-5-(N-(1-甲氧基丙烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 A, 使用 (R)-(-)-1-甲氧基-2-氨基丙烷·HCl (78mg, 0.62mmol) 以产生呈灰白色固体状的所需产物 (60mg, 24% (历经 3 步))。MS: $\text{M}+\text{H}^+$ 403。 ^1H NMR (300MHz, CDCl_3): δ 8.63 (dd, $J = 2.4, 7.0\text{Hz}$, 1H), 8.42 (d, $J = 13.2\text{Hz}$, 1H), 8.07–8.02 (m, 1H), 7.80–7.73 (m, 1H), 7.36–7.7.11 (m, 3H), 5.08 (d, $J = 6.7\text{Hz}$, 1H), 3.54–3.50 (m, 1H), 3.29–3.21 (m, 5H), 1.13 (d, $J = 6.7\text{Hz}$, 1H)。

[1049]



[1050] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-苯基乙基)氨基磺酰基)苯甲酰胺:遵循一般性程序A,使用(R)-(-)-1-甲基-苯甲胺(75mg,0.62mmol)以产生呈灰白色固体状的所需产物(136mg,51%(历经3步))。MS:M+H⁺436。¹H NMR(300MHz,CDCl₃): δ 8.41(dd, J = 2.6, 7.3Hz, 1H), 8.27(d, J = 13.5Hz, 1H), 7.79-7.72(m, 2H), 7.9(d, J = 4.4Hz, 1H), 7.26-7.03(m, 8H), 5.18(d, J = 7.0Hz, 1H), 4.58(dq, J = 6.7, 7.0Hz, 1H), 1.48(d, J = 7.0Hz, 1H)。

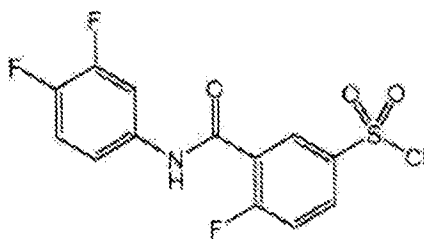
[1051]



[1052] (S)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-甲氧基丙烷-2-基)氨基磺酰基)苯甲酰胺。遵循一般性程序A,使用(S)-(-)-1-甲氧基-2-氨基丙烷(55mg,0.62mmol)以产生呈白色固体状的所需产物(64mg,26%(历经3步))。MS:M+H⁺403。¹H NMR(300MHz,MeOH-d₄): δ 8.22(dd, J = 2.6, 6.5Hz, 1H), 8.07-8.02(m, 1H), 7.85-7.78(m, 1H), 7.47-7.20(m, 3H), 3.49-3.73(m, 1H), 3.32-3.15(m, 5H), 1.04(d, J = 6.7Hz, 3H)。

[1053] 实施例2:一般性程序B

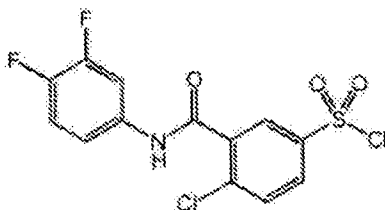
[1054]



[1055] 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯:在回流下加热5-氯磺酰基-2-氟苯甲酸(1.00g,4.19mmol)、亚硫酸氯(3.5mL)和1,2-二氯乙烷(3.5mL)的混合物1小时。浓缩反应物,接着用甲苯(5mL)处理残余物,接着浓缩混合物。粗物质不经进一步纯化即使用。

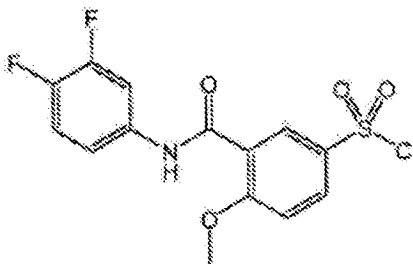
[1056] 向3,4-二氟苯胺(0.55g,4.24mmol)于甲苯(10mL)中的溶液中添加来自先前步骤的物质。搅拌反应物16小时,接着过滤。浓缩的滤液通过二氧化硅柱(0-100% EtOAc/己烷)纯化以产生呈白色固体状的所需产物(0.38g,27%)。¹H NMR(300MHz,DMSO-d₆): δ 10.72(s, 1H), 7.90-7.72(m, 2H), 7.46-7.26(m, 4H)。

[1057]



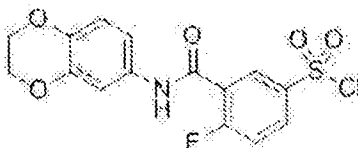
[1058] 3-(3,4-二氟苯基-氨基甲酰基)-4-氯苯-1-磺酰氯:遵循一般性程序B,使用5-氯磺酰基-2-氯苯甲酸(0.50g,2.06mmol)以产生呈灰白色固体状的所需产物(0.29g,40%(历经2步))。¹H NMR(300MHz,DMSO-d₆): δ 10.81(s,1H),7.89-7.80(m,1H),7.70-7.66(m,2H),7.46(d,J = 17.3Hz,1H),7.44-7.36(m,1H)。

[1059]



[1060] 3-(3,4-二氟苯基-氨基甲酰基)-甲氧基苯-1-磺酰氯。遵循一般性程序B,使用5-氯磺酰基-2-甲氧基苯甲酸(0.50g,2.00mmol)以产生呈灰白色固体状的所需产物(0.33g,45%(历经2步))。MS:M+H⁺362。¹H NMR(300MHz,DMSO-d₆): δ 10.33(s,1H),7.94-7.78(m,2H),7.69(dd,J = 2.2,8.5Hz,1H),7.50-7.34(m,2H),7.10(d,J = 8.8Hz,1H),3.87(s,3H)。

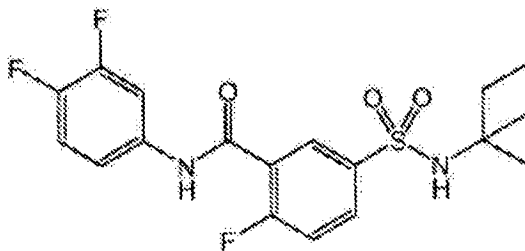
[1061]



[1062] 3-((2,3-二氢苯并[b][1,4]二氧杂环己烯-6-基)氨基甲酰基)-4-氟苯-1-磺酰氯:以与一般性程序B类似的程序,获得呈白色固体状的最终化合物(0.95g,61%)。MS(ES)m/z:372.1(M+H⁺),计算值:372.00。

[1063] 实施例3:一般性程序C

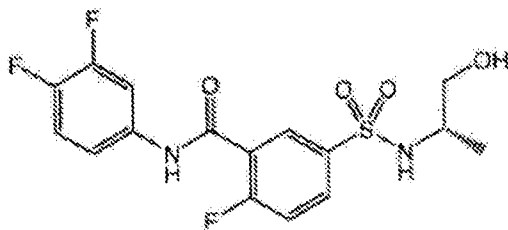
[1064]



[1065] N-(3,4-二氟苯基)-2-氟-5-(N-叔戊基氨磺酰基)苯甲酰胺:向3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(30mg,0.086mmol)于CH₂Cl₂(1mL)中的0℃溶液

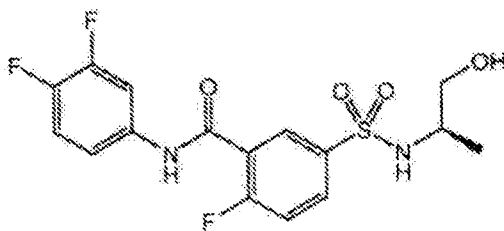
中添加 NEt_3 (17mg, 0.17mmol) 和叔戊胺 (8mg, 0.086mmol)。使反应物升温至 20°C , 并且搅拌 1.5 小时。浓缩混合物, 并且将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10–50% EtOAc/ 己烷) 纯化以产生呈透明胶状的所需产物 (26mg, 76%)。MS: $\text{M}+\text{H}^+$ 403。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 8.55 (dd, $J = 2.4, 6.5\text{Hz}$, 1H), 8.08–8.03 (m, 1H), 7.86–7.78 (m, 1H), 7.46–7.21 (m, 3H), 1.54 (q, $J = 7.6\text{Hz}$, 2H), 1.14 (s, 6H), 0.84 (t, $J = 7.3\text{Hz}$, 3H)。

[1066]



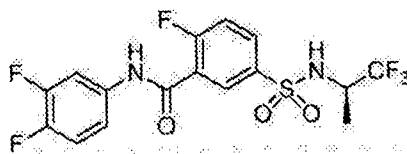
[1067] (S)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-羟基丙烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 C, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (S)-2-氨基-1-丙醇 (6mg, 0.072mmol) 以产生呈白色固体状的所需产物 (20mg, 72%)。MS: $\text{M}+\text{H}^+$ 389。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 8.22 (dd, $J = 2.4, 6.2\text{Hz}$, 1H), 8.09–8.04 (m, 1H), 7.86–7.80 (m, 1H), 7.48–7.21 (m, 3H), 3.44–3.31 (m, 3H), 1.02 (d, $J = 6.4\text{Hz}$, 3H)。

[1068]



[1069] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-羟基丙烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 C, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (R)-2-氨基-1-丙醇 (6mg, 0.072mmol) 以产生呈透明胶状的所需产物 (26mg, 93%)。MS: $\text{M}+\text{H}^+$ 389。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 8.22 (dd, $J = 2.4, 6.2\text{Hz}$, 1H), 8.09–8.04 (m, 1H), 7.86–7.78 (m, 1H), 7.49–7.21 (m, 3H), 3.44–3.29 (m, 3H), 1.02 (d, $J = 6.5\text{Hz}$, 3H)。

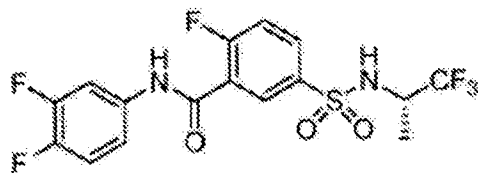
[1070]



[1071] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1,1,1-三氟丙烷-2-基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 以 13.4% 产率获得最终化合物。 ^1H NMR (300MHz, CDCl_3): δ 8.68 (dd, $J = 7.0, 2.6\text{Hz}$, 1H), 8.40 (bd, $J =$

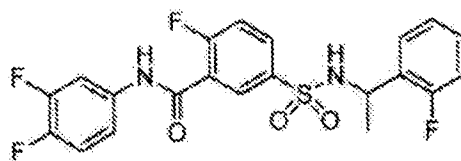
14.1Hz, 1H), 8.05(ddd, $J = 8.8, 4.7, 2.6$ Hz, 1H), 7.36(dd, $J = 11.4, 8.8$ Hz, 1H), 7.26-7.10(m, 2H), 5.24(d, $J = 9.4$ Hz, 1H), 4.12-3.98(m, 1H), 1.37(d, $J = 7.0$ Hz, 3H); $C_{16}H_{12}F_6N_2O_3S$ 的计算值: 426.05; 观测值: MS(ESI) (m/z) 427.2 ($M+1$)⁺。

[1072]



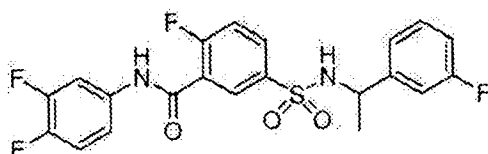
[1073] (S)-N-(3,4-二氟苯基)-2-氟-5-(N-(1,1,1-三氟丙烷-2-基)氨磺酰基)苯甲酰胺: 以与一般性程序C类似的程序, 以21%产率获得最终化合物。¹H NMR(300MHz, $CDCl_3$): δ 8.68(dd, $J = 7.0, 2.6$ Hz, 1H), 8.40(bd, $J = 14.1$ Hz, 1H), 8.05(ddd, $J = 8.8, 4.7, 2.6$ Hz, 1H), 7.36(dd, $J = 11.4, 8.8$ Hz, 1H), 7.26-7.10(m, 2H), 5.24(d, $J = 9.4$ Hz, 1H), 4.12-3.98(m, 1H), 1.37(d, $J = 7.0$ Hz, 3H); $C_{16}H_{12}F_6N_2O_3S$ 的计算值: 426.05; 观测值: MS(ESI) (m/z) 427.1 ($M+1$)⁺。

[1074]



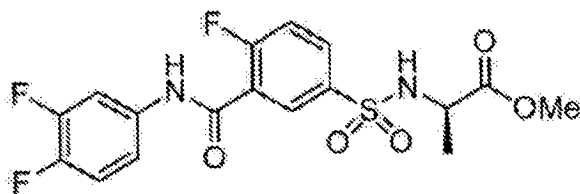
[1075] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(2-氟苯基)乙基)氨磺酰基)苯甲酰胺: 以与一般性程序C类似的程序, 以78%产率获得最终化合物。¹H NMR(300MHz, $CDCl_3$): δ 8.40(dd, $J = 7.0, 2.3$ Hz, 1H), 8.22(bd, $J = 14.1$ Hz, 1H), 7.84-7.72(m, 2H), 7.24-7.06(m, 5H), 6.99-6.92(m, 1H), 6.86-6.76(m, 1H), 5.16(d, $J = 8.5$ Hz, 1H), 4.73(dt, $J = 15.5, 7.0$ Hz, 1H), 1.53(d, $J = 7.0$ Hz, 3H); $C_{21}H_{16}F_4N_2O_3S$ 的计算值: 452.08; 观测值: MS(ESI) (m/z) 453.2 ($M+1$)⁺。

[1076]



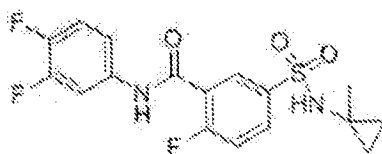
[1077] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(3-氟苯基)乙基)氨磺酰基)苯甲酰胺: 以与一般性程序C类似的程序, 以84%产率获得最终化合物。¹H NMR(300MHz, $CDCl_3$): δ 8.46(dd, $J = 7.0, 2.6$ Hz, 1H), 8.28(bd, $J = 14.1$ Hz, 1H), 7.82-7.70(m, 2H), 7.24-7.10(m, 4H), 6.94-6.88(m, 1H), 6.83(ddt, $J = 8.5, 2.6, 0.9$ Hz, 1H), 6.75(td, $J = 9.7, 2.0$ Hz, 1H), 5.10(d, $J = 6.7$ Hz, 1H), 4.64-4.52(m, 1H), 1.46(d, $J = 7.0$ Hz, 3H); $C_{21}H_{16}F_4N_2O_3S$ 的计算值: 452.08; 观测值: MS(ESI) (m/z) 453.2 ($M+1$)⁺。

[1078]



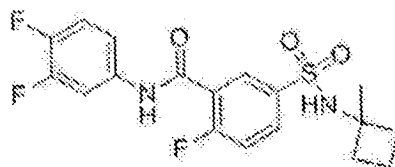
[1079] (R)-甲基-2-(3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基亚磺酰氨基)丙酸酯:¹H NMR(300MHz, CDCl₃): δ 8.56(dd, J = 7.0, 2.6Hz, 1H), 8.42(bd, J = 12.3Hz, 1H), 8.01(ddd, J = 8.7, 4.5, 2.6Hz, 1H), 7.76(ddd, J = 12.4, 7.0, 2.0Hz, 1H), 7.32(dd, J = 11.1, 8.8Hz, 1H), 7.26-7.10(m, 2H), 5.57(d, J = 7.0Hz, 1H), 4.16-4.02(m, 1H), 3.61(s, 3H), 1.42(d, J = 7.3Hz, 3H); C₁₇H₁₅F₃N₂O₅S 的计算值: 416.07; 观测值: MS(ESI) (m/z) 417.2 (M+1)⁺.

[1080]



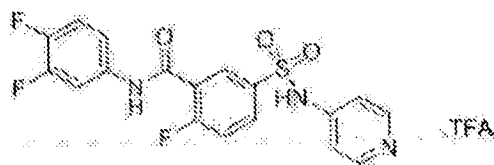
[1081] N-(3,4-二氟苯基)-2-氟-5-(N-(1-甲基环丙基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈白色固体状最终化合物 (60mg, 78%)。¹H NMR(300MHz, CD₃OD): 8.21-8.18(dd, J = 6.4, 2.3Hz, 1H), 8.07-8.01(m, 1H), 7.86-7.79(m, 1H), 7.49-7.37(m, 2H), 7.31-7.22(m, 1H), 1.17(s, 3H), 0.74-0.70(t, J = 5.7Hz, 2H), 0.48-0.46(m, 2H); MS(ES) m/z: 385.2 (M+H)⁺, 计算值: 385.08。

[1082]



[1083] N-(3,4-二氟苯基)-2-氟-5-(N-(1-甲基环丁基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈白色固体状最终化合物 (123mg, 88.5%)。¹H NMR(300MHz, CD₃OD): 8.22-8.19(dd, J = 6.3, 2.3Hz, 1H), 8.07-8.02(m, 1H), 7.86-7.79(m, 1H), 7.48-7.36(m, 2H), 7.31-7.22(m, 1H), 2.27-2.19(m, 2H), 1.84-1.67(m, 4H), 1.36(s, 3H); MS(ES) m/z: 399.2 (M+H)⁺, 计算值: 399.09。

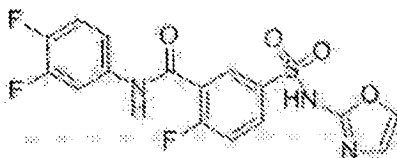
[1084]



[1085] N-(3,4-二氟苯基)-2-氟-5-(N-(吡啶-4-基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈 TFA 盐米色固体状最终化合物 (20mg, 28%)。¹H NMR(300MHz, CD₃OD): 8.38(bs, 1H), 8.31-8.29(m, 1H), 8.18-8.13(m, 1H), 7.77-7.70(m, 1H), 7.48-7.4

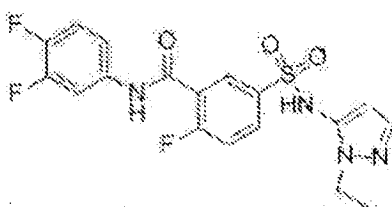
2 (m, 3H), 7.27-7.14 (m, 3H); MS (ES) m/z : 408.2 ($M+H^+$), 计算值: 408.06。

[1086]



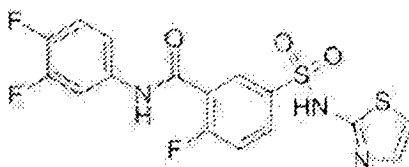
[1087] N-(3,4-二氟苯基)-2-氟-5-(N-(噁唑-2-基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈米色 TFA 盐形式的最终化合物 (7mg, 12%)。 1H NMR (300MHz, CD_3OD): 8.26-8.23 (m, 1H), 8.13-8.07 (m, 1H), 7.94 (s, 1H), 7.77-7.70 (m, 1H), 7.46-7.40 (m, 1H), 7.41-7.17 (m, 3H); MS (ES) m/z : 398.2 ($M+H^+$), 计算值: 398.03。

[1088]



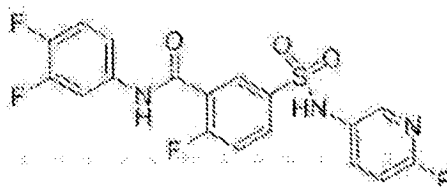
[1089] N-(3,4-二氟苯基)-5-(N-(1-乙基-1H-吡唑-5-基)氨基磺酰基)-2-氟苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈米色固体状的最终化合物 (13.5mg, 23%)。 1H NMR (300MHz, CD_3OD): 8.15-8.13 (m, 1H), 7.96-7.93 (m, 1H), 7.86-7.79 (m, 1H), 7.47-7.24 (m, 5H), 3.20-3.17 (m, 2H), 1.34-1.29 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 425.2 ($M+H^+$), 计算值: 425.08。

[1090]



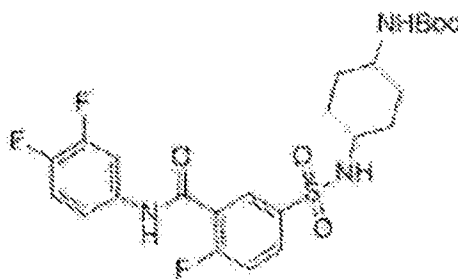
[1091] N-(3,4-二氟苯基)-2-氟-5-(N-(噻唑-2-基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈米色固体状的最终化合物 (7mg, 12%)。 1H NMR (300MHz, CD_3OD): 8.15-8.12 (m, 1H), 8.10-7.93 (m, 1H), 7.76-7.70 (m, 1H), 7.34-7.23 (m, 2H), 7.22-7.16 (m, 1H), 7.03 (bs, 1H), 6.64 (bs, 1H); MS (ES) m/z : 414.1 ($M+H^+$), 计算值: 414.01。

[1092]



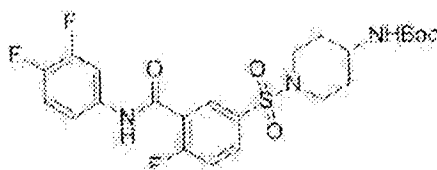
[1093] N-(3,4-二氟苯基)-2-氟-5-(N-(6-氟吡啶-3-基)氨基磺酰基)苯甲酰胺: 以与一般性程序 C 类似的程序, 获得呈米色固体状的最终化合物 (8.3mg, 14%)。 1H NMR (300MHz, CD_3OD): 8.15-8.12 (m, 1H), 7.94-7.92 (m, 1H), 7.82-7.70 (m, 3H), 7.42-7.23 (m, 3H), 6.97-6.94 (m, 1H); MS (ES) m/z : 426.2 ($M+H^+$), 计算值: 426.05。

[1094]



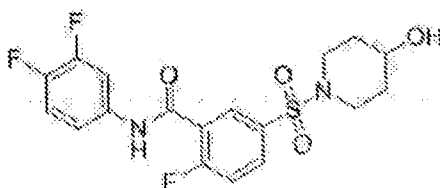
[1095] (4-(3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基亚磺酰氨基)环己基)氨基甲酸叔丁酯: 以与一般性程序C类似的程序, 获得呈白色固体状的最终化合物 (128mg, 85%)。
 ^1H NMR (300MHz, d_6 -DMSO): 10.82 (s, 1H), 8.10-8.08 (m, 1H), 8.04-7.99 (m, 1H), 7.88-7.82 (m, 1H), 7.70 (m, 1H), 7.62-7.57 (m, 1H), 7.49-7.42 (m, 2H), 6.73 (m, 1H), 3.22 (m, 1H), 3.00 (bs, 1H), 1.55-1.39 (m, 8H), 1.35 (s, 9H); MS (ES) m/z : 528.3 ($\text{M}+\text{H}^+$), 计算值: 528.17。

[1096]



[1097] (1-((3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基)磺酰基)哌啶-4-基)氨基甲酸叔丁酯: 以与一般性程序C类似的程序, 获得呈白色固体状的最终化合物 (120mg, 82%)。
 ^1H NMR (300MHz, d_4 -MeOH): 8.11-8.00 (m, 1H), 8.09-7.95 (m, 1H), 7.86-7.79 (m, 1H), 7.54-7.40 (m, 1H), 7.40-7.31 (m, 1H), 7.28-7.22 (m, 1H), 3.69-3.65 (m, 2H), 2.57-2.50 (m, 2H), 1.93-1.89 (m, 2H), 1.57-1.49 (m, 3H), 1.41 (m, 9H); MS (ES) m/z : 536.3 ($\text{M}+\text{Na}^+$), 计算值: 536.15。

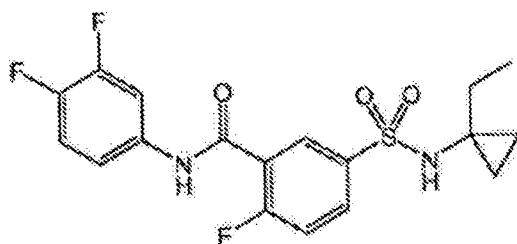
[1098]



[1099] N-(3,4-二氟苯基)-2-氟-5-((4-羟基哌啶-1-基)磺酰基)苯甲酰胺: 以与一般性程序C类似的程序, 获得呈白色固体状的最终化合物 (31mg, 41%)。
 ^1H NMR (300MHz, d_4 -MeOH): 8.12-8.09 (m, 1H), 8.01-7.95 (m, 1H), 7.86-7.78 (m, 1H), 7.54-7.48 (m, 1H), 7.40-7.37 (m, 1H), 7.31-7.22 (m, 1H), 3.69-3.63 (m, 1H), 3.41-3.30 (m, 2H), 2.89-2.82 (m, 2H), 1.92-1.86 (m, 2H), 1.64-1.54 (m, 2H); MS (ES) m/z : 415.2 ($\text{M}+\text{H}^+$), 计算值: 415.09。

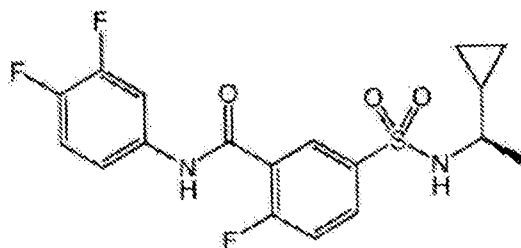
[1100] 实施例4: 一般性程序D

[1101]



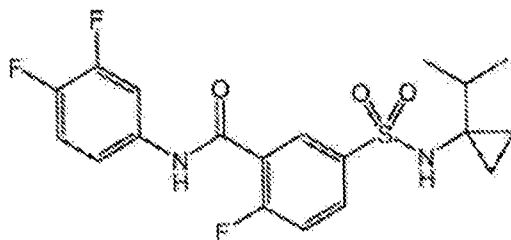
[1102] N-(3,4-二氟苯基)-5-(N-(1-乙基环丙基)氨磺酰基)-2-氟苯甲酰胺:向 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (30mg, 0.086mmol) 于 THF (1mL) 中的 0℃ 溶液中添加 NEt_3 (17mg, 0.17mmol) 和 1-乙基环丙胺·HCl (9mg, 0.072mmol)。使反应物升温至 20℃, 并且搅拌 1.5 小时。浓缩混合物, 并且将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/ 己烷) 纯化以产生呈透明胶状的所需产物 (13mg, 45%)。MS: $\text{M}+\text{H}^+$ 399。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 10.47 (s, 1H), 8.20 (d, $J = 2.4, 6.5\text{Hz}$, 1H), 8.06-8.00 (m, 1H), 7.86-7.78 (m, 1H), 7.48-7.12 (m, 4H), 1.42 (q, $J = 7.6\text{Hz}$, 2H), 0.87 (t, $J = 7.3\text{Hz}$, 3H), 0.64 (dd, $J = 1.8, 5.3\text{Hz}$, 2H), 0.4664 (dd, $J = 2.1, 5.0\text{Hz}$, 2H)。

[1103]



[1104] (R)-5-(N-(1-环丙基乙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (R)-1-环丙基乙胺 (9mg, 0.11mmol) 以产生呈白色固体状的所需产物 (16mg, 56%)。MS: $\text{M}+\text{H}^+$ 399。 ^1H NMR (300MHz, CDCl_3): δ 8.64 (dd, $J = 2.6, 7.0\text{Hz}$, 1H), 8.46 (d, $J = 13.2\text{Hz}$, 1H), 8.08-8.03 (1H), 7.80-7.73 (m, 1H), 7.36-7.11 (m, 3H), 5.03 (d, $J = 6.7\text{Hz}$, 1H), 2.75 (dt, $J = 1.8, 6.5$, 1H), 1.17 (d, $J = 26.5\text{Hz}$, 3H), 0.82-0.74 (m, 1H), 0.50-0.43 (m, 1H), 0.38-0.32 (m, 1H), 0.18-0.04 (m, 2H)。

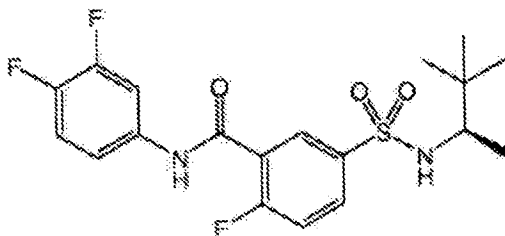
[1105]



[1106] N-(3,4-二氟苯基)-2-氟-5-(N-(1-异丙基环丙基)氨磺酰基)苯甲酰胺:遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg,

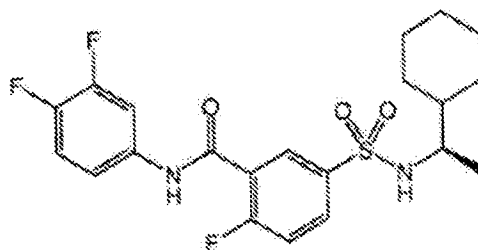
0.072mmol)、 NEt_3 (28mg, 0.28mmol) 和异丙基环丙胺·HCl (15mg, 0.11mmol) 以产生呈白色固体状的所需产物 (22mg, 74%)。MS: $\text{M}+\text{H}^+$ 413。 ^1H NMR (300MHz, CDCl_3): δ 8.56 (dd, $J = 2.4, 6.7\text{Hz}$, 1H), 8.48 (d, $J = 12.9\text{Hz}$, 1H), 8.05–7.99 (m, 1H), 7.80–7.72 (m, 1H), 7.34–7.11 (m, 3H), 5.57 (s, 1H), 1.54 (qint, $J = 6.7\text{Hz}$, 1H), 0.87 (d, $J = 6.7\text{Hz}$, 6H), 0.69–0.58 (m, 4H)。

[1107]



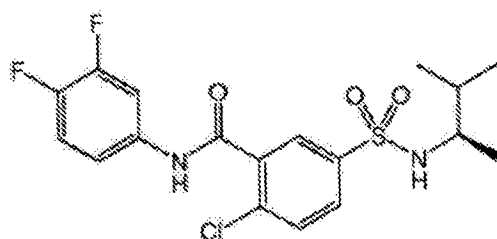
[1108] (R)-N-(3,4-二氟苯基)-5-(N-(3,3-二甲基丁烷-2-基)氨基磺酰基)-2-氟苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (R)-(-)-3,3-二甲基-2-氨基丙烷 (11mg, 0.11mmol) 以产生呈白色固体状的所需产物 (12mg, 40%)。MS: $\text{M}+\text{H}^+$ 415。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): δ 8.21 (dd, $J = 2.4, 6.5\text{Hz}$, 1H), 8.08–8.03 (m, 1H), 7.86–7.79 (m, 1H), 7.49–7.21 (m, 3H), 3.07 (q, $J = 6.7\text{Hz}$, 1H), 0.87 (s, 9H), 0.81 (d, $J = 6.7\text{Hz}$, 3H)。

[1109]



[1110] (R)-5-(N-(1-环己基乙基)氨基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (R)-(-)-环己基乙胺 (14mg, 0.11mmol) 以产生呈白色固体状的所需产物 (15mg, 47%)。MS: $\text{M}+\text{H}^+$ 441。 ^1H NMR (300MHz, CDCl_3): δ 8.63 (dd, $J = 2.4, 7.0\text{Hz}$, 1H), 8.45 (d, $J = 13.2\text{Hz}$, 1H), 8.06–8.01 (m, 1H), 7.80–7.73 (m, 1H), 7.36–7.11 (m, 3H), 4.73 (d, $J = 8.8\text{Hz}$, 1H), 3.25–3.18 (m, 1H), 1.72–1.53 (m, 4H), 1.31–1.01 (m, 5H), 0.98 (d, $J = 6.5\text{Hz}$, 3H), 0.96–0.80 (m, 1H)。

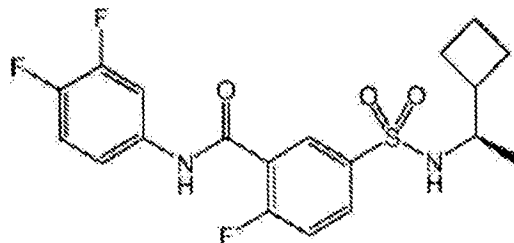
[1111]



[1112] (R)-2-氯-N-(3,4-二氟苯基)-5-(N-(3-甲基丁烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氯苯-1-磺酰氯 (25mg,

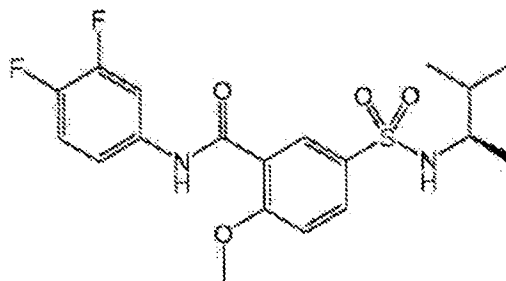
0.068mmol)、 NEt_3 (13mg, 0.14mmol) 和 (R)-(-)-2-氨基-3-甲基丁烷 (9mg, 0.10mmol) 以产生呈灰白色固体状的所需产物 (23mg, 81%)。MS: $\text{M}+\text{H}^+$ 417。 ^1H NMR (300MHz, CDCl_3): δ 8.38 (s, 1H), 8.12 (d, $J = 2.1\text{Hz}$, 1H), 7.81-7.68 (m, 2H), 7.53 (d, $J = 8.5\text{Hz}$, 1H), 7.19-7.12 (m, 2H), 4.83 (d, $J = 8.8\text{Hz}$, 1H), 3.23-3.16 (m, 1H), 1.70-1.62 (m, 1H), 1.26 (d, $J = 7.0\text{Hz}$, 3H), 0.82 (d, $J = 6.7\text{Hz}$, 6H)。

[1113]



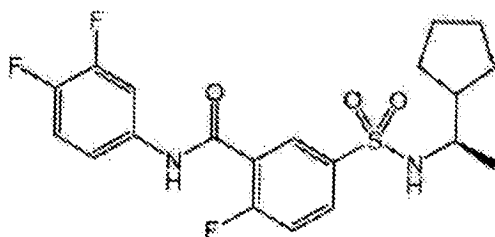
[1114] (R)-5-(N-(1-环丁基乙基)氨基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (28mg, 0.28mmol) 和 (R)-(-)-环丁基乙胺·HCl (15mg, 0.11mmol) 以产生呈白色固体状的所需产物 (19mg, 64%)。MS: $\text{M}+\text{H}^+$ 417。 ^1H NMR (300MHz, CDCl_3): δ 8.64 (dd, $J = 2.4, 7.0\text{Hz}$, 1H), 8.44 (d, $J = 13.8\text{Hz}$, 1H), 8.08-8.03 (m, 1H), 7.80-7.73 (m, 1H), 7.37-7.11 (m, 3H), 4.69 (d, $J = 8.2\text{Hz}$, 1H), 3.29-3.22 (m, 1H), 2.19 (q, $J = 8.2\text{Hz}$, 1H), 1.94-1.60 (m, 5H), 0.96 (d, $J = 6.5\text{Hz}$, 1H), 0.88-0.83 (m, 1H)。

[1115]



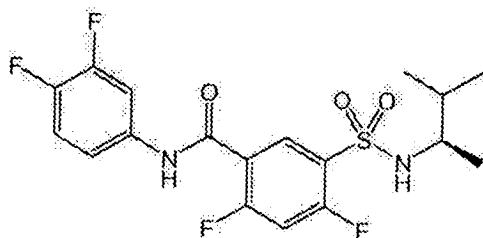
[1116] (R)-N-(3,4-二氟苯基)-2-甲氧基-5-(N-(3-甲基丁烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-甲氧基苯-1-磺酰氯 (25mg, 0.069mmol)、 NEt_3 (13mg, 0.13mmol) 和 (R)-(-)-2-氨基-3-甲基丁烷 (9mg, 0.10mmol) 以产生呈白色固体状的所需产物 (12mg, 42%)。MS: $\text{M}+\text{H}^+$ 413。 ^1H NMR (300MHz, CDCl_3): δ 9.60 (s, 1H), 8.72 (d, $J = 2.6\text{Hz}$, 1H), 7.99 (dd, $J = 2.6, 8.8\text{Hz}$, 1H), 7.81-7.74 (m, 1H), 7.22-7.08 (m, 3H), 4.61 (d, $J = 8.5\text{Hz}$, 1H), 3.23-3.17 (m, 1H), 1.68-1.61 (m, 1H), 0.95 (d, $J = 6.7\text{Hz}$, 1H), 0.82 (d, $J = 7.0\text{Hz}$, 1H)。

[1117]



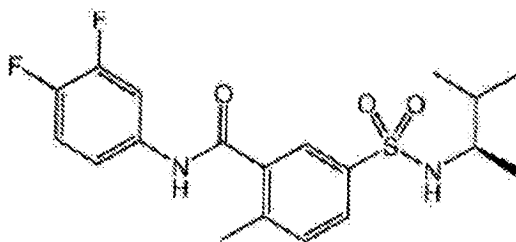
[1118] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、NEt₃ (28mg, 0.28mmol) 和 (R)-(-)-环戊基乙胺·HCl (17mg, 0.11mmol) 以产生呈白色固体状的所需产物 (24mg, 78%)。MS: M+H⁺ 427。¹H NMR (300MHz, CDCl₃): 8.62 (dd, J = 2.4, 7.0Hz, 1H), 8.47 (d, J = 13.2Hz, 1H), 8.06-8.01 (m, 1H), 7.79-7.72 (m, 1H), 7.35-7.11 (m, 3H), 4.84 (d, J = 8.5Hz, 1H), 3.26-3.19 (m, 1H), 1.84-1.43 (m, 5H), 1.39-1.06 (m, 3H), 1.03 (d, J = 6.5Hz, 1H), 0.88-0.83 (m, 1H)。

[1119]



[1120] (R)-N-(3,4-二氟苯基)-2,4-二氟-5-(N-(3-甲基丁烷-2-基)氨磺酰基)苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-2,4-二氟苯-1-磺酰氯 (25mg, 0.068mmol)、NEt₃ (13mg, 0.13mmol) 和 (R)-(-)-2-氨基-3-甲基丁烷 (9mg, 0.10mmol) 以产生呈白色固体状的所需产物 (10mg, 35%)。MS: M+H⁺ 419。¹H NMR (300MHz, CDCl₃): 8.68 (t, J = 8.2Hz, 1H), 8.28 (d, J = 12.3Hz, 1H), 7.78-7.71 (m, 1H), 7.25-7.07 (m, 3H), 7.70 (m, 1H), 3.33-3.26 (m, 1H), 1.73-1.64 (m, 1H), 1.02 (d, J = 6.5Hz, 1H), 0.86 (dd, J = 1.8, 7.0Hz, 1H)。

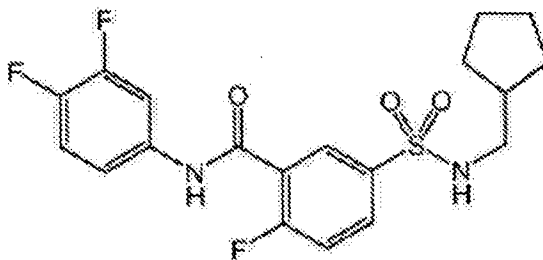
[1121]



[1122] (R)-N-(3,4-二氟苯基)-2-甲基-5-(N-(3-甲基丁烷-2-基)氨磺酰基)苯甲酰胺: 遵循一般性程序 D, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-甲基苯-1-磺酰氯 (25mg, 0.068mmol)、NEt₃ (13mg, 0.13mmol) 和 (R)-(-)-2-氨基-3-甲基丁烷 (9mg, 0.10mmol) 以产生呈白色固体状的所需产物 (10mg, 35%)。MS: M+H⁺ 397。¹H NMR (300MHz, CDCl₃): 8.23 (s, 1H), 7.93 (d, J = 1.5Hz, 1H), 7.74-7.70 (m, 2H), 7.35 (d, J = 8.2Hz, 1H), 7.26-7.12 (m, 2H), 4.59 (d, J = 8.5Hz, 1H), 3.17-3.15 (m, 1H), 2.56 (s, 3H), 1.66-1.62 (m, 1H), 0.93 (d, J =

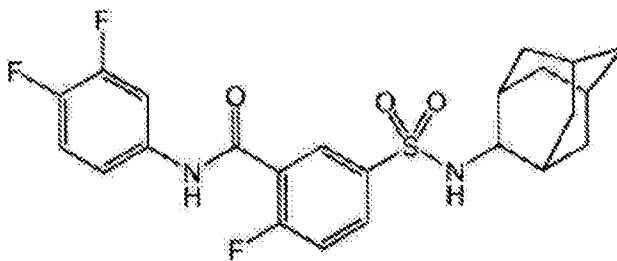
6. Hz, 1H), 0.81 (d, $J = 6.7$ Hz, 1H)。

[1123]



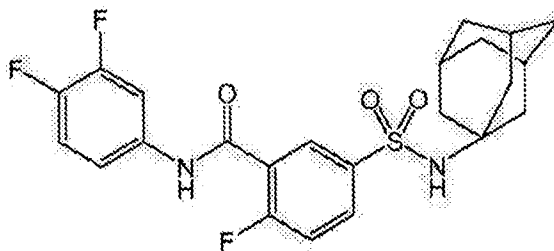
[1124] 5-(N-(环戊基甲基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(25mg,0.072mmol)、 NEt_3 (28mg,0.28mmol)和C-环戊基-甲胺(11mg,0.11mmol)以产生呈白色固体状的所需产物(14mg,47%)。MS: $\text{M}+\text{H}^+$ 413。 ^1H NMR(300MHz, $\text{DMSO}-d_6$):10.82(s, 1H), 8.06–7.96(m, 2H), 7.90–7.76(m, 2H), 7.61(t, $J = 9.2$ Hz, 1H), 7.50–7.42(m, 2H), 2.67(t, $J = 6.2$ Hz, 2H), 1.98–1.86(m, 1H), 1.64–1.43(m, 6H), 1.14–1.08(m, 2H)。

[1125]



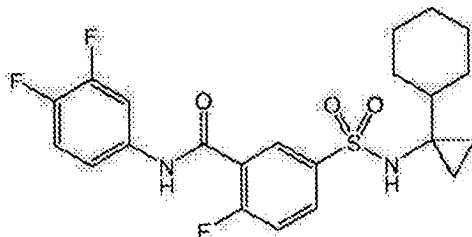
[1126] 5-(N-(2-金刚烷基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(30mg,0.086mmol)、 NEt_3 (28mg,0.28mmol)和2-氨基-金刚烷·HCl(24mg,0.13mmol)以产生呈白色固体状的所需产物(31mg,78%)。MS: $\text{M}+\text{H}^+$ 465。 ^1H NMR(300MHz, CDCl_3):8.66–8.63(m, 1H), 8.44(d, $J = 13.5$ Hz, 1H), 8.08–8.03(m, 1H), 7.79–7.72(m, 1H), 7.36–7.11(m, 3H), 5.23(d, $J = 7.3$ Hz, 1H), 3.44(d, $J = 7.0$ Hz, 1H), 1.80–1.16(m, 14H)。

[1127]



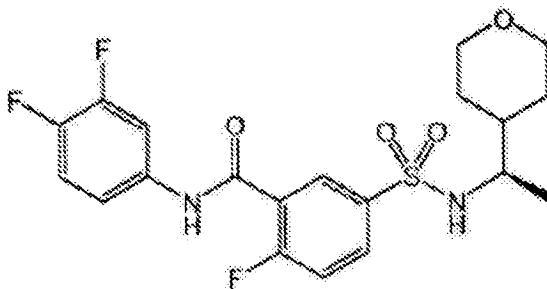
[1128] 5-(N-(1-金刚烷基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(30mg,0.086mmol)、 NEt_3 (17mg,0.17mmol)和1-氨基-金刚烷·HCl(20mg,0.13mmol)以产生呈白色固体状的所需产物(26mg,65%)。MS: $\text{M}+\text{Na}^+$ 487。 ^1H NMR(300MHz, $\text{DMSO}-d_6$):10.81(s, 1H), 8.11–8.09(m, 1H), 8.05–8.00(m, 1H), 7.90–7.83(m, 1H), 7.70(s, 1H), 7.60(d, $J = 9.4$ Hz, 1H), 7.47–7.42(m, 2H), 1.97–1.92(m, 3H), 1.69(s, 6H), 1.55–1.45(m, 6H)。

[1129]



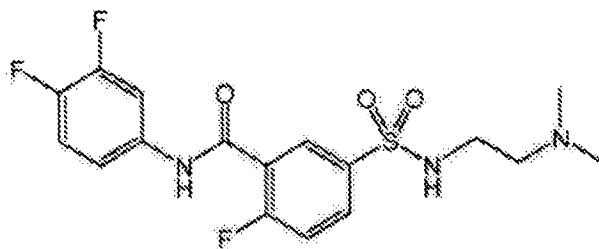
[1130] 5-(N-(1-环己基环丙基)氨基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(30mg,0.086mmol)、NEt₃(17mg,0.17mmol)和(1-环己基环丙基)胺·HCl(18mg,0.13mmol)以产生呈白色固体状的所需产物(11mg,28%)。MS:M+H⁺453。¹H NMR(300MHz,CDCl₃):8.61-8.58(m,1H),8.38(d,J=14.1Hz,1H),8.06-8.01(m,1H),7.80-7.74(m,1H),7.35-7.12(m,4H),5.20(s,1H),1.70-1.58(m,3H),1.43-0.93(m,8H),0.64(d,J=4.7Hz,4H)。

[1131]



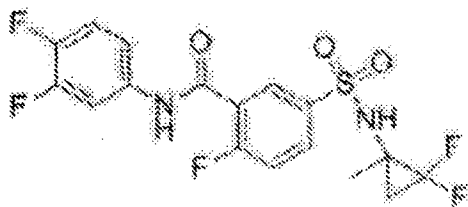
[1132] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-(四氢-2H-吡喃-4-基)乙基)氨基磺酰基)苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(50mg,0.14mmol)、NEt₃(42mg,0.42mmol)和(R)-1-(四氢-2H-吡喃-4-基)乙胺·HCl(35mg,0.21mmol)以产生呈白色固体状的所需产物(36mg,58%)。MS:M+H⁺443。¹H NMR(300MHz,DMSO-d₆):10.81(s,1H),8.08-8.05(m,1H),8.02-7.96(m,1H),7.90-7.82(m,1H),7.65(d,J=12.9Hz,1H),7.60(t,J=9.7Hz,1H),7.47-7.39(m,2H),3.83-3.78(m,2H),3.20-2.99(m,3H),1.53-1.38(m,3H),1.25-0.97(m,3H),0.80(d,J=6.7Hz,1H)。

[1133]



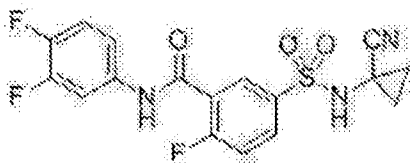
[1134] N-(3,4-二氟苯基)-5-(N-(2-(二甲基氨基)乙基)氨基磺酰基)-2-氟苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(50mg,0.14mmol)、NEt₃(28mg,0.28mmol)和N,N-二甲基乙二胺(19mg,0.22mmol)以产生呈白色固体状的所需产物(46mg,82%)。MS:M+H⁺402。

[1135]



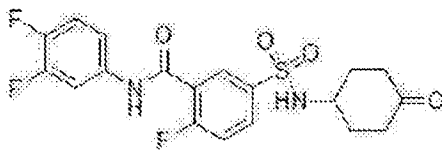
[1136] 5-(N-(2,2-二氟-1-甲基环丙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:以与一般性程序D类似的程序,获得呈白色固体状的最终化合物(29.8mg,50%)。¹H NMR(300MHz, d₄-MeOH):8.23-8.20(m, 1H), 8.08-8.03(m, 1H), 7.86-7.78(m, 1H), 7.50-7.44(t, J = 9.2Hz, 1H), 7.40-7.22(m, 2H), 1.67-1.57(m, 1H), 1.45-1.30(m, 1H), 1.29(s, 3H); MS(ES)m/z:421.2(M+H⁺), 计算值:421.06。

[1137]



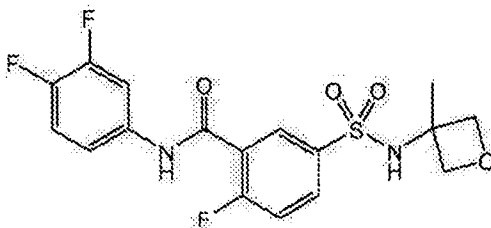
[1138] 5-(N-(1-氰基环丙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:以与一般性程序D类似的程序,获得呈白色固体状的最终化合物(30.6mg,75%)。¹H NMR(300MHz, d₄-MeOH):8.30-8.27(m, 1H), 8.15-8.10(m, 1H), 7.86-7.79(m, 1H), 7.55-7.49(m, 1H), 7.40-7.22(m, 2H), 1.43(s, 4H); MS(ES)m/z:396.2(M+H⁺), 计算值:396.06。

[1139]



[1140] N-(3,4-二氟苯基)-2-氟-5-(N-(4-氧代环己基)氨磺酰基)苯甲酰胺:以与一般性程序D类似的程序,获得呈白色固体状的最终化合物(45mg,46%)。¹H NMR(300MHz, d₄-MeOH):8.27-8.19(m, 1H), 8.13-8.03(m, 1H), 7.85-7.79(m, 1H), 7.52-7.37(m, 2H), 7.31-7.22(m, 1H), 3.61-3.53(m, 1H), 2.01-1.97(m, 2H), 1.81-1.76(m, 3H), 1.68-1.62(m, 1H), 1.49-1.45(m, 2H); MS(ES)m/z:427.2(M+H⁺), 计算值:427.09。

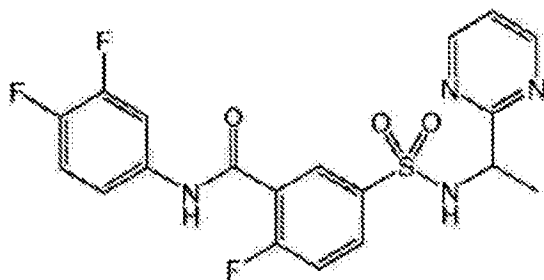
[1141]



[1142] N-(3,4-二氟苯基)-2-氟-5-(N-(3-甲基氧杂环丁烷-3-基)氨磺酰基)苯甲酰胺:遵循一般性程序D,使用3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯(50mg, 0.14mmol)、NEt₃(28mg, 0.28mmol)和3-氨基-3-甲基-氧杂环丁烷(19mg, 0.22mmol)以产生呈白色固体状的所需产物(41mg,73%)。MS:M+H⁺401。

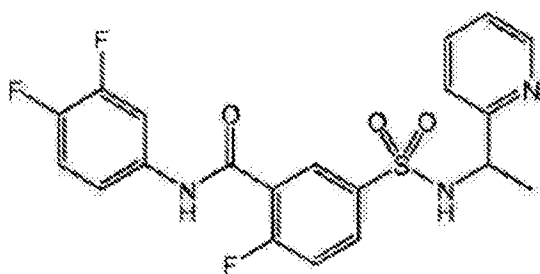
[1143] 实施例5:一般性程序E

[1144]



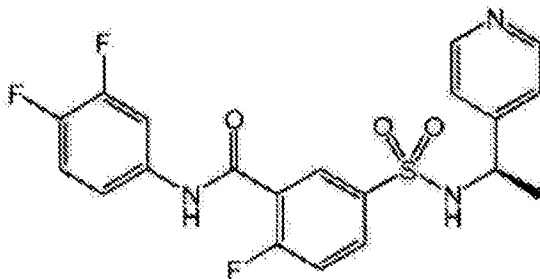
[1145] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(吡啶-2-基)乙基)氨基磺酰基)苯甲酰胺: 向 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol) 于 THF (1mL) 中的 0℃ 溶液中添加 NEt_3 (14mg, 0.14mmol) 和 1-吡啶-2-基-乙胺·HCl (18mg, 0.11mmol)。使反应物升温至 20℃, 并且搅拌 3 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与稀 NaHCO_3 (5mL) 之间。有机层用水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (20-100% EtOAc/己烷) 纯化以产生呈灰白色固体状的所需产物 (11mg, 35%)。MS: $\text{M}+\text{H}^+$ 436。 ^1H NMR (300MHz, CDCl_3): δ 8.59 (d, $J = 5.0\text{Hz}$, 1H), 8.46-8.40 (m, 1H), 7.97-7.92 (m, 1H), 7.79-7.72 (m, 1H), 7.26-7.11 (m, 4H), 6.32 (d, $J = 8.2\text{Hz}$, 1H), 4.68 (dq, $J = 1.2, 7.0\text{Hz}$, 1H), 1.54 (d, $J = 6.7\text{Hz}$, 1H)。

[1146]



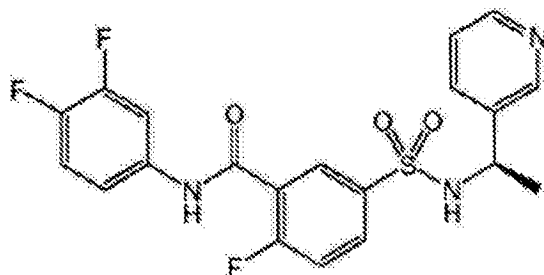
[1147] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(吡啶-2-基)乙基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 E, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 1-吡啶-2-基-乙胺 (13mg, 0.11mmol) 以产生呈白色固体状的所需产物 (24mg, 77%)。MS: $\text{M}+\text{H}^+$ 436。 ^1H NMR (300MHz, $\text{DMSO}-d_6$): 10.72 (s, 1H), 8.44 (d, $J = 7.3\text{Hz}$, 1H), 8.35-8.33 (m, 1H), 7.92-7.80 (m, 3H), 7.66-7.60 (m, 1H), 7.50-7.42 (m, 3H), 7.27 (d, $J = 7.9\text{Hz}$, 1H), 7.17-7.12 (m, 2H), 4.44 (m, 1H), 1.27 (d, $J = 7.0\text{Hz}$, 1H)。

[1148]

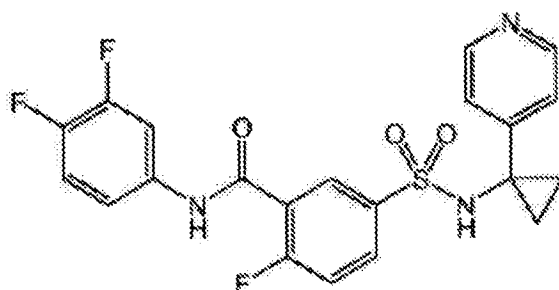


[1149] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-(吡啶-4-基)乙基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 E, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg,

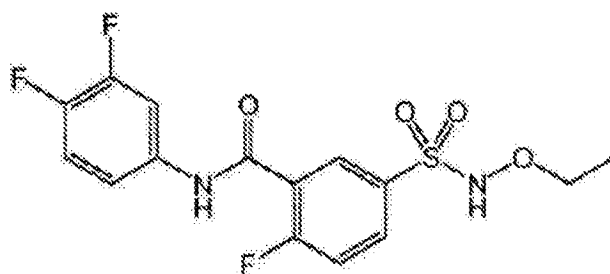
0.072mmol)、 NEt_3 (14mg, 0.14mmol) 和 (R)-1-吡啶-4-基乙胺 (13mg, 0.11mmol) 以产生呈白色固体状的所需产物 (16mg, 51%)。MS: $\text{M}+\text{H}^+$ 436。 ^1H NMR (300MHz, $\text{DMSO}-d_6$): 10.75 (s, 1H), 8.55 (d, $J = 7.9\text{Hz}$, 1H), 8.39 (dd, $J = 1.2, 4.4\text{Hz}$, 2H), 8.00-7.97 (m, 1H), 7.90-7.82 (m, 1H), 7.51-7.42 (m, 3H), 7.24 (dd, $J = 1.5, 4.7\text{Hz}$, 1H), 4.44-4.39 (m, 1H), 1.22 (d, $J = 7.0\text{Hz}$, 1H)。
[1150]



[1151] (R)-N-(3,4-二氟苯基)-2-氟-5-(N-(1-(吡啶-3-基)乙基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 E, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (25mg, 0.072mmol)、 NEt_3 (42mg, 0.42mmol) 和 (1R)-吡啶-3-基-乙胺·2HCl (21mg, 0.11mmol) 以产生呈白色固体状的所需产物 (21mg, 67%)。MS: $\text{M}+\text{H}^+$ 436。 ^1H NMR (300MHz, $\text{DMSO}-d_6$): 10.71 (s, 1H), 8.48 (d, $J = 7.9\text{Hz}$, 1H), 8.39-8.34 (m, 1H), 7.93-7.80 (m, 3H), 7.61-7.57 (m, 1H), 7.50-7.42 (m, 2H), 7.23-7.18 (m, 1H), 4.51-4.41 (m, 1H), 1.27 (d, $J = 7.0\text{Hz}$, 1H)。
[1152]



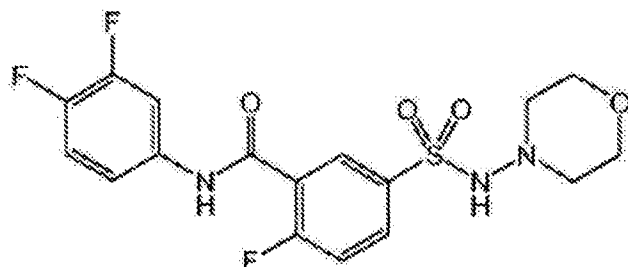
[1153] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(吡啶-4-基)环丙基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 E, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)、 NEt_3 (56mg, 0.56mmol) 和 1-吡啶-4-基-环丙胺·2HCl (44mg, 0.22mmol) 以产生呈灰白色固体状的所需产物 (15mg, 24%)。MS: $\text{M}+\text{H}^+$ 448。 ^1H NMR (300MHz, $\text{MeOH}-d_4$): 8.30 (bs, 2H), 8.07-8.04 (m, 1H), 7.89-7.78 (m, 2H), 7.39-7.22 (m, 5H), 1.40-1.36 (m, 2H), 1.33-1.21 (m, 2H)。
[1154]



[1155] N-(3,4-二氟苯基)-5-(N-乙氧基氨基磺酰基)-2-氟苯甲酰胺: 遵循一般性程序 E,

使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)、NEt₃ (42mg, 0.42mmol) 和 0-乙基羟基胺·HCl (21mg, 0.22mmol) 以产生呈白色固体状的所需产物 (24mg, 46%)。MS: M+H⁺ 375。

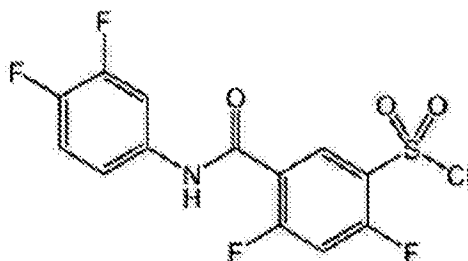
[1156]



[1157] N-(3-(3,4-二氟苯基)-2-氟-5-(N-吗啉代氨磺酰基)苯甲酰胺: 遵循一般性程序 E, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)、NEt₃ (28mg, 0.28mmol) 和 N-氨基-吗啉 (22mg, 0.22mmol) 以产生呈白色固体状的所需产物 (28mg, 48%)。MS: M+H⁺ 416。 ¹H NMR (300MHz, MeOH-d₄): 8.28 (dd, J = 2.4, 6.5Hz, 1H), 8.15-8.09 (m, 1H), 7.86-7.79 (m, 1H), 7.48 (t, J = 9.3Hz, 1H), 7.40-7.37 (m, 1H), 7.26 (q, J = 9.0Hz, 1H), 3.60-3.57 (m, 2H), 2.60-2.58 (m, 2H)。

[1158] 实施例 6: 一般性程序 F

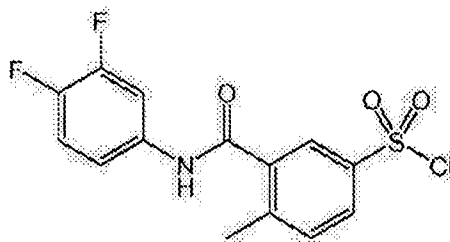
[1159]



[1160] 3-(3-(3,4-二氟苯基)-2,4-二氟苯-1-磺酰氯: 在回流下加热 5-氯磺酰基-2,4-二氟苯甲酸 (0.50g, 1.96mmol)、亚硫酸氯 (2mL) 和 1,2-二氯乙烷 (1mL) 的混合物 3 小时。浓缩反应物, 接着用甲苯 (5mL) 处理残余物, 接着浓缩混合物。粗物质在进一步纯化下使用。

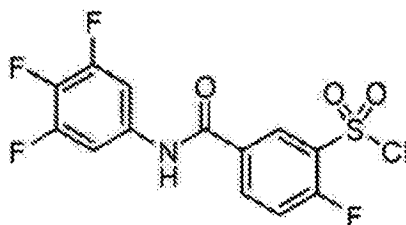
[1161] 向 3,4-二氟苯胺 (0.51g, 3.92mmol) 于甲苯 (5mL) 中的 0℃ 溶液中添加来自先前步骤的物质于甲苯 (1mL) 中的溶液。搅拌反应物 16 小时, 接着过滤。将残余物分配于 CH₂Cl₂ (25mL) 与冰和 2N HCl 的混合物 (10mL) 之间。水层用 CH₂Cl₂ (2 x 25mL) 萃取。合并的有机层用盐水 (5mL) 洗涤, 干燥 (Na₂SO₄) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/己烷) 纯化以产生呈白色固体状的所需产物 (0.53g, 74%)。MS: M+H⁺ 368。

[1162]



[1163] 3-(3,4-二氟苯基氨基甲酰基)-4-甲基苯-1-磺酰氯:遵循一般性程序 F, 使用 5-氯磺酰基-2-甲基苯甲酸 (0.50g, 2.13mmol) 以产生呈白色固体状的所需产物 (0.48g, 65% (历经 2 步))。MS: $M+H^+$ 346。

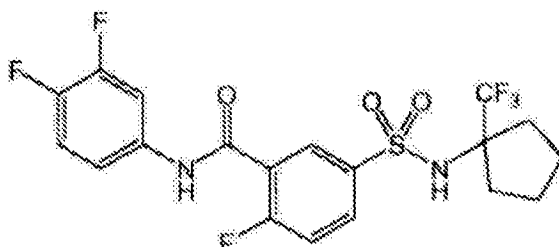
[1164]



[1165] 2-氟-5-(3,4,5-三氟苯基氨基甲酰基)-苯-1-磺酰氯:以与一般性程序 F 类似的程序, 获得呈白色固体状的最终化合物 (0.85g, 53%)。MS (ES) m/z : 367.70 ($M+H^+$), 计算值: 367.97。

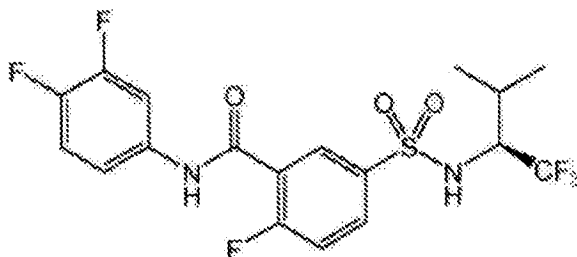
[1166] 实施例 7: 一般性程序 G

[1167]



[1168] N-(3-(3,4-二氟苯基)-2-氟-5-(N-(1-(三氟甲基)环戊胺)氨基磺酰基)苯甲酰胺: 向 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (75mg, 0.22mmol) 和 DMAP (10mg) 于吡啶 (0.2mL) 中的 0℃ 溶液中添加 1-三氟甲基-环戊烷 (67mg, 0.44mmol)。使反应物升温至 20℃, 并且搅拌 4 小时。浓缩混合物, 并且将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/己烷) 纯化以产生呈白色固体状的所需产物 (56mg, 55%)。MS: $M+H^+$ 467。 1H NMR (300MHz, $DMSO-d_6$): 10.82 (s, 1H), 8.51 (s, 1H), 8.11-8.08 (m, 1H), 8.03-7.98 (m, 1H), 7.90-7.83 (m, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.47-7.42 (m, 2H), 2.17-2.13 (m, 2H), 1.80-1.75 (m, 2H), 1.59 (bs, 4H), 1.31-1.29 (m, 2H)。

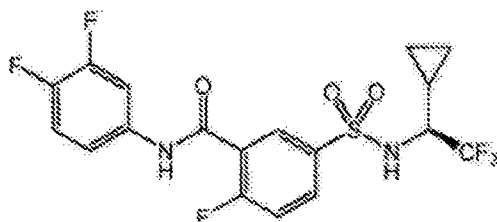
[1169]



[1170] (S)-N-(3-(3,4-二氟苯基)-2-氟-5-(N-(1,1,1-三氟-3-甲基丁烷-2-基)氨基磺酰基)苯甲酰胺: 遵循一般性程序 G, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol) 和 (S)-1,1,1-三氟-3-甲基-2-丁胺 (40mg, 0.28mmol) 以产生呈白

色固体状的所需产物 (19mg, 30%)。MS: $M+H^+$ 455。 1H NMR (300MHz, $CDCl_3$): 8.63-8.60 (m, 1H), 8.31 (d, $J = 14.4$ Hz, 1H), 7.98-7.93 (m, 1H), 7.71-7.65 (m, 1H), 7.29-7.04 (m, 3H), 5.16 (d, $J = 10.3$ Hz, 1H), 3.88-3.81 (m, 1H), 2.17-2.06 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.90 (d, $J = 6.7$ Hz, 1H)。

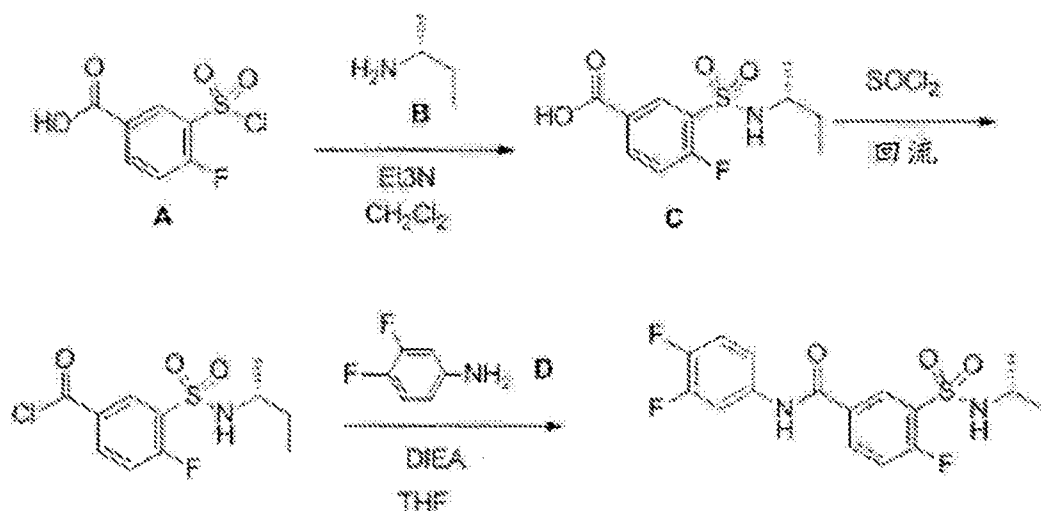
[1171]



[1172] (S)-5-(N-(1-环丙基-2,2,2-三氟乙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺。遵循一般性程序 G, 使用 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol) 和 (S)-1-环丙基-2,2,2-三氟甲基乙胺·HCl (49mg, 0.28mmol) 以产生呈白色固体状的所需产物 (25mg, 40%)。MS: $M+H^+$ 453。

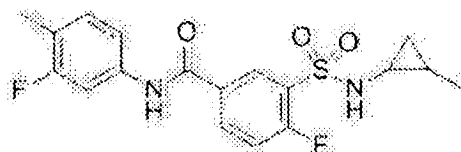
[1173] 实施例 8: 一般性程序 H

[1174]



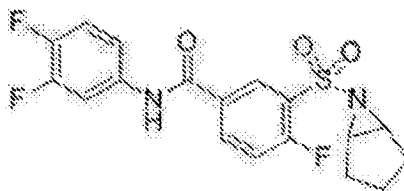
[1175] 将 A (1.007g, 0.0042mol)、B (0.3086g, 0.0042mol) 和 Et_3N (1.28g, 0.01266mol) 于 CH_2Cl_2 (20mL) 中在室温下搅拌过夜。蒸发溶剂, 并且通过柱色谱法纯化粗产物以产生化合物 C (0.462g, 40%)。在真空下干燥过夜之后, 在 $80^\circ C$ 下加热于 $SOCl_2$ 中的 C (0.176g, 0.64mmol) 8 小时。此后, 蒸发试剂, 干燥过夜。接着将残余物溶解于 THF (5mL) 中, 依次添加 D (0.15g, 1.16mmol) 和 DIEA (0.5mL) (其中 DIEA 是 N,N-二异丙基乙胺)。加热混合物至 $70^\circ C$, 过夜。蒸发溶剂, 随后进行 EtOAc 萃取。在通过柱色谱法在硅胶 (EtOAc/己烷) 上纯化之后, 获得 199mg (80%) 最终产物。 1H NMR (300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.7, 2.4$ Hz, 1H), 8.14 (m, 1H), 8.01 (m, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 4.63 (d, $J = 8.2$ Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.78 (t, $J = 7.3$ Hz, 3H); MS (ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。

[1176]



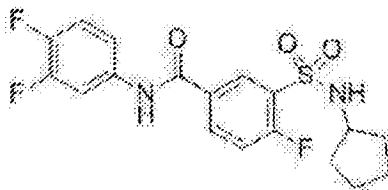
[1177] 4-氟-N-(3-氟-4-甲基苯基)-3-(N-(2-甲基环丙基)氨磺酰基)苯甲酰胺:以与一般性程序H类似的程序,获得呈白色固体状的最终化合物(108mg,100%)。¹H NMR(300MHz, CDCl₃): δ 8.28(dd, J = 6.4, 2.3Hz, 1H), 8.15(m, 1H), 8.10(s, 1H), 7.46(m, 1H), 7.24(m, 1H), 7.16(m, 2H), 5.21(s, 1H), 2.19(d, J = 1.8Hz, 3H), 1.89(m, 1H), 0.95(m, 1H), 0.87(d, J = 5.6Hz, 3H), 0.74(m, 1H), 0.35(m, 1H); MS(ES)m/z:381.1(M+H⁺), 计算值:381.10。

[1178]



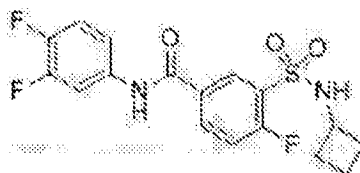
[1179] 3-(6-氮杂双环[3.1.0]己烷-6-基磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺:以与一般性程序H类似的程序,获得呈白色固体状的最终化合物(37mg,13%)。¹H NMR(300MHz, CDCl₃): δ 8.62(dd, J = 6.4, 2.5Hz, 1H), 8.17(m, 1H), 7.96(s, 1H), 7.68(m, 1H), 7.30(t, J = 9.0Hz, 1H), 7.15(m, 2H), 4.99(m, 1H), 3.96(m, 1H), 3.56(m, 1H), 2.14(m, 2H), 1.74(m, 3H), 1.44(m, 2H); MS(ES)m/z:397.1(M+H⁺), 计算值:397.08。

[1180]



[1181] 3-(N-环戊基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺:以与一般性程序H类似的程序,获得呈白色固体状的最终化合物(168mg,40%)。¹H NMR(300MHz, CDCl₃): δ 8.31(dd, J = 6.4, 2.4Hz, 1H), 8.20(m, 1H), 8.06(s, 1H), 7.74(m, 1H), 7.33(t, J = 9.0Hz, 1H), 7.19(m, 2H), 4.80(d, J = 7.6Hz, 1H), 3.65(m, 1H), 1.78(m, 2H), 1.63(m, 2H), 1.53(m, 2H), 1.39(m, 2H); MS(ES)m/z:399.2(M+H⁺), 计算值:399.09。

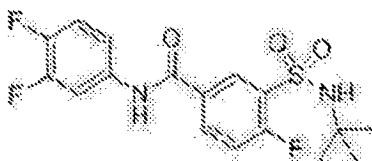
[1182]



[1183] 3-(N-环丁基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺:以与一般性程序H类似的程序,获得呈白色固体状的最终化合物(328mg,78%)。¹H NMR(300MHz, CDCl₃): δ 8.24(dd, J = 6.7, 2.4Hz, 1H), 8.14(m, 2H), 7.68(m, 1H), 7.22(m, 1H), 7.17(m, 2H), 5.05(d, J = 9.4Hz, 1H), 3.79(m, 1H), 2.06(m, 2H), 1.79(m, 2H), 1.67(m, 1H);

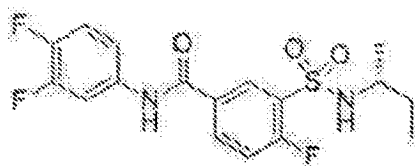
MS(ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

[1184]



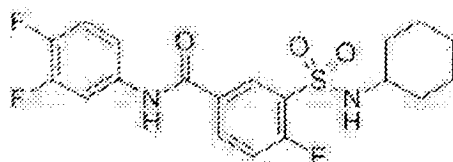
[1185] 3-(N-(叔丁基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (261mg, 37 %)。 1H NMR (300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.5, 2.4$ Hz, 1H), 8.12 (m, 1H), 7.97 (s, 1H), 7.68 (m, 1H), 7.21 (m, 1H), 7.17 (m, 1H), 4.83 (s, 1H), 1.19 (s, 9H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。

[1186]



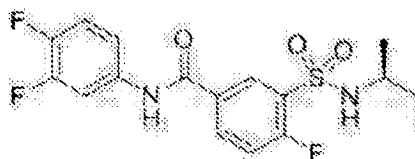
[1187] (R)-3-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (199mg, 80 %)。 1H NMR (300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.7, 2.4$ Hz, 1H), 8.14 (m, 1H), 8.01 (m, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 4.63 (d, $J = 8.2$ Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.78 (t, $J = 7.3$ Hz, 3H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。

[1188]



[1189] 3-(N-环己基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (106mg, 43 %)。 1H NMR (300MHz, $CDCl_3$): δ 8.26 (dd, $J = 6.6, 2.5$ Hz, 1H), 8.14 (m, 2H), 7.69 (m, 1H), 7.22 (m, 1H), 7.14 (m, 2H), 4.76 (d, $J = 5.9$ Hz, 1H), 3.18 (m, 1H), 1.65 (m, 2H), 1.58 (m, 2H), 1.48 (m, 2H), 1.17 (m, 4H); MS(ES) m/z : 413.2 ($M+H^+$), 计算值: 413.11。

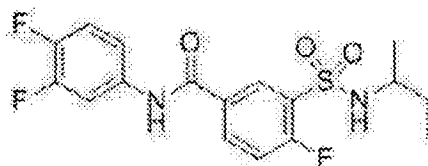
[1190]



[1191] (S)-3-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (66mg, 24 %)。 1H NMR (300MHz, $CDCl_3$): δ 8.26 (dd, $J = 6.7, 2.3$ Hz, 1H), 8.15 (m, 1H), 8.01 (m, 1H), 7.70 (m, 1H), 7.22 (m, 1H), 7.17 (m, 2H), 4.62 (d, $J = 7.2$ Hz, 1H), 3.29 (m, 1H), 1.40 (m, 2H), 1.02 (d, $J =$

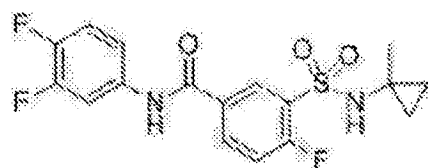
6.7Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。

[1192]



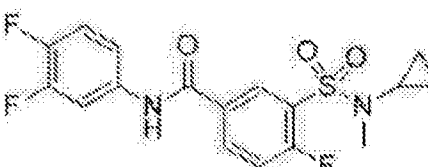
[1193] 3-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (120mg, 43%)。 1H NMR(300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.5, 2.3$ Hz, 1H), 8.14 (m, 1H), 7.90 (s, 1H), 7.68 (m, 1H), 7.20 (m, 1H), 7.17 (m, 2H), 4.57 (d, $J = 8.2$ Hz, 1H), 3.28 (m, 1H), 1.39 (m, 2H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.79 (t, $J = 7.0$ Hz, 3H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。

[1194]



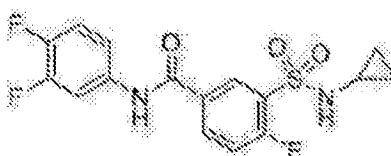
[1195] N-(3,4-二氟苯基)-4-氟-3-(N-(1-甲基环丙基)氨磺酰基)苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (63mg, 15%)。 1H NMR(300MHz, $CDCl_3$): δ 8.28 (dd, $J = 6.5, 2.5$ Hz, 1H), 8.16 (m, 1H), 7.89 (s, 1H), 7.70 (m, 1H), 7.21 (m, 1H), 7.16 (m, 2H), 5.23 (d, $J = 2.3$ Hz, 1H), 1.17 (m, 5H), 0.80 (m, 2H); MS(ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

[1196]



[1197] 3-(N-环丙基-N-甲基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (158mg, 83%)。 1H NMR(300MHz, $CDCl_3$): δ 8.24 (dd, $J = 6.2, 2.6$ Hz, 1H), 8.13 (m, 1H), 8.01 (s, 1H), 7.69 (m, 1H), 7.21 (m, 1H), 7.17 (m, 2H), 2.85 (d, $J = 2.1$ Hz, 3H), 2.06 (m, 1H), 0.77 (m, 2H), 0.67 (m, 2H); MS(ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

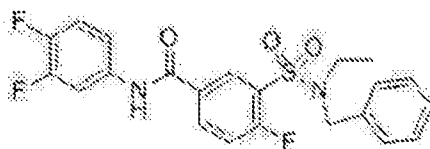
[1198]



[1199] 3-(N-环丙基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (118mg, 35%)。 1H NMR(300MHz, $CDCl_3$): δ 8.30 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.19 (m, 1H), 7.98 (s, 1H), 7.70 (m, 1H), 7.31 (t, $J = 8.9$ Hz, 1H), 7.16 (m, 2H), 5.18 (s, 1H), 2.23 (m, 1H), 0.61 (m, 4H); MS(ES) m/z :

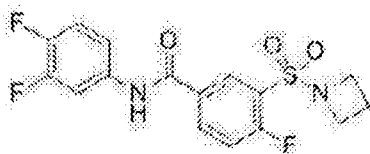
z:371.1 ($M+H^+$), 计算值:371.35。

[1200]



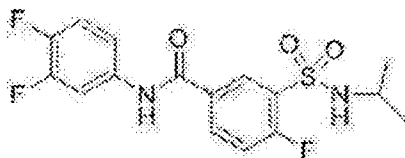
[1201] 3-(N-苯甲基-N-乙基氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (60mg, 11%)。 1H NMR(300MHz, $CDCl_3$): δ 8.21 (dd, $J = 6.2, 2.4$ Hz, 1H), 8.11 (m, 1H), 7.94 (s, 1H), 7.69 (m, 1H), 7.25 (m, 1H), 7.18 (m, 7H), 4.45 (s, 2H), 3.26 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H); MS (ES) m/z : 449.2 ($M+H^+$), 计算值: 449.11。

[1202]



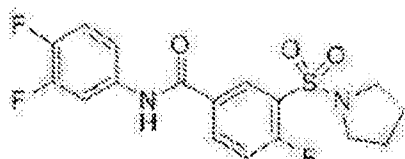
[1203] 3-(氮杂环丁烷-1-基磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (5mg, 2%)。 1H NMR(300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.2, 2.3$ Hz, 1H), 8.16 (m, 2H), 7.68 (m, 1H), 7.21 (m, 1H), 7.15 (m, 2H), 3.54 (m, 4H), 2.08 (m, 2H); MS (ES) m/z : 371.1 ($M+H^+$), 计算值: 371.06。

[1204]



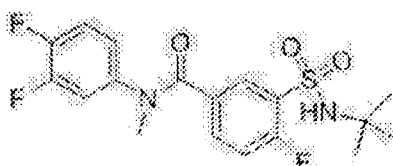
[1205] N-(3,4-二氟苯基)-4-氟-3-(N-异丙基氨磺酰基)苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (410mg, 87%)。 1H NMR(300MHz, $CDCl_3$): δ 8.26 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.14 (m, 1H), 8.02 (s, 1H), 7.68 (m, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 4.64 (d, $J = 7.6$ Hz, 1H), 3.50 (m, 1H), 1.07 (d, $J = 6.4$ Hz, 2H); MS (ES) m/z : 373.1 ($M+H^+$), 计算值: 373.08。

[1206]



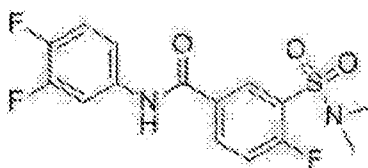
[1207] N-(3,4-二氟苯基)-4-氟-3-(吡咯烷-1-基磺酰基)苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (350mg, 70%)。 1H NMR(300MHz, $CDCl_3$): δ 8.25 (dd, $J = 6.2, 2.3$ Hz, 1H), 8.11 (m, 2H), 7.69 (m, 1H), 7.22 (m, 1H), 7.11 (m, 2H), 3.32 (m, 4H), 1.80 (m, 4H); MS (ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

[1208]



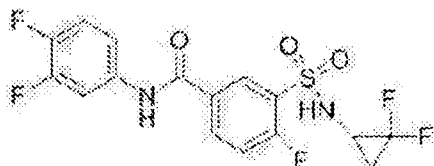
[1209] 3-(N-(叔丁基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟-N-甲基苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈米色固体状的最终化合物 (118mg, 43.4%)。¹H NMR (300 MHz, CD₃OD): 7.73-7.67 (m, 2H), 7.31-7.14 (m, 3H), 7.04-7.02 (m, 1H), 3.45 (s, 3H), 1.06 (s, 9H); MS (ES) m/z: 401.2 (M+H⁺), 计算值: 401.11。

[1210]



[1211] N-(3,4-二氟苯基)-3-(N,N-二甲基氨磺酰基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (128mg, 44%)。¹H NMR (300MHz, CD₃OD): 8.13-8.10 (dd, J = 6.1, 2.3Hz, 1H), 8.02-7.97 (m, 1H), 7.86-7.79 (m, 1H), 7.55-7.49 (dd, J = 10, 8.8Hz, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 2.73 (s, 6H); MS (ES) m/z: 359.1 (M+H⁺), 计算值: 359.06。

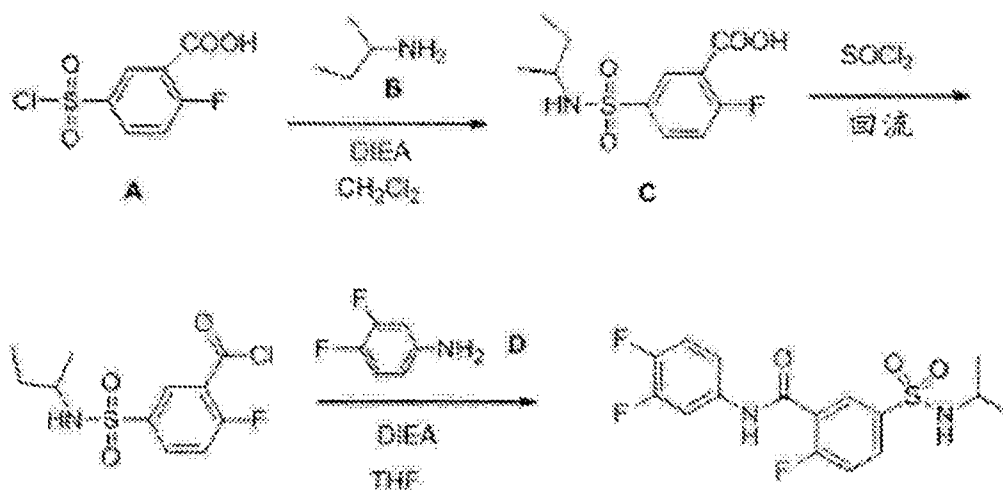
[1212]



[1213] 3-(N-(2,2-二氟环丙基)氨磺酰基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 H 类似的程序, 获得呈白色固体状的最终化合物 (3mg, 3%)。¹H NMR (300MHz, CDCl₃): δ 8.32 (m, 1H), 8.20 (m, 1H), 7.98 (s, 1H), 7.70 (m, 1H), 7.30 (m, 1H), 7.16 (m, 2H), 5.18 (s, 1H), 2.06 (m, 1H), 0.77 (m, 1H), 0.68 (m, 1H); MS (ES) m/z: 407.1 (M+H⁺), 计算值: 407.04。

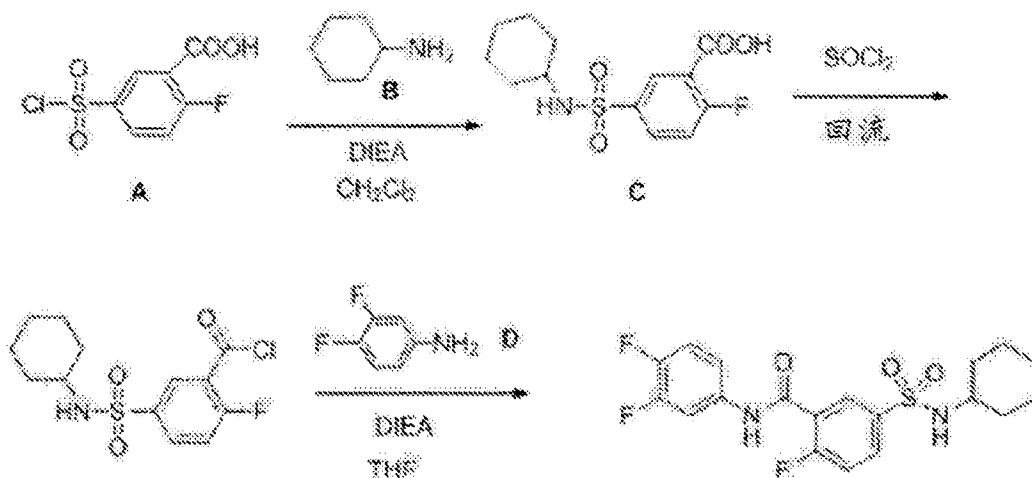
[1214] 实施例 9: 一般性程序 I:

[1215]



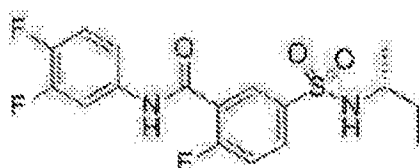
[1216] 将 A(0.506g, 0.0021mol)、B(0.155g, 0.00212mol) 和 DIEA(1.1mL, 0.00636mol) (其中 DIEA 是 N,N-二异丙基乙胺) 于 CH_2Cl_2 中在室温下搅拌过夜。蒸发溶剂, 并且粗产物通过柱色谱法在硅胶上纯化以产生化合物 C(0.56g, 96%)。在真空下干燥过夜之后, 在 80°C 下加热于 SOCl_2 中的 C(0.56g, 0.0020mol) 8 小时。此后, 蒸发试剂, 在真空下干燥。接着将残余物溶解于 THF(5mL) 中, 依次添加 D(0.26g, 0.0020mol) 和 DIEA(0.8mL)。加热混合物至 70°C , 过夜。蒸发溶剂, 随后进行 EtOAc 萃取。在通过柱色谱法在硅胶 (EtOAc/己烷) 上纯化之后, 获得 0.45g(57%) 最终产物。 ^1H NMR(300MHz, CDCl_3): δ 8.61(dd, $J = 7.1, 2.5\text{Hz}$, 1H), 8.30(d, $J = 14.1\text{Hz}$, 1H), 8.00(m, 1H), 7.70(m, 1H), 7.26(m, 1H), 7.15(m, 2H), 4.46(d, $J = 8.2\text{Hz}$, 1H), 3.25(m, 1H), 1.34(m, 2H), 1.01(d, $J = 6.4\text{Hz}$, 3H), 0.75(t, $J = 7.3\text{Hz}$, 3H); MS(ES) m/z : 387.2 ($\text{M}+\text{H}^+$), 计算值: 387.09。

[1217]



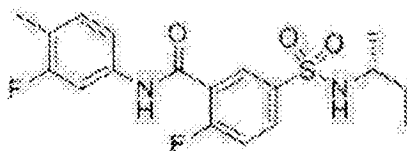
[1218] 将 A(0.508g, 0.0021mol)、B(0.211g, 0.00212mol) 和 DIEA(1.1mL, 0.00636mol) (其中 DIEA 是 N,N-二异丙基乙胺) 于 CH_2Cl_2 中在室温下搅拌过夜。蒸发溶剂, 并且粗产物通过柱色谱法在硅胶上纯化以产生化合物 C(0.6g, 95%)。在真空下干燥过夜之后, 在 80°C 下将于 SOCl_2 (5mL) 中的 C(0.22g, 0.737mmol) 加热过夜。此后, 蒸发试剂, 在真空下干燥。接着将残余物溶解于 THF(5mL) 中, 依次添加 D(95mg, 0.737mmol) 和 DIEA(0.8mL)。加热混合物至 70°C , 过夜。蒸发溶剂, 随后进行 EtOAc 萃取。在通过柱色谱法在硅胶 (EtOAc/己烷) 上纯化之后, 获得并提交 0.192g(63%) 最终产物 18083。 ^1H NMR(300MHz, CDCl_3): δ 8.59(dd, $J = 7.2, 2.4\text{Hz}$, 1H), 8.33(d, $J = 13.4\text{Hz}$, 1H), 8.00(m, 1H), 7.70(m, 1H), 7.20(m, 1H), 7.12(m, 2H), 4.62(d, $J = 7.9\text{Hz}$, 1H), 3.12(m, 1H), 1.72(m, 2H), 1.59(m, 2H), 1.46(m, 2H), 1.17(m, 4H); MS(ES) m/z : 413.2 ($\text{M}+\text{H}^+$), 计算值: 413.11。

[1219]

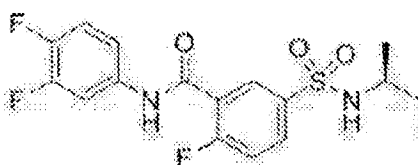


[1220] (R)-5-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物(137mg, 75%)。 ^1H NMR(300MHz, CDCl_3): δ 8.60(dd, $J = 7.1, 2.5\text{Hz}$, 1H), 8.32(d, $J = 13.8\text{Hz}$, 1H), 8.00(m, 1H)

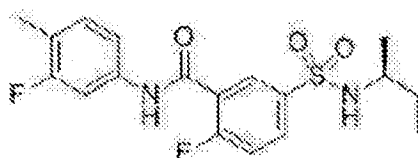
, 7.70 (m, 1H), 7.24 (m, 1H), 7.13 (m, 2H), 4.45 (d, $J = 8.2\text{Hz}$, 1H), 3.26 (m, 1H), 1.37 (m, 2H), 1.01 (d, $J = 6.4\text{Hz}$, 3H), 0.75 (t, $J = 7.4\text{Hz}$, 3H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。
[1221]



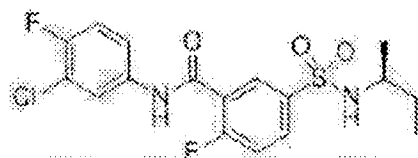
[1222] (R)-5-(N-(叔丁基)氨基磺酰基)-2-氟-N-(3-氟-4-甲基苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (117mg, 65%)。
 ^1H NMR(300MHz, CDCl_3): δ 8.60 (dd, $J = 7.0, 2.4\text{Hz}$, 1H), 8.29 (d, $J = 13.8\text{Hz}$, 1H), 7.99 (m, 1H), 7.47 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.46 (m, 1H), 3.25 (m, 1H), 2.20 (d, $J = 2.0\text{Hz}$, 3H), 1.36 (m, 2H), 1.00 (d, $J = 6.4\text{Hz}$, 3H), 0.75 (t, $J = 7.5\text{Hz}$, 3H); MS(ES) m/z : 383.2 ($M+H^+$), 计算值: 383.12。
[1223]



[1224] (S)-5-(N-(叔丁基)氨基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (134mg, 45%)。
 ^1H NMR(300MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5\text{Hz}$, 1H), 8.29 (d, $J = 14.9\text{Hz}$, 1H), 8.00 (m, 1H), 7.71 (m, 1H), 7.23 (m, 1H), 7.15 (m, 2H), 4.31 (d, $J = 8.2\text{Hz}$, 1H), 3.26 (m, 1H), 1.37 (m, 2H), 1.01 (d, $J = 6.4\text{Hz}$, 3H), 0.75 (t, $J = 7.4\text{Hz}$, 3H); MS(ES) m/z : 387.1 ($M+H^+$), 计算值: 387.09。
[1225]



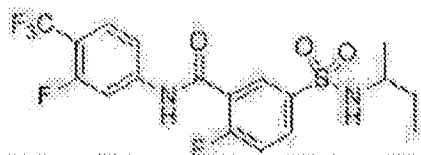
[1226] (S)-5-(N-(叔丁基)氨基磺酰基)-2-氟-N-(3-氟-4-甲基苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (86mg, 44%)。
 ^1H NMR(300MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5\text{Hz}$, 1H), 8.29 (d, $J = 14.4\text{Hz}$, 1H), 8.00 (m, 1H), 7.49 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.40 (m, 1H), 3.26 (m, 1H), 2.20 (d, $J = 2.0\text{Hz}$, 3H), 1.36 (m, 2H), 1.00 (d, $J = 6.4\text{Hz}$, 3H), 0.75 (t, $J = 7.5\text{Hz}$, 3H); MS(ES) m/z : 383.2 ($M+H^+$), 计算值: 383.12。
[1227]



[1228] (S)-5-(N-(叔丁基)氨基磺酰基)-N-(3-氯-4-氟苯基)-2-氟苯甲

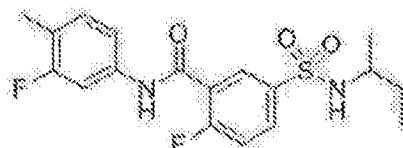
酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (97mg, 47 %)。 ^1H NMR (300MHz, CDCl_3): δ 8.60 (dd, $J = 7.2, 2.5\text{Hz}$, 1H), 8.27 (d, $J = 14.1\text{Hz}$, 1H), 8.00 (m, 1H), 7.78 (dd, $J = 6.6, 2.8\text{Hz}$, 1H), 7.39 (m, 1H), 7.25 (m, 1H), 7.09 (t, $J = 8.7\text{Hz}$, 1H), 4.40 (d, $J = 8.2\text{Hz}$, 1H), 3.26 (m, 1H), 1.35 (m, 2H), 1.00 (d, $J = 6.7\text{Hz}$, 3H), 0.75 (t, $J = 7.5\text{Hz}$, 3H); MS (ES) m/z : 403.1 ($\text{M}+\text{H}^+$), 计算值: 403.06。

[1229]



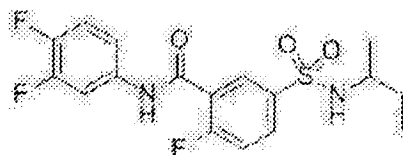
[1230] 5-(N-(仲丁基)氨磺酰基)-2-氟-N-(3-氟-4-(三氟甲基)苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (68mg, 38 %)。 ^1H NMR (300MHz, CDCl_3): δ 8.60 (dd, $J = 7.2, 2.4\text{Hz}$, 1H), 8.48 (d, $J = 14.4\text{Hz}$, 1H), 8.02 (m, 1H), 7.77 (d, $J = 11.7\text{Hz}$, 1H), 7.53 (t, $J = 8.2\text{Hz}$, 1H), 7.27 (m, 1H), 4.38 (d, $J = 8.2\text{Hz}$, 1H), 3.25 (m, 1H), 1.38 (m, 2H), 1.01 (m, 3H), 0.75 (t, $J = 7.5\text{Hz}$, 3H); MS (ES) m/z : 437.2 ($\text{M}+\text{H}^+$), 计算值: 437.09。

[1231]



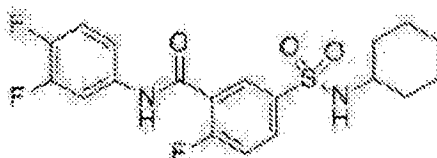
[1232] 5-(N-(仲丁基)氨磺酰基)-2-氟-N-(3-氟-4-甲基苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (113mg, 72 %)。 ^1H NMR (300MHz, CDCl_3): δ 8.60 (dd, $J = 7.0, 2.6\text{Hz}$, 1H), 8.29 (d, $J = 13.5\text{Hz}$, 1H), 7.99 (m, 1H), 7.47 (m, 1H), 7.25 (m, 1H), 7.09 (m, 2H), 4.46 (m, 1H), 3.25 (m, 1H), 2.20 (d, $J = 2.0\text{Hz}$, 3H), 1.36 (m, 2H), 1.00 (m, 3H), 0.75 (t, $J = 7.5\text{Hz}$, 3H); MS (ES) m/z : 383.2 ($\text{M}+\text{H}^+$), 计算值: 383.12。

[1233]



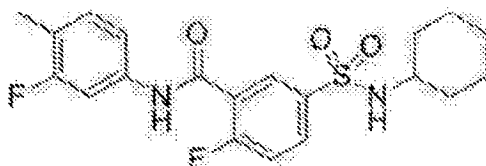
[1234] 5-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (101mg, 63 %)。 ^1H NMR (300MHz, CDCl_3): δ 8.61 (dd, $J = 7.1, 2.5\text{Hz}$, 1H), 8.30 (d, $J = 14.1\text{Hz}$, 1H), 8.00 (m, 1H), 7.70 (m, 1H), 7.26 (m, 1H), 7.15 (m, 2H), 4.46 (d, $J = 8.2\text{Hz}$, 1H), 3.25 (m, 1H), 1.34 (m, 2H), 1.01 (d, $J = 6.4\text{Hz}$, 3H), 0.75 (t, $J = 7.3\text{Hz}$, 3H); MS (ES) m/z : 387.2 ($\text{M}+\text{H}^+$), 计算值: 387.09。

[1235]



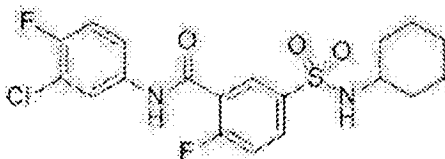
[1236] 5-(N-环己基氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (238mg, 46 %)。¹H NMR(300MHz, CDCl₃): δ 8.59(dd, J = 7.2, 2.4Hz, 1H), 8.33(d, J = 13.4Hz, 1H), 8.00(m, 1H), 7.70(m, 1H), 7.20(m, 1H), 7.12(m, 2H), 4.62(d, J = 7.9Hz, 1H), 3.12(m, 1H), 1.72(m, 2H), 1.59(m, 2H), 1.46(m, 2H), 1.17(m, 4H); MS(ES)m/z: 413.2(M+H⁺), 计算值: 413.11。

[1237]



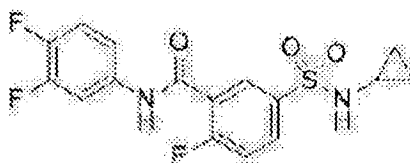
[1238] 5-(N-环己基氨磺酰基)-2-氟-N-(3-氟-4-甲基苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (131mg, 34 %)。¹H NMR(300MHz, CDCl₃): δ 8.59(dd, J = 7.2, 2.4Hz, 1H), 8.33(d, J = 14.1Hz, 1H), 8.00(m, 1H), 7.48(m, 1H), 7.25(m, 1H), 7.11(m, 2H), 4.59(d, J = 7.9Hz, 1H), 3.12(m, 1H), 2.20(s, 3H), 1.72(m, 2H), 1.59(m, 2H), 1.46(m, 2H), 1.15(m, 4H); MS(ES)m/z: 409.2(M+H⁺), 计算值: 409.13。

[1239]



[1240] N-(3-氯-4-氟苯基)-5-(N-环己基氨磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (139mg, 35 %)。¹H NMR(300MHz, CDCl₃): δ 8.59(dd, J = 7.1, 2.6Hz, 1H), 8.33(d, J = 13.7Hz, 1H), 8.00(m, 1H), 7.78(m, 1H), 7.39(m, 1H), 7.26(m, 1H), 7.18(m, 1H), 4.67(d, J = 7.9Hz, 1H), 3.12(m, 1H), 1.71(m, 2H), 1.59(m, 2H), 1.46(m, 2H), 1.12(m, 4H); MS(ES)m/z: 429.1(M+H⁺), 计算值: 429.08。

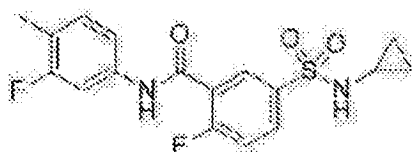
[1241]



[1242] 5-(N-环丙基氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (238mg, 26 %)。¹H NMR(300MHz, CDCl₃): δ 8.60(dd, J = 7.0, 2.4Hz, 1H), 8.30(d, J = 13.7Hz, 1H), 8.00(m, 1H), 7.71(m, 1H), 7.32(m, 1H), 7.15(m, 2H), 4.97(s, 1H), 2.23(m, 1H), 0.78(m, 2H); MS(ES)m/z:

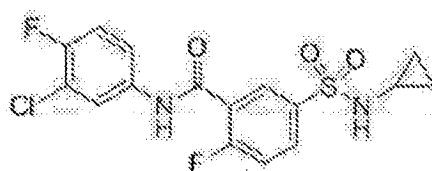
z:371.1 ($M+H^+$), 计算值:371.06。

[1243]



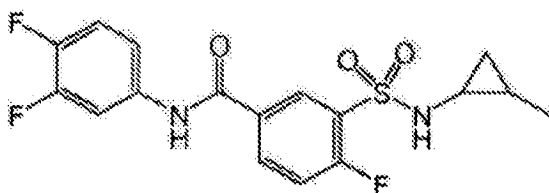
[1244] 5-(N-环丙基氨磺酰基)-2-氟-N-(3-氟-4-甲基苯基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (156mg, 32%)。 1H NMR (300MHz, $CDCl_3$): δ 8.61 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.30 (d, $J = 13.8$ Hz, 1H), 8.00 (m, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 7.11 (m, 2H), 4.99 (s, 1H), 2.23 (m, 1H), 2.21 (s, 3H), 0.80 (m, 1H), 0.58 (m, 3H); MS (ES) m/z : 367.1 ($M+H^+$), 计算值: 367.08。

[1245]



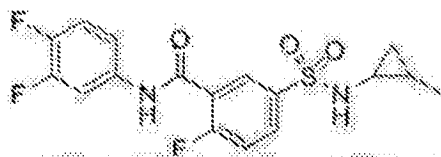
[1246] N-(3-氯-4-氟苯基)-5-(N-环丙基氨磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (119mg, 26%)。 1H NMR (300MHz, $CDCl_3$): δ 8.61 (dd, $J = 7.0, 2.5$ Hz, 1H), 8.29 (d, $J = 13.7$ Hz, 1H), 8.00 (m, 1H), 7.78 (m, 1H), 7.41 (m, 1H), 7.30 (m, 1H), 7.11 (m, 1H), 4.99 (s, 1H), 2.22 (m, 1H), 0.78 (m, 1H), 0.58 (m, 3H); MS (ES) m/z : 387.1 ($M+H^+$), 计算值: 387.03。

[1247]



[1248] N-(3,4-二氟苯基)-4-氟-3-(N-(2-甲基环丙基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (90mg, 85%)。 1H NMR (300MHz, $CDCl_3$): δ 8.61 (dd, $J = 6.5, 2.3$ Hz, 1H), 8.17 (m, 1H), 8.01 (s, 1H), 7.69 (m, 1H), 7.29 (m, 1H), 7.17 (m, 1H), 5.17 (s, 1H), 1.89 (m, 1H), 1.52 (d, $J = 9.0$ Hz, 3H), 0.88 (m, 2H), 0.75 (m, 1H); MS (ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

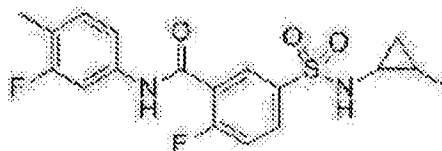
[1249]



[1250] N-(3,4-二氟苯基)-2-氟-5-(N-(2-甲基环丙基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (4mg, 2%)。 1H NMR (300MHz, $CDCl_3$): δ 8.61 (dd, $J = 7.1, 2.5$ Hz, 1H), 8.30 (d, $J = 13.5$ Hz, 1H), 8.02 (m, 1H), 7.70 (m, 1H), 7.30 (m, 1H), 7.15 (m, 2H), 4.93 (s, 1H), 1.88 (m, 1H), 0.91 (m, 3H), 0.81 (m, 1H)

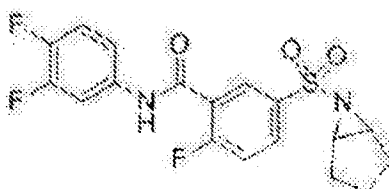
, 0.70 (m, 1H), 0.37 (m, 1H); MS (ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

[1251]



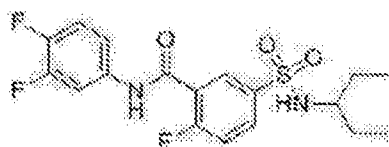
[1252] 2-氟-N-(3-氟-4-甲基苯基)-5-(N-(2-甲基环丙基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (5mg, 5%)。 1H NMR (300MHz, $CDCl_3$): δ 8.62 (dd, $J = 7.0, 2.6$ Hz, 1H), 8.26 (d, $J = 14.1$ Hz, 1H), 8.01 (m, 1H), 7.49 (d, $J = 12.0$ Hz, 1H), 7.29 (dd, $J = 11.7, 8.2$ Hz, 1H), 7.11 (m, 2H), 4.84 (s, 1H), 2.20 (d, $J = 2.2$ Hz, 3H), 1.89 (m, 1H), 0.90 (m, 3H), 0.74 (m, 2H), 0.35 (m, 1H); MS (ES) m/z : 381.2 ($M+H^+$), 计算值: 381.10。

[1253]



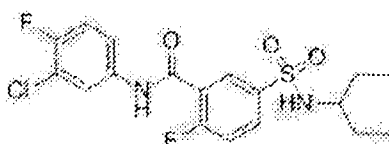
[1254] 5-(6-氮杂双环[3.1.0]己烷-6-基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (27mg, 12%)。 1H NMR (300MHz, $CDCl_3$): δ 8.62 (dd, $J = 7.0, 2.3$ Hz, 1H), 8.29 (d, $J = 14.4$ Hz, 1H), 8.04 (m, 1H), 7.69 (m, 1H), 7.30 (dd, $J = 11.4, 8.8$ Hz, 1H), 7.16 (m, 2H), 4.78 (d, $J = 6.2$ Hz, 1H), 3.94 (m, 1H), 3.54 (m, 1H), 2.15 (m, 2H), 1.78 (m, 2H), 1.66 (m, 1H), 1.41 (m, 2H); MS (ES) m/z : 397.2 ($M+H^+$), 计算值: 397.08。

[1255]



[1256] N-(3,4-二氟苯基)-2-氟-5-(N-(戊烷-3-基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈米色固体状的最终化合物 (239mg, 74%)。 1H NMR (300MHz, CD_3OD): δ 8.22-8.19 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.48-7.36 (m, 2H), 7.31-7.21 (m, 1H), 3.11-3.06 (m, 1H), 1.51-1.42 (m, 2H), 1.40-1.28 (m, 2H), 0.79-0.74 (t, $J = 7.3$ Hz, 6H); MS (ES) m/z : 401.2 ($M+H^+$), 计算值: 401.11。

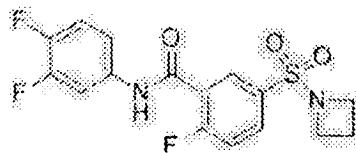
[1257]



[1258] N-(3-氯-4-氟苯基)-2-氟-5-(N-(戊烷-3-基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈米色固体状的最终化合物 (244mg, 72%)。 1H NMR (300MHz, CD_3

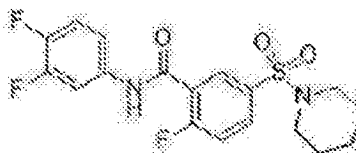
OD): 8.23-8.20 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.07-8.02 (m, 1H), 7.98-7.94 (dd, $J = 6.6, 2.6$ Hz, 1H), 7.61-7.56 (m, 1H), 7.48-7.42 (dd, $J = 9.9, 8.8$ Hz, 1H), 7.28-7.22 (t, $J = 9.1$ Hz, 1H), 3.11-3.06 (m, 1H), 1.51-1.40 (m, 2H), 1.38-1.28 (m, 2H), 0.79-0.74 (t, $J = 7.6$ Hz, 6H); MS(ES) m/z : 417.1 ($M+H^+$), 计算值: 417.08。

[1259]



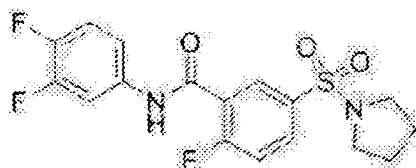
[1260] 5-(氮杂环丁烷-1-基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈米色固体状最终化合物 (34mg, 12%)。 1H NMR (300MHz, CD_3OD): δ 8.56 (bs, 1H), 8.10-8.07 (dd, $J = 6.4, 2.4$ Hz, 1H), 7.89-7.84 (m, 1H), 7.38-7.32 (dd, $J = 10, 8.6$ Hz, 1H), 7.18-7.02 (m, 2H), 6.89-6.83 (m, 1H), 3.66-3.62 (t, $J = 6.5$ Hz, 2H), 3.56-3.50 (m, 2H), 2.11-2.01 (m, 2H); MS(ES) m/z : 371.1 ($M+H^+$), 计算值: 371.06。

[1261]



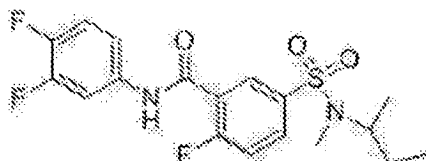
[1262] N-(3,4-二氟苯基)-2-氟-5-(哌啶-1-基磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈米色固体状最终化合物 (74mg, 26%)。 1H NMR (300MHz, CD_3OD): δ 8.10-8.07 (dd, $J = 6.4, 2.4$ Hz, 1H), 7.99-7.94 (m, 1H), 7.85-7.79 (m, 1H), 7.54-7.47 (dd, $J = 9.6, 8.6$ Hz, 1H), 7.40-7.36 (m, 1H), 7.31-7.22 (m, 1H), 3.04-3.01 (t, $J = 5.3$ Hz, 4H), 1.68-1.61 (m, 4H), 1.50-1.44 (m, 2H); MS(ES) m/z : 399.2 ($M+H^+$), 计算值: 399.09。

[1263]



[1264] N-(3,4-二氟苯基)-2-氟-5-(吡咯烷-1-基磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈米色固体状最终化合物 (164mg, 58%)。 1H NMR (300MHz, CD_3OD): 8.17-8.14 (dd, $J = 6.4, 2.4$ Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.54-7.47 (dd, $J = 9.8, 8.8$ Hz, 1H), 7.40-7.37 (m, 1H), 7.31-7.22 (m, 1H), 3.29-3.25 (m, 4H), 1.81-1.76 (m, 4H); MS(ES) m/z : 385.1 ($M+H^+$), 计算值: 385.08。

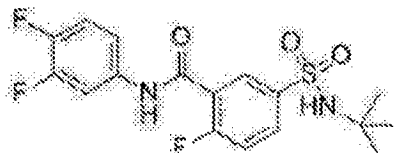
[1265]



[1266] 5-(N-(仲丁基)-N-甲基氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与

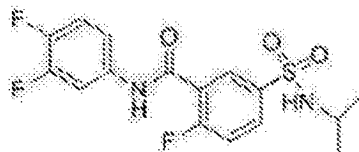
一般性程序 I 类似的程序, 获得呈米色固体状的最终化合物 (31mg, 12%)。¹H NMR(300 MHz, CD₃OD): 7.93-7.70 (m, 1H), 7.69-7.66 (m, 1H), 7.42-7.34 (m, 1H), 7.19-7.03 (m, 2H), 6.89-6.83 (m, 1H), 4.69-4.59 (m, 1H), 2.92 (s, 3H), 1.64-1.48 (m, 2H), 1.22-1.20 (d, J = 6.7Hz, 3H), 0.98-0.90 (m, 3H); MS(ES) m/z: 401.2 (M+H⁺), 计算值: 401.11。

[1267]



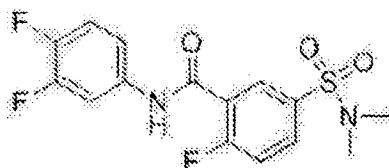
[1268] 5-(N-(叔丁基)氨基磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (171mg, 52%)。¹H NMR(300MHz, CD₃OD): 8.23-8.20 (dd, J = 6.5, 2.3Hz, 1H), 8.09-8.03 (m, 1H), 7.86-7.79 (m, 1H), 7.47-7.36 (m, 2H), 7.31-7.21 (m, 1H), 1.21 (s, 9H); MS(ES) m/z: 387.2 (M+H⁺), 计算值: 387.09。

[1269]



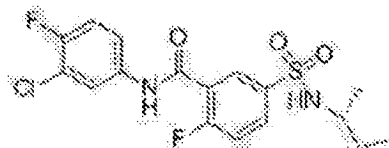
[1270] N-(3,4-二氟苯基)-2-氟-5-(N-异丙基氨基磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (262mg, 72%)。¹H NMR(300MHz, CD₃OD): 8.22-8.19 (dd, J = 6.4, 2.3Hz, 1H), 8.07-8.02 (m, 1H), 7.86-7.79 (m, 1H), 7.49-7.43 (dd, J = 10.0, 8.8Hz, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 3.45-3.36 (m, 1H), 1.06-1.04 (d, J = 6.4Hz, 6H); MS(ES) m/z: 373.1 (M+H⁺), 计算值: 373.08。

[1271]



[1272] N-(3,4-二氟苯基)-5-(N,N-二甲基氨基磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (196mg, 66%)。¹H NMR(300MHz, CD₃OD): 8.13-8.10 (dd, J = 6.4, 2.3Hz, 1H), 8.02-7.97 (m, 1H), 7.87-7.80 (m, 1H), 7.79-7.49 (m, 1H), 7.41-7.36 (m, 1H), 7.31-7.22 (m, 1H), 2.73 (s, 6H); MS(ES) m/z: 359.1 (M+H⁺), 计算值: 359.06。

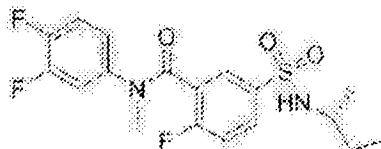
[1273]



[1274] (R)-5-(N-(仲丁基)氨基磺酰基)-N-(3-氯-4-氟苯基)-2-氟苯甲酰胺: 以与一

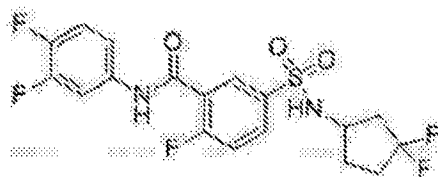
一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (59mg, 24%)。 ^1H NMR (300MHz, CD_3OD): 8.23-8.20 (m, 1H), 8.07-8.04 (m, 1H), 7.98-7.94 (m, 1H), 7.58-7.57 (m, 1H), 7.49-7.43 (m, 1H), 7.28-7.22 (m, 1H), 3.24-3.20 (m, 1H), 1.43-1.38 (m, 2H), 1.00-0.98 (d, $J = 6.7\text{Hz}$, 3H), 0.84-0.79 (t, $J = 7.5\text{Hz}$, 3H); MS (ES) m/z : 403.1 ($\text{M}+\text{H}^+$), 计算值: 403.06。

[1275]



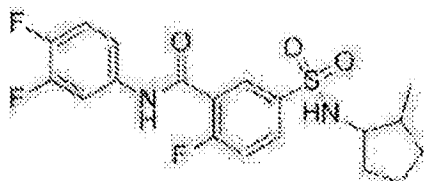
[1276] (R)-5-(N-(仲丁基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟-N-甲基苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (67mg, 24%)。 ^1H NMR (300MHz, CD_3OD): 7.84-7.82 (m, 2H), 7.32-7.06 (m, 4H), 3.46 (s, 3H), 3.01-2.95 (m, 1H), 1.36-1.29 (m, 2H), 0.88-0.86 (d, $J = 6.4\text{Hz}$, 3H), 0.77-0.72 (t, $J = 7.3\text{Hz}$, 3H); MS (ES) m/z : 401.2 ($\text{M}+\text{H}^+$), 计算值: 401.11。

[1277]



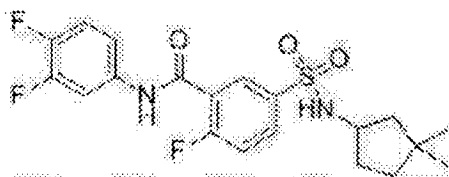
[1278] 5-(N-(3,3-二氟环戊基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (41mg, 53%)。 ^1H NMR (300MHz, CD_3OD): 8.22-8.19 (m, 1H), 8.07-8.02 (m, 1H), 7.85-7.79 (m, 1H), 7.49-7.36 (m, 2H), 7.31-7.22 (m, 1H), 3.07-2.99 (m, 1H), 3.79-3.71 (m, 1H), 2.34-2.06 (m, 1H), 2.03-1.87 (m, 2H), 1.71-1.61 (m, 1H), 1.33-1.24 (m, 1H), 0.89-0.79 (m, 1H); MS (ES) m/z : 435.2 ($\text{M}+\text{H}^+$), 计算值: 435.07

[1279]



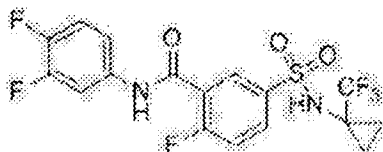
[1280] N-(3,4-二氟苯基)-2-氟-5-(N-(2-甲基环戊基)氨磺酰基)苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (62mg, 85%)。 ^1H NMR (300MHz, CD_3OD): 8.22-8.19 (m, 1H), 8.07-8.02 (m, 1H), 7.85-7.79 (m, 1H), 7.49-7.36 (m, 2H), 7.31-7.22 (m, 1H), 3.07-2.99 (m, 1H), 1.33-1.24 (m, 1H), 2.34-2.06 (m, 1H), 2.03-1.87 (m, 2H), 1.71-1.61 (m, 1H), 1.33-1.24 (m, 1H), 0.89-0.79 (m, 1H); MS (ES) m/z : 435.2 ($\text{M}+\text{H}^+$), 计算值: 435.07。

[1281]



[1282] N-(3,4-二氟苯基)-5-(N-(3,3-二甲基环戊基)氨磺酰基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈白色固体状的最终化合物(54mg,89%)。¹H NMR(300MHz, CD₃OD):¹H NMR(300MHz, CD₃OD):8.21-8.18(dd, J = 6.4, 2.3Hz, 1H), 8.07-8.01(m, 1H), 7.86-7.79(m, 1H), 7.46-7.37(m, 2H), 7.31-7.22(m, 1H), 3.72-3.54(m, 1H), 2.01-1.84(m, 1H), 1.64-1.53(m, 1H), 1.50-1.40(m, 2H), 1.37-1.15(m, 2H), 1.01(s, 3H), 0.91(s, 3H);MS(ES)m/z:427.2(M+H⁺), 计算值:427.12。

[1283]



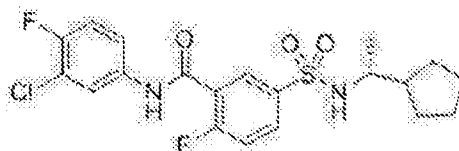
[1284] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(三氟甲基)环丙基)氨磺酰基)苯甲酰胺:以与一般性程序 I 类似的程序,获得呈白色固体状的最终化合物(22.3mg,18%)。¹H NMR(300MHz, CD₃OD):8.20-8.18(m, 1H), 8.10-8.04(m, 1H), 7.90-7.79(m, 1H), 7.49-7.37(m, 2H), 7.31-7.21(m, 1H), 1.21(s, 4H);MS(ES)m/z:439.2(M+H⁺), 计算值:439.05。

[1285]



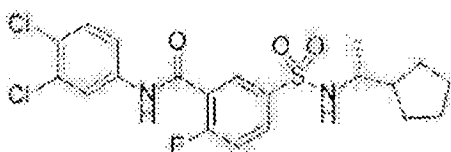
[1286] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-2-氟-N-(2,4,5-三氟苯基)苯甲酰胺:以与一般性程序 I 类似的程序,获得呈白色固体状的最终化合物(8.3mg,14%)。¹H NMR(300MHz, CD₃OD):8.31-8.28(dd, J = 6.4, 2.3Hz, 1H), 8.13-8.04(m, 2H), 7.50-7.43(m, 1H), 7.37-7.28(m, 1H), 3.18-3.13(m, 1H), 1.85-1.74(m, 1H), 1.68-1.51(m, 6H), 1.20-1.15(m, 2H), 0.96-0.94(d, J = 6.4Hz, 3H);MS(ES)m/z:445.2(M+H⁺), 计算值:445.11。

[1287]



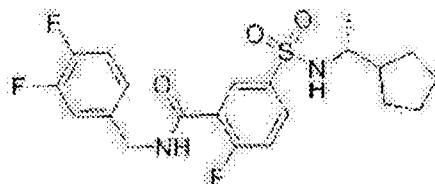
[1288] (R)-N-(3-氯-4-氟苯基)-5-(N-(1-环戊基乙基)氨磺酰基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈米色固体状的最终化合物(18mg,10%)。¹H NMR(300MHz, CD₃OD):8.22-8.19(dd, J = 6.4, 2.3Hz, 1H), 8.07-8.02(m, 1H), 7.97-7.94(m, 1H), 7.61-7.56(m, 1H), 7.48-7.42(m, 1H), 7.28-7.25(m, 1H), 3.18-3.13(m, 1H), 1.82-1.74(m, 1H), 1.67-1.51(m, 6H), 1.29-1.12(m, 2H), 0.96-0.94(d, J = 6.4Hz, 3H);MS(ES)m/z:443.2(M+H⁺), 计算值:443.09。

[1289]



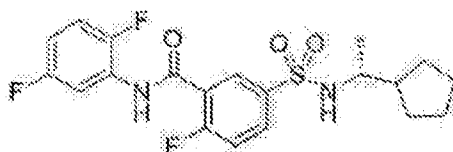
[1290] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-N-(3,4-二氯苯基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈米色固体状的最终化合物(49mg,25%)。¹H NMR(300MHz, CD₃OD):8.22-8.19(dd, J = 6.4, 2.3Hz, 1H), 8.06-8.02(m, 2H), 7.61-7.57(m, 1H), 7.52-7.42(m, 2H), 3.17-3.13(m, 1H), 1.84-1.47(m, 7H), 1.28-1.11(m, 2H), 0.96-0.94(d, J = 6.4Hz, 3H);MS(ES)m/z:459.2(M+H⁺), 计算值:459.06。

[1291]



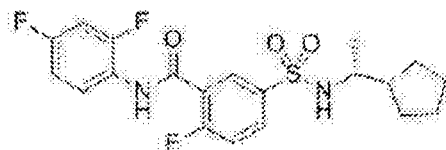
[1292] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈无色油状的最终化合物(29.1mg,16%)。¹H NMR(300MHz, CD₃OD):8.22-8.19(dd, J = 6.6, 2.6Hz, 1H), 8.04-7.98(m, 1H), 7.45-7.38(m, 1H), 7.31-7.18(m, 2H), 4.55(s, 2H), 3.15-3.10(m, 1H), 1.83-1.75(m, 1H), 1.68-1.46(m, 6H), 1.29-1.08(m, 2H), 0.94-0.92(d, J = 6.4Hz, 3H);MS(ES)m/z:441.3(M+H⁺), 计算值:441.14。

[1293]



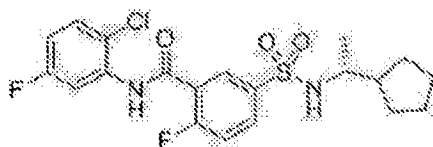
[1294] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-N-(2,5-二氟苯基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈白色固体状的最终化合物(47mg,32%)。¹H NMR(300MHz, CD₃OD):8.32-8.30(dd, J = 6.4, 2.0Hz, 1H), 8.09-8.00(m, 2H), 7.50-7.44(m, 1H), 7.27-7.19(m, 1H), 7.00-6.92(m, 1H), 3.20-3.11(m, 1H), 1.85-1.75(m, 1H), 1.68-1.51(m, 6H), 1.29-1.14(m, 2H), 0.97-0.95(d, J = 6.4Hz, 3H);MS(ES)m/z:427.2(M+H⁺), 计算值:427.12。

[1295]



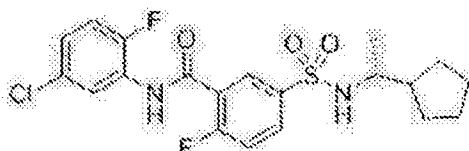
[1296] (R)-5-(N-(1-环戊基乙基)氨磺酰基)-N-(2,4-二氟苯基)-2-氟苯甲酰胺:以与一般性程序 I 类似的程序,获得呈白色固体状的最终化合物(54mg,29%)。¹H NMR(300MHz, CD₃OD):8.30-8.27(dd, J = 6.4, 2.4Hz, 1H), 8.09-8.03(m, 1H), 7.92-7.87(m, 1H), 7.50-7.44(m, 1H), 7.14-7.00(m, 2H), 3.20-3.13(m, 1H), 1.85-1.74(m, 1H), 1.68-1.51(m, 6H), 1.29-1.12(m, 2H), 0.97-0.94(d, J = 6.7Hz, 3H);MS(ES)m/z:427.3(M+H⁺), 计算值:427.12。

[1297]



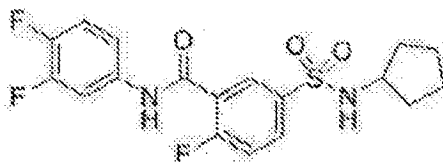
[1298] (R)-N-(2-氯-5-氟苯基)-5-(N-(1-环戊基乙基)氨磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (24mg, 13%)。¹H NMR (300MHz, CD₃OD): 8.46-8.43 (dd, J = 6.7, 2.3Hz, 1H), 8.12-8.07 (m, 2H), 7.55-7.47 (m, 2H), 7.04-6.97 (m, 1H), 3.18-3.14 (m, 1H), 1.86-1.77 (m, 1H), 1.68-1.51 (m, 6H), 1.28-1.11 (m, 2H), 0.97-0.95 (d, J = 6.7Hz, 3H); MS (ES) m/z: 443.2 (M+H⁺), 计算值: 443.09。

[1299]



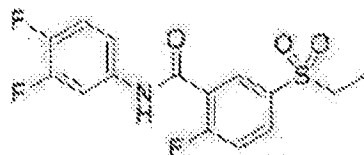
[1300] (R)-N-(5-氯-2-氟苯基)-5-(N-(1-环戊基乙基)氨磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (30mg, 16%)。¹H NMR (300MHz, CD₃OD): 8.32-8.29 (dd, J = 6.5, 2.2Hz, 1H), 8.19-8.17 (m, 1H), 8.09-8.04 (m, 1H), 7.50-7.44 (m, 1H), 7.24-7.21 (m, 2H), 3.20-3.11 (m, 1H), 1.85-1.75 (m, 1H), 1.72-1.51 (m, 6H), 1.28-1.12 (m, 2H), 0.97-0.95 (d, J = 6.5Hz, 3H); MS (ES) m/z: 443.2 (M+H⁺), 计算值: 443.09。

[1301]



[1302] 5-(N-环戊基氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (300mg, 45%)。¹H NMR (300MHz, CDCl₃): δ 8.67-8.65 (m, 1H), 8.64-8.37 (m, 1H), 8.10-8.04 (m, 1H), 7.80-7.73 (m, 1H), 7.26-7.12 (m, 3H), 4.72-4.13 (m, 1H), 3.69-3.62 (m, 1H), 1.88-1.78 (m, 2H), 1.69-1.26 (m, 6H); MS (ES) m/z: 399.1 (M+H⁺), 计算值: 399.09。

[1303]



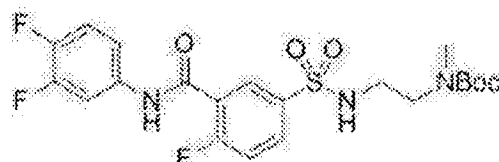
[1304] N-(3,4-二氟苯基)-5-(乙基磺酰基)-2-氟苯甲酰胺: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (155.5mg, 96.4%)。¹H NMR (300MHz, d₄-MeOH): 8.27-8.24 (m, 1H), 8.14-8.09 (m, 1H), 7.86-7.79 (m, 1H), 7.57-7.51 (t, J = 9.1Hz, 1H), 7.40-7.22 (m, 2H), 3.30-3.24 (m, 2H), 1.28-1.23 (t, J = 7.6Hz, 3H); MS (ES) m/z: 344.2 (M+H⁺), 计算值: 344.05。

[1305]



[1306] (2-(3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基亚磺酰氨基)乙基)氨基甲酸叔丁酯: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (54.6mg, 40%)。¹H NMR (300MHz, d₄-MeOH): 8.20-8.17 (m, 1H), 8.06-8.01 (m, 1H), 7.86-7.78 (m, 1H), 7.49-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.12-3.07 (m, 2H), 2.98-2.94 (t, J = 6.3Hz, 2H), 1.40 (s, 9H); MS (ES) m/z: 496.2 (M+Na⁺), 计算值: 496.12。

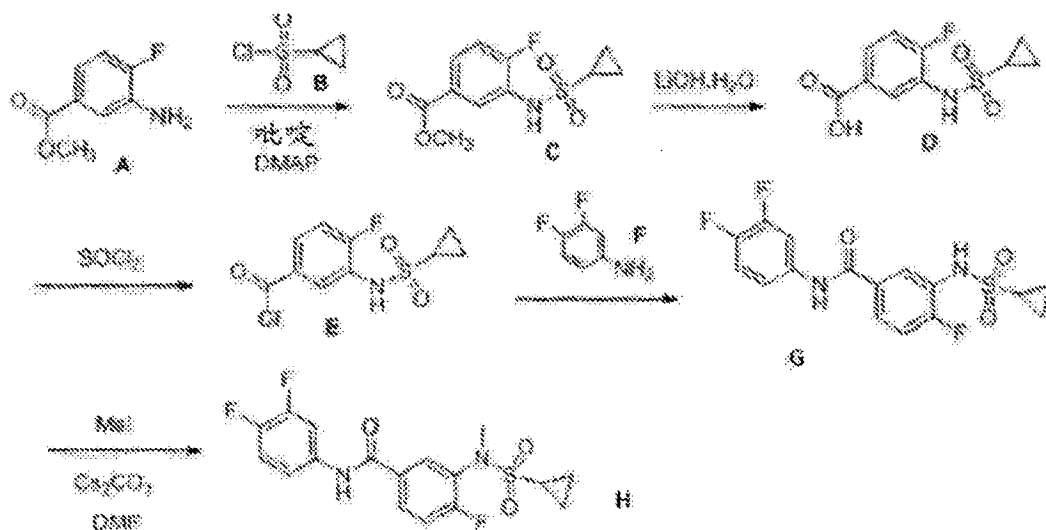
[1307]



[1308] (2-(3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基亚磺酰氨基)乙基)(甲基)氨基甲酸叔丁酯: 以与一般性程序 I 类似的程序, 获得呈白色固体状的最终化合物 (102mg, 72%)。¹H NMR (300MHz, d₄-MeOH): 8.19-8.18 (m, 1H), 8.06-8.01 (m, 1H), 7.86-7.77 (m, 1H), 7.50-7.37 (m, 2H), 7.31-7.22 (m, 1H), 3.06-2.99 (m, 2H), 2.89-2.82 (m, 2H), 1.44 (s, 9H), 1.42 (s, 3H); MS (ES) m/z: 510.2 (M+Na⁺), 计算值: 510.14。

[1309] 实施例 10: 一般性程序 J:

[1310]



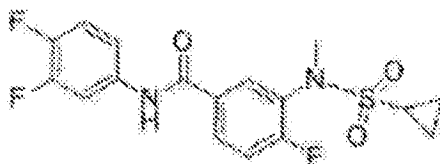
[1311] 将 A (0.255g, 1.51mmol) 溶解于吡啶中, 添加 B (0.344g, 1.88mmol) 和 DMAP (92.2mg, 0.755mmol), 并且将混合物在 110℃ 下搅拌过夜。蒸发溶剂, 并且粗产物用 CH₂Cl₂ 萃取, 并且依次用 1N HCl、2N H₂SO₄、H₂O 和盐水洗涤, 干燥 (Na₂SO₄) 并浓缩以产生粗产物 C, 其直接用于下一步骤。产物 C 用 LiOH·H₂O 于二噁烷和 H₂O 中处理过夜。蒸发溶剂, 用 1N HCl 调整 pH 至略微酸性, 用 EtOAc 萃取, 干燥并浓缩以产生产物 D。在干燥过夜之后, 使 D (0.37g, 1.4mmol) 于 SOCl₂ (5mL) 中回流 2 小时, 在蒸发过量 SOCl₂ 之后, 干燥以

产生 E (0.4188g)。接着将残余物 E 溶解于 THF (5mL) 中, 依次添加 F (195mg, 1.5mmol) 和 DIEA (0.6mL) (其中 DIEA 是 N, N-二异丙基乙胺)。将混合物在室温下搅拌过夜。蒸发溶剂, 随后进行 EtOAc 萃取。在通过 isco (EtOAc/ 己烷) 纯化之后, 获得 0.337g (63%) 最终产物 G。向于 DMF (2mL) 中的 G (20mg, 0.054mmol) 添加 MeI (1 当量) 和 CS_2CO_3 (19.3mg, 0.059mmol)。将混合物在室温下搅拌过夜。蒸发溶剂, 并且进行制备型 TLC 以产生产物 H (18.3mg, 88%)。[1312]



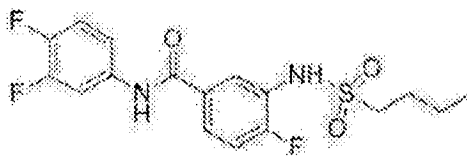
[1313] 3-(环丙烷亚磺酰氨基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 J 类似的程序, 获得呈白色固体状的最终化合物 (336.7mg, 63%)。 ^1H NMR (300MHz, CD_3OD): 8.11-8.09 (m, 1H), 7.83-7.80 (m, 2H), 7.40-7.20 (m, 3H), 2.70-2.60 (m, 1H), 1.03-0.98 (m, 4H); MS (ES) m/z : 371.2 ($\text{M}+\text{H}^+$), 计算值: 371.06。

[1314]



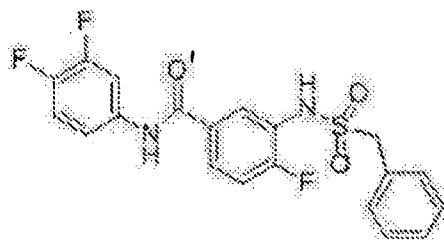
[1315] N-(3,4-二氟苯基)-4-氟-3-(N-乙基环丙烷亚磺酰氨基)苯甲酰胺: 以与一般性程序 J 类似的程序, 获得呈白色固体状的最终化合物 (18.3mg, 88.4%)。 ^1H NMR (300MHz, CD_3OD): 8.11-8.07 (dd, $J = 7.3, 2.1\text{Hz}$, 1H), 8.02-7.97 (m, 1H), 7.85-7.77 (m, 1H), 7.43-7.34 (m, 2H), 7.29-7.20 (m, 1H), 3.36 (s, 3H), 2.76-2.69 (m, 1H), 1.10-1.01 (m, 4H); MS (ES) m/z : 385.2 ($\text{M}+\text{H}^+$), 计算值: 385.08。

[1316]



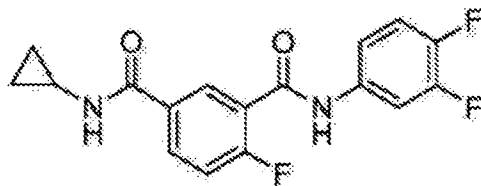
[1317] 3-(丁基亚磺酰氨基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺: 以与一般性程序 J 类似的程序, 获得呈白色固体状的最终化合物 (94.8mg, 79%)。 ^1H NMR (300MHz, CD_3OD): 8.09-8.06 (dd, $J = 7.8, 2.2\text{Hz}$, 1H), 7.82-7.74 (m, 2H), 7.39-7.20 (m, 3H), 3.18-3.13 (m, 2H), 1.86-1.76 (m, 2H), 1.49-1.42 (m, 2H), 0.96-0.91 (t, $J = 7.3\text{Hz}$, 3H); MS (ES) m/z : 387.2 ($\text{M}+\text{H}^+$), 计算值: 387.09。

[1318]



[1319] N-(3,4-二氟苯基)-4-氟-3-(苯基甲基亚磺酰氨基)苯甲酰胺: 以与一般性程序 J 类似的程序, 获得呈白色固体状最终化合物 (30.4mg, 24%)。 ^1H NMR (300MHz, $\text{d}_4\text{-MeOH}$): 7.93-7.90 (m, 1H), 7.83-7.75 (m, 1H), 7.71-7.65 (m, 1H), 7.42-7.35 (m, 3H), 7.32-7.20 (m, 5H), 4.51 (s, 2H); MS (ES) m/z : 421.2 ($\text{M}+\text{H}^+$), 计算值: 421.08。

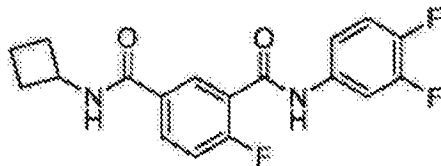
[1320]



[1321] 实施例 11: 一般性程序 K: N^1 -环丙基- N^3 -(3,4-二氟苯基)-4-氟间苯二甲酰胺: 在微波小瓶 (Biotage) 中装入 N-(3,4-二氟苯基)-2-氟-5-碘苯甲酰胺 (100.0mg, 0.26mmol)、乙酸钼 (8.9mg, 0.013mmol)、碳酸钠 (82.7mg, 0.78mmol)、 $\text{Mo}(\text{CO})_6$ (34.3mg, 0.13mmol) 和水 (1mL)。密封混合物, 抽空, 并且用 Ar 再填充。添加环丙胺 (0.09mL, 1.33mmol) 至混合物中, 接着在微波反应器中在 100°C 下将其加热 15 分钟。混合物用乙酸乙酯稀释, 用两次 HCl (2N)、饱和 NaHCO_3 和盐水洗涤。浓缩有机相, 并且在硅胶 (24g) 上纯化残余物, 用 2:8 至 1:1 的乙酸乙酯和己烷梯度洗脱以产生呈淡黄色固体状的化合物 (22.2mg, 25%)。 ^1H NMR (300MHz, $\text{CDCl}_3\text{-MeOD}$): δ 8.21 (dd, $J = 7.3, 2.3\text{Hz}$, 1H), 7.99 (ddd, $J = 8.5, 5.0, 2.3\text{Hz}$, 1H), 7.70 (ddd, $J = 12.0, 7.3, 2.3\text{Hz}$, 1H), 7.25-7.04 (m, 3H), 2.87-2.77 (m, 1H), 0.84-0.75 (m, 2H), 0.62-0.55 (m, 2H); $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$ 的计算值: 334.09; 观测值: MS (ESI) (m/z) 335.1 ($\text{M}+1$) $^+$ 。

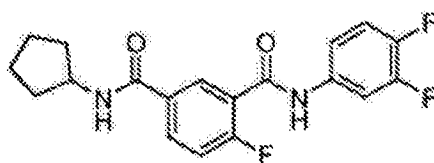
[1322] 以下化合物可通过遵循一般性程序 K 来制备, 所述一般性程序 K 即用于合成 N^1 -环丙基- N^3 -(3,4-二氟苯基)-4-氟间苯二甲酰胺的程序。

[1323]



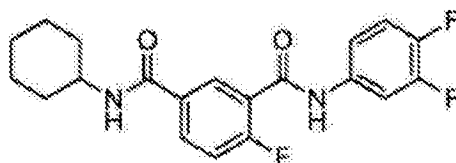
[1324] N^1 -环丁基- N^3 -(3,4-二氟苯基)-4-氟间苯二甲酰胺: 产率: 38%; ^1H NMR (300MHz, $\text{CDCl}_3\text{-MeOD}$): δ 8.26 (dd, $J = 7.0, 2.3\text{Hz}$, 1H), 7.98 (ddd, $J = 8.5, 5.0, 2.3\text{Hz}$, 1H), 7.71 (ddd, $J = 12.0, 7.0, 2.3\text{Hz}$, 1H), 7.30-7.14 (m, 3H), 4.55-4.40 (m, 1H), 2.42-2.28 (m, 2H), 2.06-1.88 (m, 2H), 1.82-1.64 (m, 2H); $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2$ 的计算值: 348.11; MS (ESI) (m/z) 观测值: 349.1 ($\text{M}+1$) $^+$ 。

[1325]



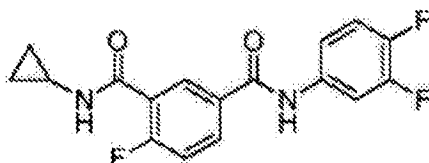
[1326] N^1 -环戊基- N^3 -(3,4-二氟苯基)-4-氟间苯二甲酰胺: 产率, 27 %; ^1H NMR (300MHz, CDCl_3 -MeOD): δ 8.15 (dd, $J = 6.7, 2.3\text{Hz}$, 1H), 7.92 (ddd, $J = 8.8, 5.0, 2.3\text{Hz}$, 1H), 7.70 (ddd, $J = 12.3, 7.0, 2.3\text{Hz}$, 1H), 7.25-7.04 (m, 3H), 4.36-4.20 (m, 1H), 2.08-1.90 (m, 2H), 1.75-1.38 (m, 6H); $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$ 的计算值: 362.12; 观测值: MS (ESI) (m/z) 363.2 ($M+1$) $^+$.

[1327]



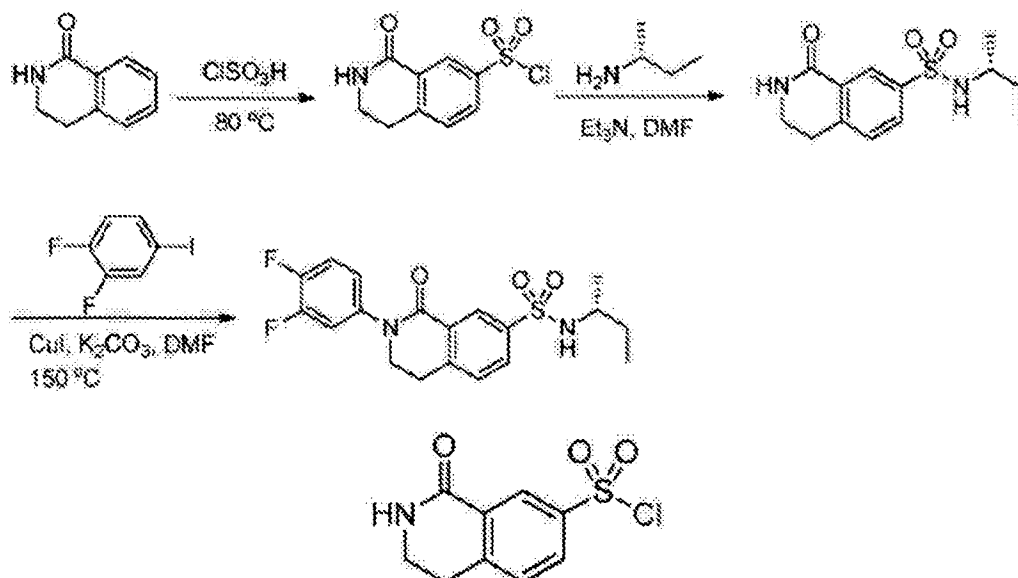
[1328] N^1 -环己基- N^3 -(3,4-二氟苯基)-4-氟间苯二甲酰胺: 产率, 30 %; ^1H NMR (300MHz, CDCl_3 -MeOD): δ 8.22-8.15 (m, 1H), 7.98-7.90 (m, 1H), 7.75-7.65 (m, 1H), 7.24-7.04 (m, 3H), 3.92-3.76 (m, 1H), 2.00-1.00 (m, 10H); $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$ 的计算值: 376.14; 观测值: MS (ESI) (m/z) 377.2 ($M+1$) $^+$.

[1329]



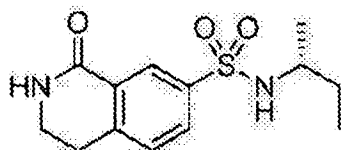
[1330] N^3 -环丙基- N^1 -(3,4-二氟苯基)-4-氟间苯二甲酰胺: 在微波小瓶 (Biotage) 中装入 3-溴- N -(3,4-二氟苯基)-4-氟苯甲酰胺 (86.0mg, 0.26mmol)、乙酸钯 (8.9mg, 0.013mmol)、碳酸钠 (82.7mg, 0.78mmol)、Xantphos (15.0mg, 0.026mmol)、 $\text{Mo}(\text{CO})_6$ (34.3mg, 0.13mmol) 和水 (2mL)。密封混合物, 抽空, 并且用 Ar 再填充。添加环丙胺 (0.09mL, 1.33mmol) 至混合物中, 接着在微波反应器中在 170℃ 下将其加热 15 分钟。混合物用乙酸乙酯稀释, 用两次 HCl (2N)、饱和 NaHCO_3 和盐水洗涤。浓缩有机相, 并且在硅胶 (24g) 上纯化残余物, 用 1:9 至 3:7 的乙酸乙酯和己烷梯度洗脱以产生呈淡黄色固体状的化合物 (26.0mg, 30 %)。 ^1H NMR (300MHz, CDCl_3 -MeOD): δ 8.31 (dd, $J = 6.7, 2.3\text{Hz}$, 1H), 8.00 (ddd, $J = 8.5, 4.7, 2.3\text{Hz}$, 1H), 7.73-7.63 (m, 1H), 7.36-7.26 (m, 1H), 7.21-7.02 (m, 2H), 2.87-2.77 (m, 1H), 0.85-0.77 (m, 2H), 0.62-0.55 (m, 2H); $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$ 的计算值: 334.09; 观测值: MS (ESI) (m/z) 335.2 ($M+1$) $^+$.

[1331]



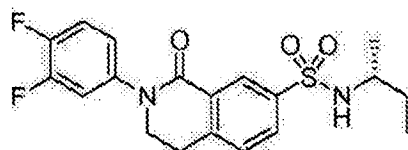
[1332] 1-氧代-1,2,3,4-四氢异喹啉-7-磺酰氯:将3,4-二氢异喹啉-1(2H)-酮(300mg,2.0mmol)溶解于氯磺酸(3mL)中。在80℃下加热溶液4小时,并且冷却至室温。在分液漏斗中将混合物倾于冰上,并且用二氯甲烷(10mL x 3)萃取。合并的有机相用水、盐水洗涤,并且经Na₂SO₄干燥。浓缩提供白色固体,其直接用于下一步骤中。C₉H₉ClNO₃S的计算值:244.99;观测值:MS(ESI)(m/z)246.0(M+1)⁺。

[1333]



[1334] (R)-N-(仲丁基)-1-氧代-1,2,3,4-四氢异喹啉-7-磺酰胺:将以上获得的白色固体溶解于DMF(2mL)中,并且在室温下添加至(R)-丁烷-2-胺(0.41mL,4.0mmol)和三乙胺(1.1mL,8mmol)于DMF(3mL)中搅拌溶液中。在这个温度下30分钟之后,混合物用乙酸乙酯稀释,用HCl(2N,5mL x 2)、饱和NaHCO₃、盐水洗涤并浓缩。在硅胶(40g)上,以1:1至1:0的乙酸乙酯:己烷梯度纯化残余物产生呈白色固体状的所需产物(300mg,52%(对于2步而言))。¹H NMR(300MHz,DMSO):δ 8.26(d,J = 2.0Hz,1H),8.16(bs,1H,CONH),7.86(d,d,J = 7.9,2.0Hz,1H),7.60(d,J = 7.9Hz,1H,SO₂NH),7.52(d,J = 8.0Hz,1H),3.40(td,J = 6.4,2.9Hz,2H),3.10-2.95(m,3H),1.30(dt,J = 14.1,7.6Hz,2H),0.87(d,J = 6.7Hz,3H),0.71(t,J = 7.3Hz,3H);C₁₃H₁₈N₂O₃S的计算值:282.1;观测值:MS(ESI)(m/z)283.2(M+1)⁺。

[1335]



[1336] (R)-N-(仲丁基)-2-(3,4-二氟苯基)-1-氧代-1,2,3,4-四氢异喹啉-7-磺酰胺:向压力管中装入(R)-N-(仲丁基)-1-氧代-1,2,3,4-四氢异喹啉-7-磺酰胺(135mg,

0.48mmol)、1,2-二氟-4-碘苯(230mg,0.96mmol)、碳酸钾(78mg,0.56mmol)、CuI(9.5mg,0.05mmol)和DMF(5mL)。将混合物真空脱气,并且用He再填充,接着在150℃下加热5天。混合物用乙酸乙酯稀释,用氨(10%)和盐水洗涤并浓缩。在硅胶(24g)上,以1:9至1:1的乙酸乙酯:己烷梯度纯化残余物产生呈淡黄色固体状的所需产物(82.4mg,44%)。¹H NMR(300MHz,MeOD): δ 8.46(d,J=1.8Hz,1H),7.95(dd,J=7.9,2.0Hz,1H),7.51(d,J=8.2Hz,1H),7.47-7.19(m,3H),4.02(t,J=6.4Hz,2H),3.26(t,J=6.4Hz,2H),3.24-3.10(m,1H),1.373(td,J=14.4,7.0Hz,2H),0.95(d,J=6.4Hz,3H),0.78(t,J=7.3Hz,3H); C₁₉H₂₀F₂N₂O₃S的计算值:394.1;观测值:MS(ESI)(m/z)395.2(M+1)⁺。

[1337] 实施例12:一般性程序L:

[1338]



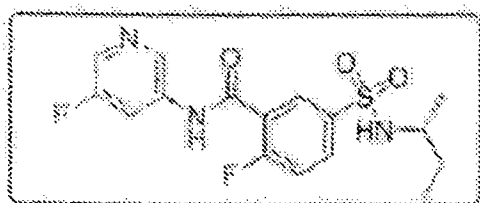
[1339] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟苯甲酸,将5-(氯磺酰基)-2-氟苯甲酸(239mg)溶解于CH₂Cl₂(20ml)中,冷却反应混合物至0℃。接着添加Et₃N(405mg),在搅拌15分钟之后,添加(R)-丁烷-2-胺(73mg)。搅拌所得混合物3小时直至反应完成。汽提去除溶剂,并且粗产物不经进一步纯化即使用。

[1340] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟苯甲酰氯,添加(R)-5-(N-(仲丁基)氨磺酰基)-2-氟苯甲酸(300mg)至SOCl₂(15ml)中,加热反应混合物至75℃,并且搅拌1小时直至反应完成。汽提去除溶剂,并且产物(R)-5-(N-(仲丁基)氨磺酰基)-2-氟苯甲酰氯不经纯化即用于下一步骤。

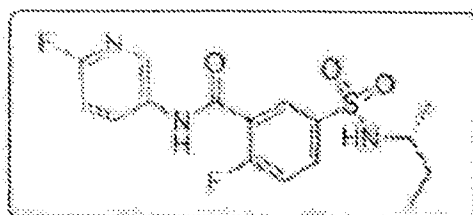
[1341] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-R-苯甲酰胺:将(R)-5-(N-(仲丁基)氨磺酰基)-2-氟苯甲酰氯(400mg)溶解于THF(20ml)中,接着添加Et₃N(405mg)和RNH₂(224mg)。加热反应混合物至85℃,并且搅拌5小时直至反应完成。汽提去除反应混合物的溶剂,并且所得粗产物通过二氧化硅柱(EtOAc/石油醚=1:3)纯化以得到产物(R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-R-苯甲酰胺。通过LC-MS确认化合物。

[1342] 使用以上一般性程序合成以下16种化合物:

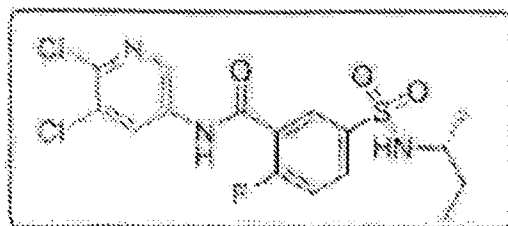
[1343]



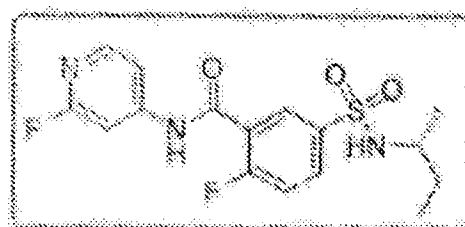
化合物A



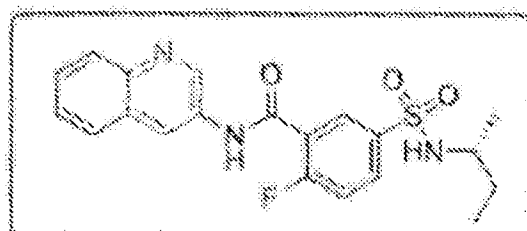
化合物B



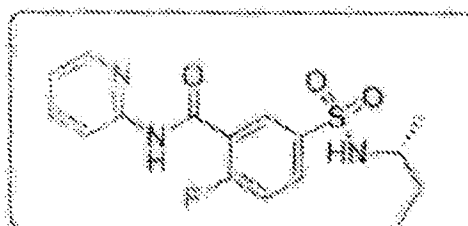
化合物C



化合物D

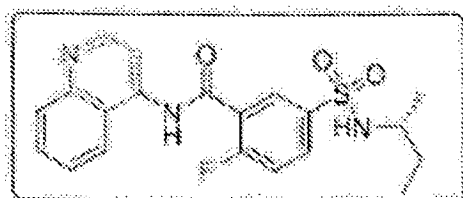


化合物E

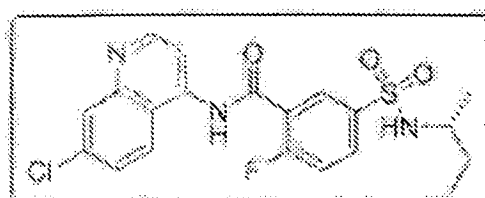


化合物F

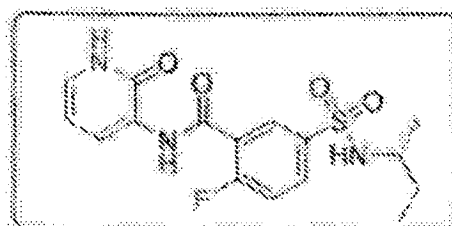
[1344]



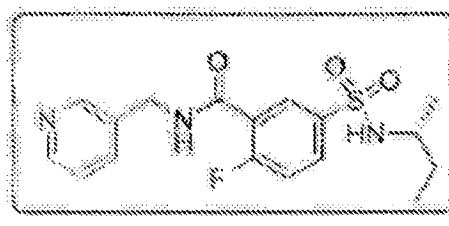
化合物G



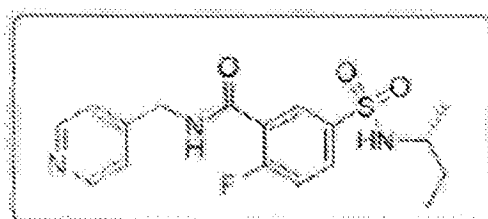
化合物H



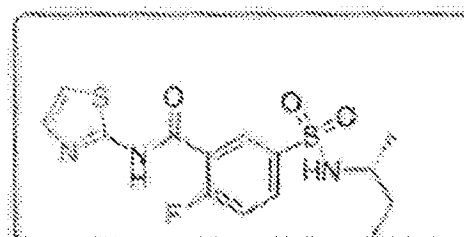
化合物I



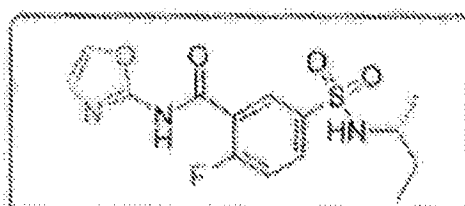
化合物J



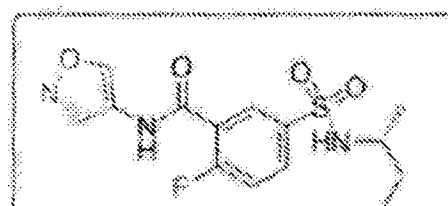
化合物K



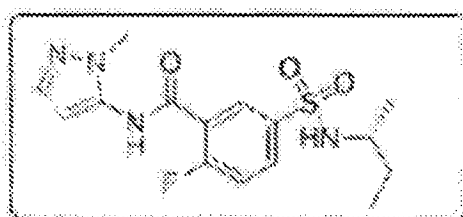
化合物L



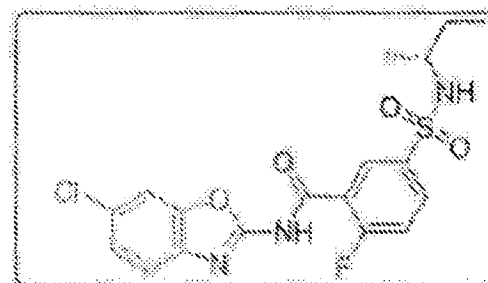
化合物M



化合物N



化合物O



化合物P

[1345] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(5-氟吡啶-3-基)苯甲酰胺(化合物A), 40mg, 呈灰白色固体状, HPLC 纯度: 90%。MS 计算值: 369.1; MS 实测值: 370.0[M+H]⁺。

[1346] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(6-氟吡啶-3-基)苯甲酰胺(化合物B), 50mg, 呈灰白色固体状, HPLC 纯度: 90%。MS 计算值: 369.1; MS 实测值: 370.0[M+H]⁺。

[1347] (R)-5-(N-(仲丁基)氨磺酰基)-N-(5,6-二氯吡啶-3-基)-2-氟苯甲酰胺(化合物C), 20mg, 呈灰白色固体状, HPLC 纯度: 90%。

[1348] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(2-氟吡啶-4-基)苯甲酰胺(化合物

D), 14mg, 呈灰白色固体状, HPLC 纯度 :90%。MS 计算值 :369.1 ;MS 实测值 :370.0 [M+H]⁺。

[1349] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(喹啉-3-基)苯甲酰胺(化合物 E), 50mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1350] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(吡啶-2-基)苯甲酰胺(化合物 F), 60mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1351] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(喹啉-4-基)苯甲酰胺(化合物 G), 55mg, 呈灰白色固体状, HPLC 纯度 :90%。MS 计算值 :401.4 ;MS 实测值 :402.4 [M+H]⁺。

[1352] (R)-5-(N-(仲丁基)氨磺酰基)-N-(7-氯喹啉-4-基)-2-氟苯甲酰胺(化合物 H), 40mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1353] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(2-氧代-1,2-二氢吡啶-3-基)苯甲酰胺(化合物 I), 40mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1354] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(吡啶-3-基甲基)苯甲酰胺(化合物 J), 50mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1355] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(吡啶-4-基甲基)苯甲酰胺(化合物 K), 40mg, 呈灰白色固体状, HPLC 纯度 :90%。MS 计算值 :365.4 ;MS 实测值 :366.4 [M+H]⁺。

[1356] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(噻唑-2-基)苯甲酰胺(化合物 L), 40mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1357] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(噁唑-2-基)苯甲酰胺(化合物 M), 22mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1358] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(异噁唑-4-基)苯甲酰胺(化合物 N), 22mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1359] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(1-甲基-1H-吡唑-5-基)苯甲酰胺(化合物 O), 40mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1360] (R)-5-(N-(仲丁基)氨磺酰基)-N-(6-氯苯并[d]噁唑-2-基)-2-氟苯甲酰胺(化合物 P), 15mg, 呈灰白色固体状, HPLC 纯度 :90%。

[1361] 实施例 13 :一般性程序 M :

[1362]



[1363] 3-(N-环丙基氨磺酰基)-4-氟苯甲酸, 将 5-(氯磺酰基)-2-氟苯甲酸 (239mg) 溶解于 CH₂Cl₂ (20mL) 中, 冷却反应混合物至 0℃。接着添加 Et₃N (405mg), 在搅拌 15 分钟之后, 添加环丙胺 (57.1mg)。搅拌所得混合物 3 小时直至反应完成。汽提去除溶剂, 并且获得呈白色固体状的粗产物 3-(N-环丙基氨磺酰基)-4-氟苯甲酸。它不经进一步纯化即使用。

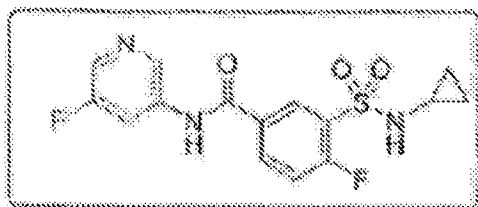
[1364] 3-(N-环丙基氨磺酰基)-4-氟苯甲酰氯, 添加 3-(N-环丙基氨磺酰基)-4-氟苯甲酸 (300mg) 至 SOCl₂ (15ml) 中, 加热反应混合物至 75℃, 并且搅拌 1 小时直至反应完成。汽提去除溶剂, 并且呈灰白色固体状的产物 3-(N-环丙基氨磺酰基)-4-氟苯甲酰氯不经纯化即用于下一步骤。

[1365] 3-(N-环丙基氨磺酰基)-4-氟-N-R-苯甲酰胺, 将 3-(N-环丙基氨磺酰基)-4-氟苯甲酰氯 (400mg) 溶解于 THF (20ml) 中, 接着添加 Et₃N (405mg) 和 RNH₂ (112mg)。加热反

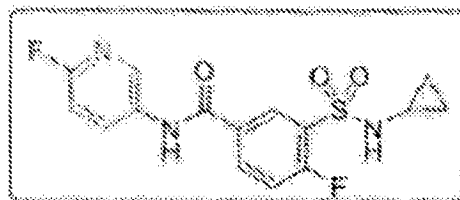
应混合物至 85℃, 并且搅拌 5 小时直至反应完成。汽提去除反应混合物的溶剂, 并且所得粗产物通过二氧化硅柱 (EtOAc/ 石油醚 = 1:3) 纯化以得到产物 3-(N-环丙基氨磺酰基)-4-氟-N-R-苯甲酰胺。通过 LC-MS 和 ¹H-NMR 确认化合物。

[1366] 使用以上一般性程序合成以下 16 种化合物:

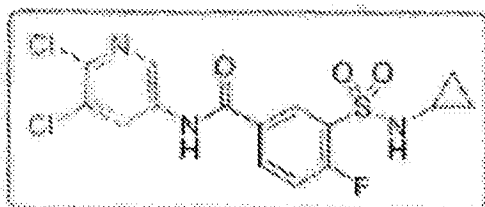
[1367]



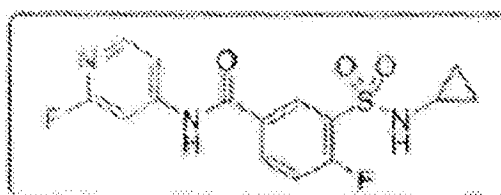
化合物 AA



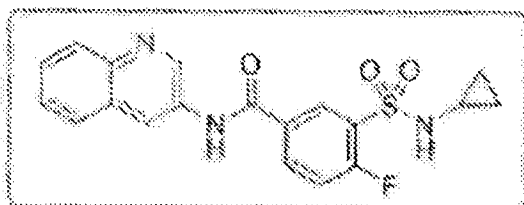
化合物 BB



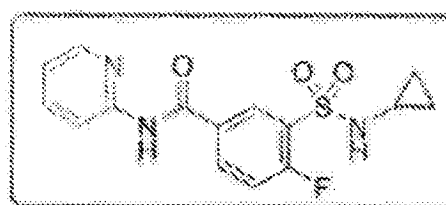
化合物 CC



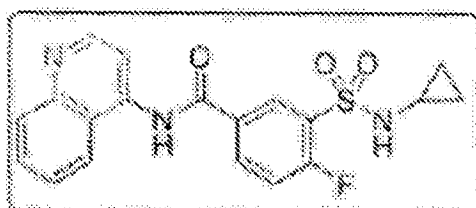
化合物 DD



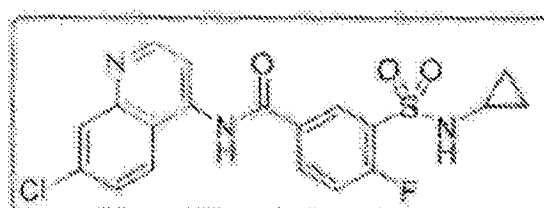
化合物 EE



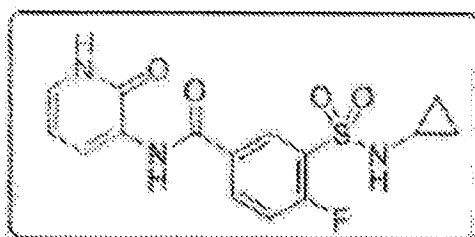
化合物 FF



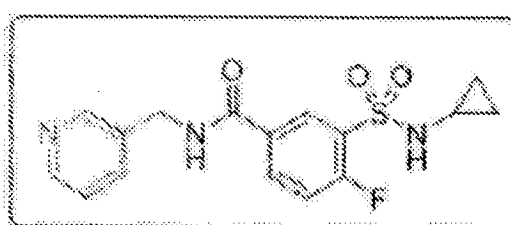
化合物 GG



化合物 HH

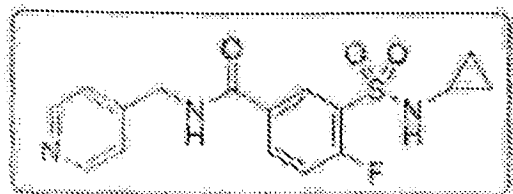


化合物 II

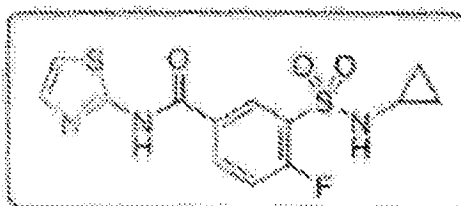


化合物 JJ

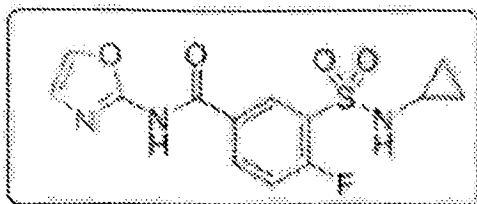
[1368]



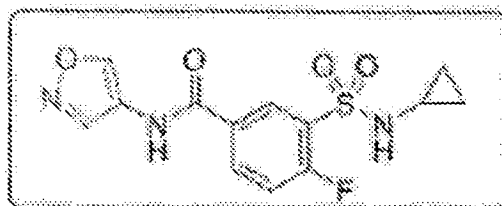
化合物 KK



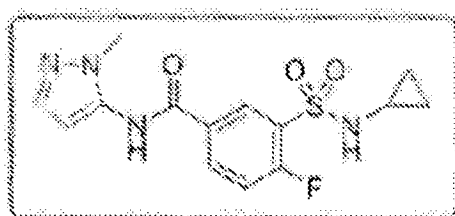
化合物 LL



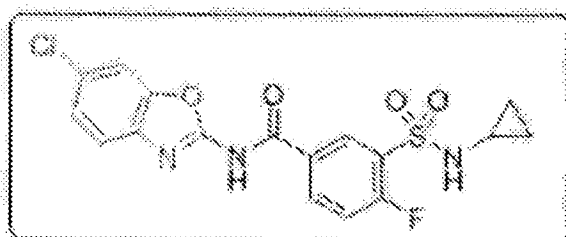
化合物 MM



化合物 NN



化合物 OO



化合物 PP

[1369] 3-(N-环丙基氨磺酰基)-4-氟-N-(5-氟吡啶-3-基)苯甲酰胺(化合物AA), 100mg, 呈灰白色固体状, MS: $M+H^+$ 354。

[1370] 3-(N-环丙基氨磺酰基)-4-氟-N-(6-氟吡啶-3-基)苯甲酰胺(化合物BB), 100mg, 呈灰白色固体状, $M+H^+$ 354。

[1371] 3-(N-环丙基氨磺酰基)-N-(5,6-二氯吡啶-3-基)-4-氟苯甲酰胺(化合物CC), 100mg, 呈灰白色固体状, $M+H^+$ 404。

[1372] 3-(N-环丙基氨磺酰基)-4-氟-N-(2-氟吡啶-4-基)苯甲酰胺(化合物DD), 60mg, 呈灰白色固体状, $M+H^+$ 354。

[1373] 3-(N-环丙基氨磺酰基)-4-氟-N-(喹啉-3-基)苯甲酰胺(化合物EE), 110mg, 呈灰白色固体状, $M+H^+$ 386。¹H NMR(CDCl₃, Bruker Avance 400MHz) δ : 0.41-0.48(2H, m), 0.51-0.56(2H, m), 2.25-2.32(1H, m), 7.59-7.64(1H, m), 7.68-7.72(2H, m), 8.01(1H, d, J = 5.6Hz), 8.39-8.42(2H, m), 8.91(1H, d, J = 3.6Hz), 8.83(1H, s), 9.16(1H, s), 10.99(1H, brs)。

[1374] 3-(N-环丙基氨磺酰基)-4-氟-N-(吡啶-2-基)苯甲酰胺(化合物FF), 100mg, 呈灰白色固体状, $M+H^+$ 336。

[1375] 3-(N-环丙基氨磺酰基)-4-氟-N-(喹啉-4-基)苯甲酰胺(化合物GG), 100mg, 呈灰白色固体状, $M+H^+$ 386。¹H NMR(CDCl₃, Bruker Avance 400MHz) δ : 0.41-0.48(2H, m), 0.51-0.60(2H, m), 2.25-2.32(1H, m), 7.63-7.67(1H, m), 7.71(1H, t, J = 6.4Hz), 7.81(1H, t, J = 5.2Hz), 7.89(1H, d, J = 3.2Hz), 8.06(1H, d, J = 2.4Hz), 8.25(1H, d, J = 5.2Hz), 8.42-8.48(2H, m), 8.51(1H, d, J = 4.4Hz), 8.91(1H, d, J = 3.6Hz), 10.95(1H, brs)。

[1376] N-(7-氯喹啉-4-基)-3-(N-环丙基氨磺酰基)-4-氟苯甲酰胺(化合物 HH), 120mg, 呈灰白色固体状, $M+H^+$ 420. 1H NMR($CDCl_3$, Bruker Avance 400MHz) δ : 0.35-0.41(2H, m), 0.44-0.51(2H, m), 2.25-2.30(1H, m), 7.67-7.73(2H, m), 7.91-7.93(1H, m), 8.11(1H, d, $J = 1.2$ Hz), 8.28-8.32(1H, m), 8.42-8.47(2H, m), 8.48-8.50(1H, m), 8.93-8.96(1H, m), 11.00(1H, brs)。

[1377] 3-(N-环丙基氨磺酰基)-4-氟-N-(2-氧代-1,2-二氢吡啶-3-基)苯甲酰胺(化合物 II), 120mg, 呈灰白色固体状, $M+H^+$ 352。

[1378] 3-(N-环丙基氨磺酰基)-4-氟-N-(吡啶-3-基甲基)苯甲酰胺(化合物 JJ), 60mg, 呈灰白色固体状, $M+H^+$ 350。

[1379] 3-(N-环丙基氨磺酰基)-4-氟-N-(吡啶-4-基甲基)苯甲酰胺(化合物 KK), 100mg, 呈灰白色固体状, $M+H^+$ 350, 1H NMR($CDCl_3$, Bruker Avance 400MHz) δ : 0.35-0.41(2H, m), 0.44-0.51(2H, m), 2.25-2.30(1H, m), 4.51(2H, d, $J = 3.6$ Hz), 7.32(2H, d, $J = 3.6$ Hz), 7.61(1H, t, $J = 6.0$ Hz), 8.26(1H, brs), 8.37-8.40(2H, m), 8.49-8.53(2H, m), 9.44(1H, t, $J = 4.0$ Hz)。

[1380] 3-(N-环丙基氨磺酰基)-4-氟-N-(噻唑-2-基)苯甲酰胺(化合物 LL), 90mg, 呈灰白色固体状, $M+H^+$ 342。

[1381] 3-(N-环丙基氨磺酰基)-4-氟-N-(噁唑-2-基)苯甲酰胺(化合物 MM), 15mg, 呈灰白色固体状, $M+H^+$ 326。

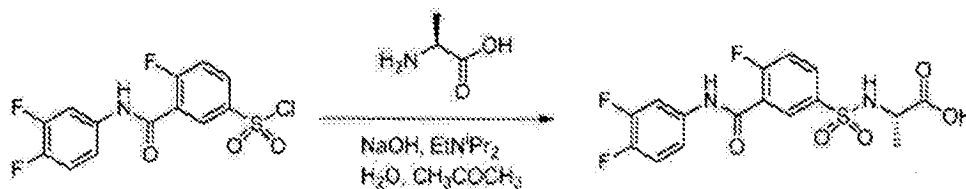
[1382] 3-(N-环丙基氨磺酰基)-4-氟-N-(异噁唑-4-基)苯甲酰胺(化合物 NN), 10mg, 呈灰白色固体状, $M+H^+$ 326。

[1383] 3-(N-环丙基氨磺酰基)-4-氟-N-(1-甲基-1H-吡唑-5-基)苯甲酰胺(化合物 OO), 110mg, 呈灰白色固体状, $M+H^+$ 339。

[1384] N-(6-氯苯并[d]噁唑-2-基)-3-(N-环丙基氨磺酰基)-4-氟苯甲酰胺(化合物 PP), 40mg, 呈灰白色固体状, $M+H^+$ 410。

[1385] 实施例 14:一般性程序 N:

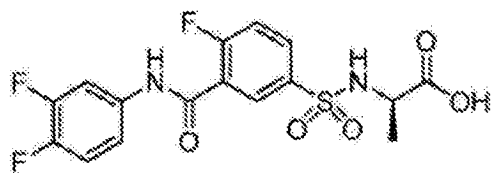
[1386]



[1387] (S)-2-(3-((3,4-二氟苯基)氨基)丙酰基)-4-氟苯基亚磺酰氨基)丙酸:向小瓶(2ml)中装入 L-丙氨酸(25.5mg, 0.28mmol)、NaOH(2M, 0.15ml, 0.28mmol)。冷却混合物至 0°C, 并且依次用磺酰氯(100mg, 0.28mmol)、 EtN^iPr_2 (0.055ml, 0.31mmol)和丙酮(0.15ml)处理以得到澄清溶液。在 0°C 下搅拌混合物 15 分钟, 接着在室温下搅拌 6 小时。真空去除挥发物, 残余物用水(1ml)稀释, 用 NaOH(2M, 0.15ml)碱化, 用乙醚萃取。水相用浓 HCl 酸化至 pH 1, 并且用乙酸乙酯萃取。有机相用盐水洗涤并浓缩。将残余物溶解于乙腈中, 并且在 15 分钟内在具有 20% 至 100% 乙腈于水中的梯度的制备型 HPLC 上纯化。在冻干之后获得白色固体(45mg, 39%)。 1H NMR(300MHz, $CDCl_3$): δ 8.62(dd, $J = 6.7, 2.0$ Hz, 1H), 8.40(bd, $J = 13.2$ Hz, 1H), 8.10-8.00(m, 1H), 7.77-7.66(m, 1H), 7.33(dd, $J = 10.8, 8.5$ Hz, 1H), 7.26-7.

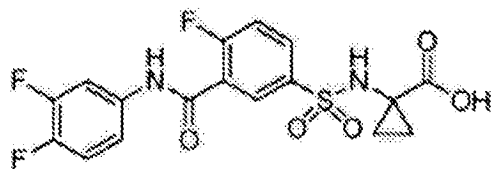
10 (m, 2H), 5.63 (bd, $J = 8.2$ Hz, 1H), 4.16–4.04 (m, 1H), 1.46 (d, $J = 7.3$ Hz, 3H); $C_{16}H_{13}F_3N_2O_5S$ 的计算值: 402.05; 观测值: MS (ESI) (m/z) 403.2 ($M+1$)⁺。

[1388]



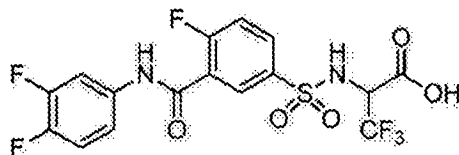
[1389] (R)-2-(3-((3,4-二氟苯基)氨基)乙酰基)-4-氟苯基亚磺酰氨基)丙酸: 通过与对于一般性程序 N 所述的程序类似的程序制备。¹H NMR (300 MHz, MeOD): δ 8.20 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.04 (ddd, $J = 8.5, 4.7, 2.6$ Hz, 1H), 7.81 (ddd, $J = 13.0, 7.3, 2.3$ Hz, 1H), 7.48–7.34 (m, 2H), 7.32–7.18 (m, 1H), 3.98 (q, $J = 7.3$ Hz, 1H), 1.34 (d, $J = 7.0$ Hz, 3H); $C_{16}H_{13}F_3N_2O_5S$ 的计算值: 402.05; 观测值: MS (ESI) (m/z) 403.2 ($M+1$)⁺。

[1390]



[1391] 1-(3-((3,4-二氟苯基)氨基)乙酰基)-4-氟苯基亚磺酰氨基)环丙烷甲酸: 通过与对于一般性程序 N 所述的程序类似的程序制备。¹H NMR (300 MHz, MeOD): δ 8.20 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.04 (ddd, $J = 8.5, 4.7, 2.6$ Hz, 1H), 7.82 (ddd, $J = 12.7, 7.6, 2.6$ Hz, 1H), 7.48–7.34 (m, 2H), 7.32–7.20 (m, 1H), 1.44–1.37 (m, 2H), 1.35–1.29 (m, 2H); $C_{17}H_{13}F_3N_2O_5S$ 的计算值: 414.05; 观测值: MS (ESI) (m/z) 415.1 ($M+1$)⁺。

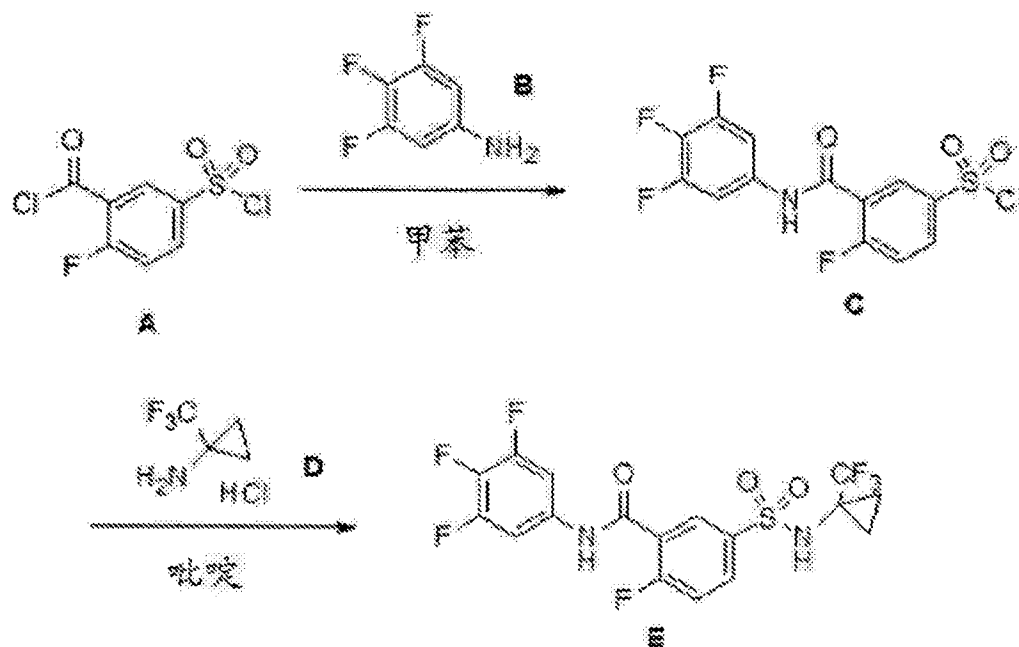
[1392]



[1393] 2-(3-((3,4-二氟苯基)氨基)乙酰基)-4-氟苯基亚磺酰氨基)-3,3,3-三氟丙酸: 通过与对于一般性程序 N 所述的程序类似的程序制备。¹H NMR (300 MHz, MeOD): δ 8.25 (dd, $J = 6.4, 2.6$ Hz, 1H), 8.08 (ddd, $J = 8.8, 4.7, 2.3$ Hz, 1H), 7.82 (ddd, $J = 12.7, 7.3, 2.6$ Hz, 1H), 7.49–7.37 (m, 2H), 7.32–7.20 (m, 1H), 4.79 (q, $J = 7.9$ Hz, 1H); $C_{16}H_{10}F_6N_2O_5S$ 的计算值: 456.02; 观测值: MS (ESI) (m/z) 457.2 ($M+1$)⁺。

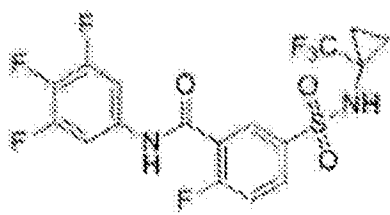
[1394] 实施例 15: 一般性程序 O

[1395]



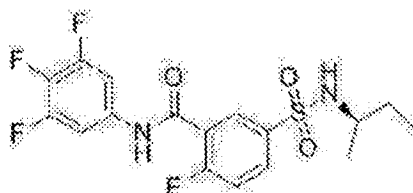
[1396] N-(3,4,5-三氟苯基)-2-氟-5-(N-(1-(三氟甲基)环丙基)氨磺酰基)苯甲酰胺:向3,4,5-三氟苯胺(0.618g,0.0042mol)于甲苯(5mL)中的0℃溶液中逐滴添加5-氯磺酰基-2-氟苯甲酰氯(1.08g,0.0042mol)(如一般性程序B的第一步中所制备)于5mL甲苯中的溶液。将混合物在室温下搅拌过夜。蒸发溶剂,并且粗产物通过柱色谱法(EtOAc/己烷)纯化以产生化合物3-(3,4,5-三氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯(1.14g,74%)。在真空下干燥过夜之后,将3-(3,4,5-三氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯(59mg,0.16mmol)和1-三氟甲基-环丙胺·HCl(39mg,0.24mmol)于吡啶(0.2mL)中的混合物在室温下搅拌过夜。此后,蒸发试剂,将残余物溶解于EtOAc中,依次用1N HCl和盐水洗涤,干燥并通过色谱法(EtOAc/己烷)纯化以产生呈白色固体状的所需产物(58.2mg,80%)。¹H NMR(300MHz, d₄-MeOH):8.20-8.18(m, 1H), 8.06-8.01(m, 1H), 7.58-7.43(m, 3H), 1.22(m, 4H); MS(ES)m/z:457.2(M+H⁺), 计算值:457.04。

[1397]



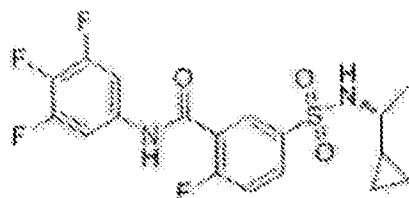
[1398] 2-氟-5-(N-(1-(三氟甲基)环丙基)氨磺酰基)-N-(3,4,5-三氟苯基)苯甲酰胺:以与一般性程序O类似的程序,获得呈白色固体状的最终化合物(58.2mg,80%)。¹H NMR(300MHz, d₄-MeOH):8.20-8.18(m, 1H), 8.06-8.01(m, 1H), 7.58-7.43(m, 3H), 1.22(m, 4H); MS(ES)m/z:457.2(M+H⁺), 计算值:457.04。

[1399]



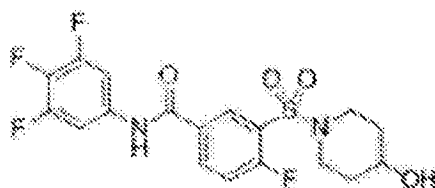
[1400] (R)-5-(N-(仲丁基)氨磺酰基)-2-氟-N-(3,4,5-三氟苯基)苯甲酰胺:以与一般性程序O类似的程序,获得呈白色固体状的最终化合物(29mg,42%)。¹H NMR(300MHz, d₄-MeOH):8.22-8.19(m, 1H), 8.08-8.03(m, 1H), 7.58-7.43(m, 3H), 3.24-3.18(m, 1H), 1.42-1.35(m, 2H), 1.01-0.98(d, J = 6.7Hz, 3H), 0.83-0.78(t, J = 7.3Hz, 3H);MS(ES)m/z:405.2(M+H⁺), 计算值:405.08。

[1401]



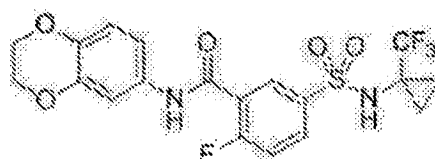
[1402] (R)-5-(N-(1-环丙基乙基)氨磺酰基)-2-氟-N-(3,4,5-三氟苯基)苯甲酰胺:以与一般性程序O类似的程序,获得呈白色固体状的最终化合物(23.1mg,36%)。¹H NMR(300MHz, d₄-MeOH):8.24-8.21(m, 1H), 8.09-8.05(m, 1H), 7.59-7.44(m, 3H), 2.71-2.66(m, 1H), 1.14-1.12(d, J = 6.7Hz, 3H), 0.82-0.76(m, 1H), 0.48-0.40(m, 1H), 0.35-0.29(m, 1H), 0.19-0.14(m, 1H), 0.06-0.03(m, 1H);MS(ES)m/z:417.2(M+H⁺), 计算值:417.08。

[1403]



[1404] 4-氟-3-((4-羟基哌啶-1-基)磺酰基)-N-(3,4,5-三氟苯基)苯甲酰胺:以与一般性程序O类似的程序,获得呈白色固体状的最终化合物(53mg,77%)。¹H NMR(300MHz, d₄-MeOH):8.42-8.39(m, 1H), 8.27-8.22(m, 1H), 7.62-7.47(m, 3H), 3.75-3.70(m, 1H), 3.54-3.52(m, 2H), 3.08-3.01(m, 2H), 1.92-1.86(m, 2H), 1.62-1.52(m, 2H);MS(ES)m/z:433.2(M+H⁺), 计算值:433.08。

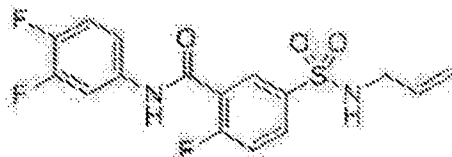
[1405]



[1406] N-(2,3-二氢苯并[b][1,4]二氧杂环己烯-6-基)-2-氟-5-(N-(1-(三氟甲基)环丙基)氨磺酰基)苯甲酰胺:以与一般性程序O类似的程序,获得呈白色固体状的最终化合物(73mg,69.2%)。¹H NMR(300MHz, d₄-MeOH):8.19-8.16(m, 1H), 8.03-7.99(m, 1H), 7.47-7.41(t, J = 9.2Hz, 1H), 7.30(s, 1H), 7.07-7.04(m, 1H), 6.83-6.80(d, J =

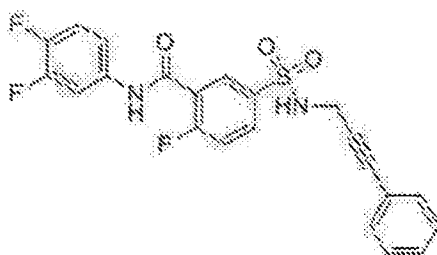
8.7Hz, 1H), 4.24(s, 4H), 1.24(s, 4H); MS(ES) m/z: 461.2 (M+H⁺), 计算值: 461.07。

[1407]



[1408] 5-(N-烯丙基氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 以与一般性程序 0 类似的程序, 获得呈白色固体状的最终化合物 (6.4mg, 12%)。¹H NMR(300MHz, d₄-MeOH): 8.20-8.17(m, 1H), 8.06-8.01(m, 1H), 7.86-7.78(m, 1H), 7.49-7.36(m, 2H), 7.31-7.22(m, 1H), 5.80-5.67(m, 1H), 5.21-5.14(m, 1H), 5.08-5.03(m, 1H), 4.87-4.84(m, 2H); MS(ES) m/z: 371.2 (M+H⁺), 计算值: 371.06。

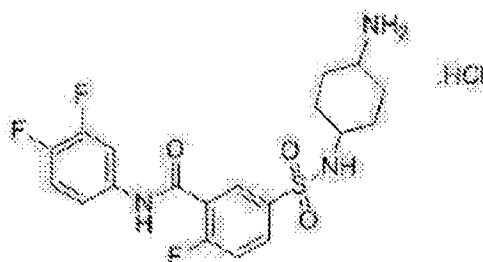
[1409]



[1410] N-(3,4-二氟苯基)-2-氟-5-(N-(3-苯基丙-2-炔-1-基)氨磺酰基)苯甲酰胺: 以与一般性程序 0 类似的程序, 获得呈白色固体状的最终化合物 (58.8mg, 65.2%)。¹H NMR(300MHz, d₄-MeOH): 8.33-8.30(m, 1H), 8.12-8.07(m, 1H), 7.81-7.75(m, 1H), 7.41-7.19(m, 8H), 4.07(s, 2H); MS(ES) m/z: 445.2 (M+H⁺), 计算值: 445.08。

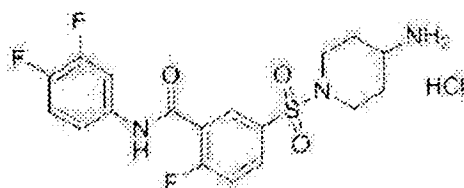
[1411] 实施例 16: 一般性程序 P

[1412]



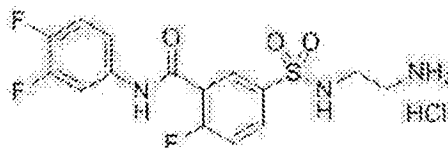
[1413] 5-(N-(4-氨基环己基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺盐酸盐: 用 4N HCl 于二噁烷 (0.5mL) 中处理 (4-(3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯基亚磺酰氨基)环己基)氨基甲酸叔丁酯 (25mg, 0.047mmol)。将混合物在室温下搅拌过夜。过滤白色固体, 并且用醚洗涤产生呈盐酸盐形式的所需产物 (25mg, 100%)。¹H NMR(300MHz, CD₃OD): 8.24-8.21(m, 1H), 8.10-8.05(m, 1H), 7.87-7.79(m, 1H), 7.51-7.48(m, 1H), 7.45-7.35(m, 1H), 7.31-7.22(m, 1H), 3.28-3.25(m, 1H), 3.15-3.09(m, 1H), 1.87-1.56(m, 8H); MS(ES) m/z: 428.2 (M+H⁺), 计算值: 428.12。

[1414]



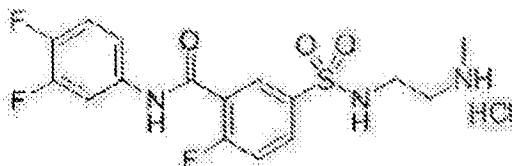
[1415] 5-((4-氨基吡啶-1-基)磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺盐酸盐: 以与一般性程序P类似的程序,获得呈盐酸盐形式的最终产物(49mg,100%)。¹H NMR(300 MHz, d₄-MeOH): 8.14-8.11(m, 1H), 8.03-7.98(m, 1H), 7.87-7.79(m, 1H), 7.56-7.50(m, 1H), 7.40-7.36(m, 1H), 7.32-7.23(m, 1H), 3.92-3.88(m, 2H), 3.15-3.07(m, 1H), 2.56-2.47(m, 2H), 2.08-2.05(m, 2H), 1.73-1.63(m, 2H); MS(ES) m/z: 414.2 (M+H⁺), 计算值: 414.10。

[1416]



[1417] 5-(N-(2-氨基乙基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺盐酸盐: 以与一般性程序P类似的程序,获得呈盐酸盐形式的最终产物(8.3mg,37%)。¹H NMR(300 MHz, d₄-MeOH): 8.24-8.22(m, 1H), 8.10-8.05(m, 1H), 7.87-7.79(m, 1H), 7.55-7.49(m, 1H), 7.40-7.36(m, 1H), 7.32-7.23(m, 1H), 3.16-3.05(m, 4H); MS(ES) m/z: 374.2 (M+H⁺), 计算值: 374.07。

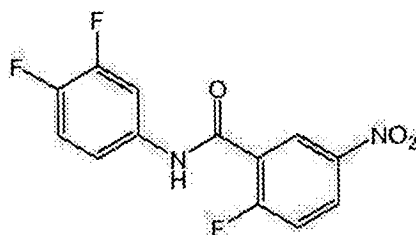
[1418]



[1419] N-(3,4-二氟苯基)-2-氟-5-(N-(2-(甲基氨基)乙基)氨磺酰基)苯甲酰胺盐酸盐: 以与一般性程序P类似的程序,获得呈盐酸盐形式的最终产物(20mg,56%)。MS(ES) m/z: 388.2 (M+H⁺), 计算值: 388.09。

[1420] 实施例17: 其它合成

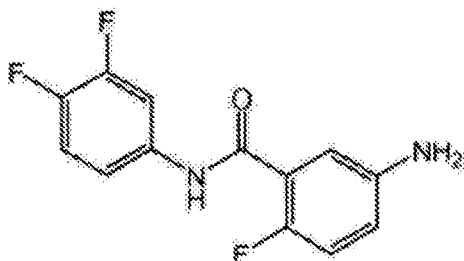
[1421]



[1422] N-(3,4-二氟苯基)-2-氟-5-硝基苯甲酰胺: 向3,4-二氟苯胺(0.64g,4.92mmol)和NEt₃(0.82g,8.22mmol)于CH₂Cl₂(18mL)中的溶液中逐滴添加2-氟-5-硝基-苯甲酰氯(1.00g,4.92mmol)于CH₂Cl₂(18mL)中的溶液。搅拌反应物14天,接着浓缩。将残余物分配于EtOAc(50mL)与稀NaHCO₃(20mL)之间。有机层用d5mL)、稀NaHCO₃(10mL)、水(10mL)、2N HCl(2 x 15mL)和盐水(5mL)洗涤,干燥(Na₂SO₄)并浓缩。粗物质通过二氧化硅柱(10-20%

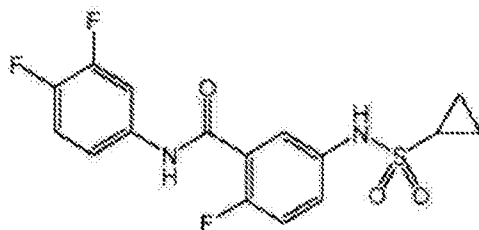
EtOAc/ 己烷) 纯化以产生呈浅黄色固体状的所需产物 (0.91g, 62%)。MS: $M+H^+$ 273。 1H NMR (300MHz, $CDCl_3$): 8.62 (dd, $J = 2.9, 6.7$ Hz, 1H), 8.46-8.41 (m, 1H), 8.35 (d, $J = 14.1$ Hz, 1H), 7.80-7.73 (m, 1H), 7.41 (dd, $J = 1.5, 9.1$ Hz, 1H), 7.26-7.14 (m, 3H)。

[1423]



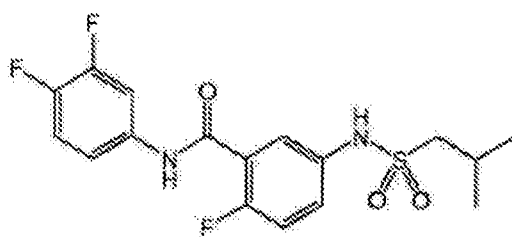
[1424] 5-氨基-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 将 N-(3,4-二氟苯基)-2-氟-5-硝基苯 (0.50g, 1.69mmol) 和 10% Pd/C (30mg) 于甲醇 (8mL) 中的混合物抽空, 接着用氢气吹扫三次。在氢气氛围下搅拌反应物 16 小时。将反应物经硅藻土过滤, 并且浓缩滤液以产生呈浅黄色固体状的所需产物 (0.43g, 96%)。MS: $M+H^+$ 267。 1H NMR (300MHz, $DMSO-d_6$): 10.46 (s, 1H), 7.89-7.82 (m, 1H), 7.47-7.35 (m, 2H), 6.98 (dd, $J = 1.2, 8.8$ Hz, 1H), 6.77-6.65 (m, 2H), 5.20 (s, 2H)。

[1425]



[1426] 5-(环丙烷亚磺酰氨基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺: 向 5-氨基-N-(3,4-二氟苯基)-2-氟苯甲酰胺 (40mg, 0.15mmol) 于 THF (1mL) 中的 0℃ 溶液中添加 NEt_3 (30mg, 0.30mmol) 和环丙基-磺酰氯 (24mg, 0.17mmol)。使反应物升温至 20℃, 并且搅拌 3 小时。冷却反应物至 0℃, 并且再添加于 THF (1mL) 中的 NEt_3 (19mg, 0.19mmol), 添加环丙基-磺酰氯 (24mg, 0.17mmol)。使反应物升温至 20℃, 并且搅拌 60 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/ 己烷) 纯化以产生呈灰白色固体状的所需产物 (44mg, 79%)。MS: $M+H^+$ 371。 1H NMR (300MHz, $DMSO-d_6$): 10.64 (s, 1H), 9.9 (s, 1H), 7.90-7.81 (m, 1H), 7.47-7.41 (m, 5H), 2.66-2.60 (m, 1H), 1.00-0.91 (m, 4H)。

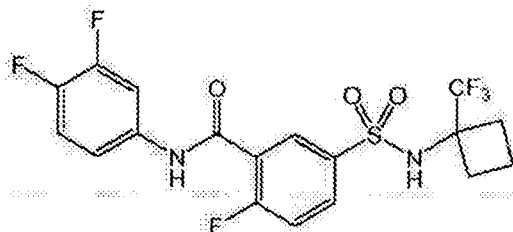
[1427]



[1428] N-(3,4-二氟苯基)-2-氟-5-(2-甲基丙基亚磺酰氨基)苯甲酰胺: 用异丁

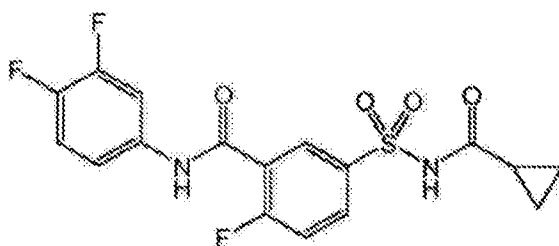
烷-磺酰氯 (16mg, 0.11mmol) 处理 5-氨基-(N-(3,4-二氟苯基)-2-氟苯甲酰胺 (25mg, 0.094mmol) 和 DMAP (10mg) 于吡啶 (1mL) 中的混合物。在 110℃ 下加热反应物 16 小时。再添加 DMAP (10mg) 和异丁烷-磺酰氯 (32mg, 0.22mmol), 并且在 110℃ 下加热反应物 3 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/己烷) 纯化以产生呈灰白色固体状的所需产物 (15mg, 41%)。MS: $\text{M}+\text{H}^+$ 387。 ^1H NMR (300MHz, $\text{DMSO}-d_6$): 10.64 (s, 1H), 9.97 (s, 1H), 7.89-7.82 (m, 1H), 7.45-7.34 (m, 5H), 2.99 (d, $J = 6.5\text{Hz}$, 1H), 2.16-2.07 (m, 1H), 0.98 (d, $J = 6.7\text{Hz}$, 1H)。

[1429]



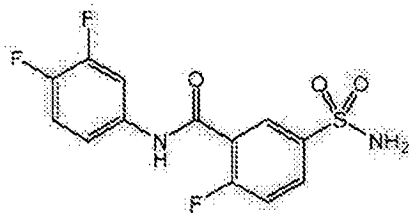
[1430] N-(3,4-二氟苯基)-2-氟-5-(N-(1-(三氟甲基)环丁基)氨磺酰基)苯甲酰胺: 用 1-三氟甲基-环丁烷 (36mg, 0.26mmol) 处理 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (30mg, 0.086mmol) 和 DMAP (10mg) 于吡啶 (1mL) 中的混合物。在 95℃ 下加热反应物 4 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (10-50% EtOAc/己烷) 纯化以产生呈透明胶状的所需产物 (2mg, 5%)。MS: $\text{M}+\text{H}^+$ 453。 ^1H NMR (300MHz, $\text{DMSO}-d_6$): 8.22-8.20 (m, 1H), 8.10-8.06 (m, 1H), 7.82-7.76 (m, 1H), 7.49 (d, $J = 9.4\text{Hz}$, 1H), 7.32-7.23 (m, 3H), 2.47-2.41 (m, 4H), 1.92-1.83 (m, 2H)。

[1431]



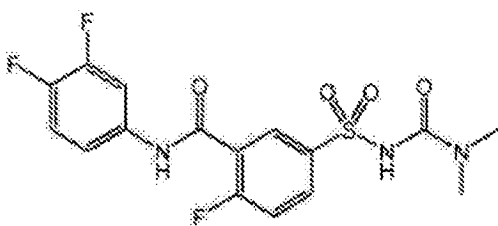
[1432] 5-(N-(环丙烷羰基)氨磺酰基)-N-(3,4-二氟苯基)-2-氟苯甲酰胺。向环丙烷甲酰胺 (29mg, 0.28mmol) 于 THF (1mL) 中的 0℃ 溶液中添加 NaH 于矿物油中的 60% 分散液 (11mg, 0.28mmol)。使反应物升温至 20℃, 并且搅拌 30 分钟。冷却混合物至 0℃, 接着添加 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)。使反应物升温至 20℃, 并且搅拌 16 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与稀 NaHCO_3 (5mL) 之间。有机层用水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na_2SO_4) 并浓缩。粗物质依次通过二氧化硅柱 (20-100% EtOAc/己烷) 和制备型 TLC (70% EtOAc/己烷) 纯化以产生呈透明胶状的所需产物 (3mg, 5%)。MS: $\text{M}+\text{H}^+$ 399。

[1433]



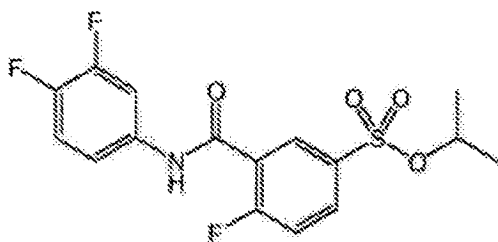
[1434] N-(3,4-二氟苯基)-2-氟-5-氨磺酰基苯甲酰胺。向 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯 (0.50g, 1.43mmol) 于 THF (4mL) 中的溶液中逐滴添加 28-30% 于水中的氨 (1mL)。搅拌反应物 60 小时。浓缩混合物,接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤,干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (20-100% EtOAc/己烷) 纯化以产生呈白色固体状的所需产物 (410mg, 87%)。MS: $\text{M}+\text{H}^+$ 331。

[1435]



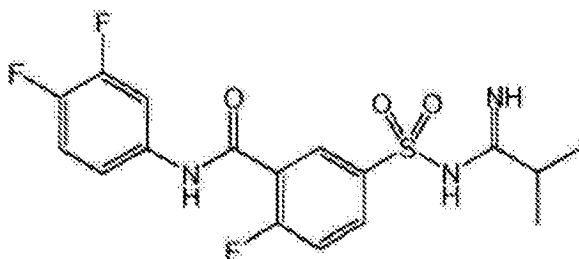
[1436] N-(3,4-二氟苯基)-5-(N-(二甲基氨基甲酰基)氨磺酰基)-2-氟苯甲酰胺。用二甲基氨基甲酰氯 (48mg, 0.45mmol) 处理 N-(3,4-二氟苯基)-2-氟-5-氨磺酰基苯甲酰胺 (50mg, 0.15mmol) 和 DMAP (10mg) 于吡啶 (0.1mL) 中的混合物。在 90℃ 下加热反应物 2 小时。浓缩混合物,接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤,干燥 (Na_2SO_4) 并浓缩。粗物质通过二氧化硅柱 (1-10% MeOH/ CH_2Cl_2) 纯化以产生呈白色固体状的所需产物 (12mg, 20%)。MS: $\text{M}+\text{H}^+$ 402。

[1437]



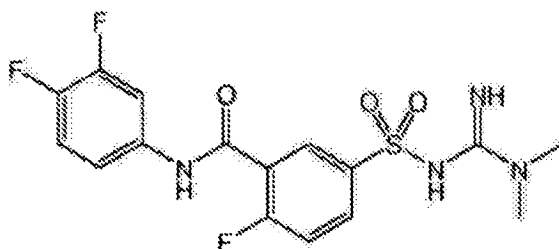
[1438] 3-((3,4-二氟苯基)氨基甲酰基)-4-氟苯磺酸异丙酯。向异丙醇 (0.1mL) 和吡啶 (0.1mL) 的 0℃ 溶液中逐份添加 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)。使反应物升温至 20℃,并且搅拌 16 小时。浓缩混合物,接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤,干燥 (Na_2SO_4) 并浓缩以产生呈白色固体状的所需产物 (22mg, 42%)。MS: $\text{M}+\text{H}^+$ 374。

[1439]



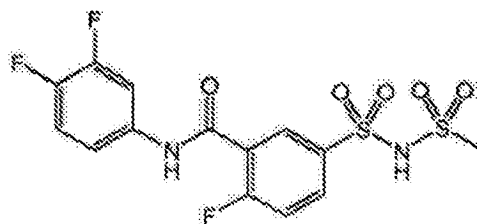
[1440] N-(3,4-二氟苯基)-2-氟-5-(N-(1-亚氨基-2-甲基丙基)氨磺酰基)苯甲酰胺。向 2-甲基-丙脒·HCl (35mg, 0.28mmol) 于 THF (0.2mL) 中的混合物中依次添加 10N NaOH 溶液 (4 滴) 和 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol) 于 THF (0.2mL) 中的溶液。搅拌反应物 16 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与稀 NaHCO₃ (5mL) 之间。有机层用水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na₂SO₄) 并浓缩。粗物质通过制备型 HPLC 纯化以产生呈灰白色固体状的所需产物 (2mg, 5%)。MS: M+H⁺ 400。

[1441]



[1442] N-(3,4-二氟苯基)-5-(N,N-二甲基脒基)氨磺酰基)-2-氟苯甲酰胺。在 40°C 下加热 1,1-二甲基胍硫酸盐 (76mg, 0.28mmol) 和 10N NaOH 水溶液 (9 滴) 的混合物 10 分钟。向该混合物中添加 THF (0.3mL), 并且冷却混合物至 0°C。向冷却的溶液中添加 3-(3,4-二氟苯基氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)。使反应物升温至 20°C, 并且搅拌 16 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与稀 NaHCO₃ (5mL) 之间。有机层用水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na₂SO₄) 并浓缩以产生呈浅黄色固体状的所需产物 (33mg, 59%)。MS: M+H⁺ 401。

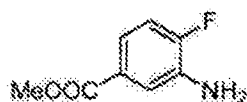
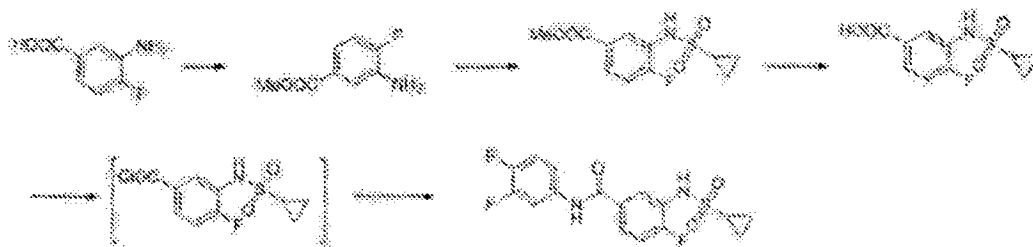
[1443]



[1444] N-(3,4-二氟苯基)-2-氟-5-(N-(甲基磺酰基)氨磺酰基)苯甲酰胺: 向甲烷磺酰胺 (38mg, 0.14mmol) 和 NEt₃ (40mg, 40mmol) 于乙腈 (1mL) 中的溶液中添加 3-(3,4-二氟苯基-氨基甲酰基)-4-氟苯-1-磺酰氯 (50mg, 0.14mmol)。在回流下加热反应物 2 小时。浓缩混合物, 接着将残余物分配于 EtOAc (20mL) 与 1N HCl (5mL) 之间。有机层用 2N HCl (5mL)、水 (5mL) 和盐水 (1mL) 洗涤, 干燥 (Na₂SO₄) 并浓缩以产生呈浅棕色固体状的所需产物 (33mg, 60%)。MS: M+H⁺ 409。

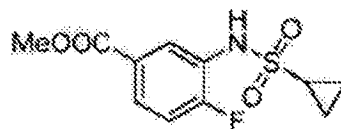
[1445] 3-(环丙烷亚磺酰氨基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺的合成

[1446]



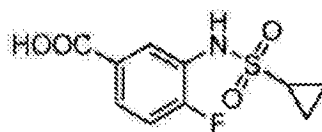
[1447] 3-氨基-4-氟苯甲酸甲酯:将3-氨基-4-氟苯甲酸(0.5g)溶解于甲醇(10ml)中,接着添加浓硫酸(1ml)。加热反应溶液至回流直至反应完成。接着冷却反应混合物,并且倾入水中,用2N NaOH溶液调节所得溶液的pH至8。将产物萃取至EtOAc层,并且汽提去除溶剂。获得290mg 3-氨基-4-氟苯甲酸甲酯。

[1448]



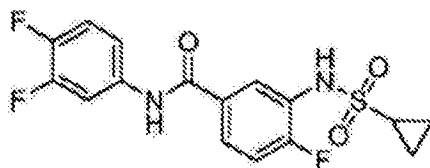
[1449] 3-(环丙烷亚磺酰氨基)-4-氟苯甲酸甲酯:将3-氨基-4-氟苯甲酸甲酯(275mg)和DMAP(100mg)溶解于吡啶(10ml)中。接着添加环丙烷磺酰氯(330mg)至溶液中。加热反应混合物至110℃,并且搅拌12小时直至反应完成。汽提去除溶剂,将固体依次溶解于CH₂Cl₂(50ml)和1N HCl溶液(50ml)中。分离去除底部水层,并且有机层用水洗涤并由无水Na₂SO₄干燥。汽提去除CH₂Cl₂,并且270mg 3-(环丙烷亚磺酰氨基)-4-氟苯甲酸甲酯直接用于下一步骤。

[1450]



[1451] 3-(环丙烷亚磺酰氨基)-4-氟苯甲酸:将粗3-(环丙烷亚磺酰氨基)-4-氟苯甲酸甲酯(270mg)溶解于MeOH(15ml)中,并且添加10% LiOH溶液(15ml)。将反应混合物在环境温度下搅拌过夜直至反应完成。汽提去除溶剂,并且用1N HCl溶液调节所得水溶液的pH至1.0。产物用EtOAc萃取,并且EtOAc层用无水Na₂SO₄干燥。汽提去除溶剂,并且所得3-(环丙烷亚磺酰氨基)-4-氟苯甲酸(250mg)直接用于下一步骤。

[1452]

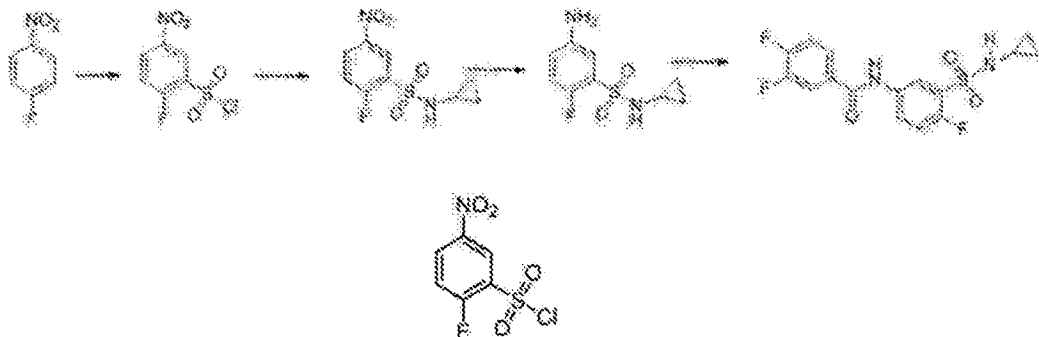


[1453] 3-(环丙烷亚磺酰氨基)-N-(3,4-二氟苯基)-4-氟苯甲酰胺:将3-(环丙烷亚

磺酰氨基)-4-氟苯甲酸 (250mg) 溶解于 SOCl_2 (5ml) 中, 并且加热溶液至回流并保持 1 小时直至反应完成。汽提去除溶剂, 接着加入 CH_2Cl_2 (10ml)。冷却所得溶液至 0°C , 接着添加 Et_3N (1ml) 和 3, 4-二氟苯胺 (0.25g)。将所得溶液在环境温度下搅拌过夜直至反应完成。将反应混合物倾入水 (10ml) 中, 并且分离去除底部水层。有机层依次用 1N HCl 溶液和盐水溶液洗涤, 接着用无水 Na_2SO_4 干燥。汽提去除溶剂, 并且粗产物通过二氧化硅柱纯化两次。获得 35mg 3-(环丙烷亚磺酰氨基)-N-(3, 4-二氟苯基)-4-氟苯甲酰胺。HPLC 纯度: 96%。LC-MS: 计算值: 370.3; 测量值: $[\text{M}+1] = 371.3$ 。

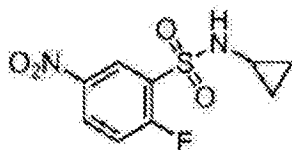
[1454] N-(3-(N-环丙基氨磺酰基)-4-氟苯基)-3, 4-二氟苯甲酰胺的合成:

[1455]



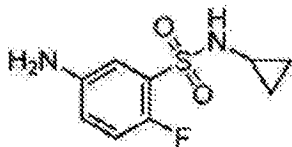
[1456] 2-氟-5-硝基苯-1-磺酰氯: 将 1-氟-4-硝基苯 (20g) 溶解于氯磺酸 (35ml) 中, 加热反应混合物至 115°C , 并且搅拌 9 小时直至反应完成。接着冷却反应物至环境温度, 并且倾入冰水 (300g) 中, 将化合物萃取至 EtOAc 中。分离去除水层。 EtOAc 层依次用水和盐水溶液洗涤, 用无水 Na_2SO_4 干燥。汽提去除溶剂, 粗产物通过二氧化硅柱 (石油醚/ $\text{EtOAc} = 10:1$) 纯化。获得 15g 2-氟-5-硝基苯-1-磺酰氯。

[1457]



[1458] N-环丙基-2-氟-5-硝基苯磺酰胺: 在 0°C 下向环丙胺 (7.92g) 和 N,N-二异丙基乙胺 (11g) 以及 CH_2Cl_2 (60ml) 的混合物中逐滴加入 2-氟-5-硝基苯-1-磺酰氯 (7.2g) 溶解于 CH_2Cl_2 (50ml) 中的溶液, 在 0°C 下搅拌反应混合物 2 小时直至反应完成。汽提去除溶剂, 并且将粗产物溶解于 CH_2Cl_2 中并用水洗涤两次。粗产物通过二氧化硅柱 (石油醚/ $\text{EtOAc} = 3:1$) 纯化, 并且获得 4.3g N-环丙基-2-氟-5-硝基苯磺酰胺, 产率: 67%。

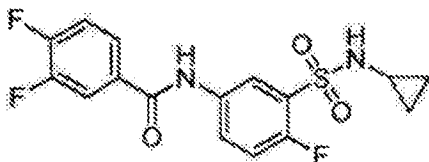
[1459]



[1460] 5-氨基-N-环丙基-2-氟苯磺酰胺: 将 N-环丙基-2-氟-5-硝基苯磺酰胺 (2.2g) 溶解于 1, 4-二噁烷 (44ml) 中, 接着添加 6N HCl (4.4ml) 和 SnCl_2 (7.7g) 至反应混合物中。在环境温度下搅拌所得混合物 2 小时直至反应完成。将反应混合物倾入 EtOAc (100ml) 和

水 (50ml) 的混合物中, 并且用 2N NaOH 调节所得混合物的 pH 至 11。分离去除底部水层, 并且有机层用水洗涤并用无水 Na_2SO_4 干燥。通过旋转蒸发器来汽提去除溶剂, 并且获得 2g 呈棕色油状的 5-氨基-N-环丙基-2-氟苯磺酰胺。

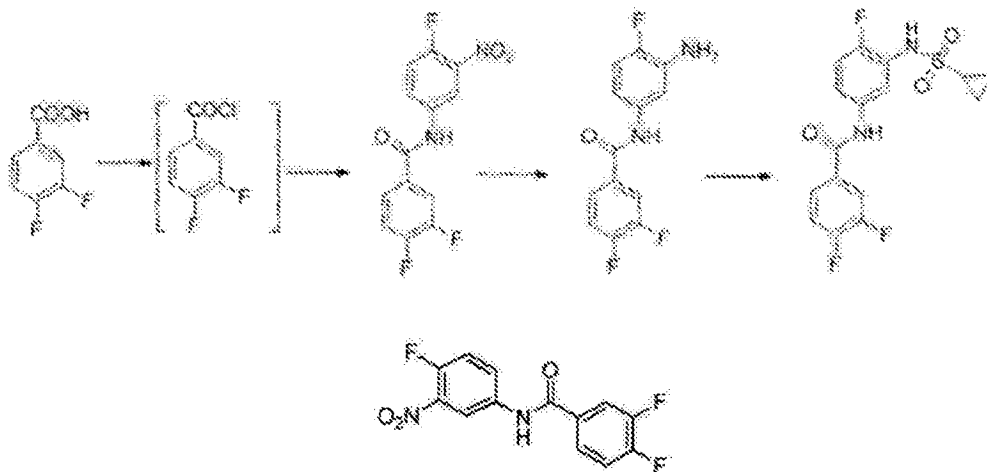
[1461]



[1462] N-(3-(N-环丙基氨磺酰基)-4-氟苯基)-3,4-二氟苯甲酰胺: 向 5-氨基-N-环丙基-2-氟苯磺酰胺 (2g)、 CH_2Cl_2 (50ml) 和 Et_3N (1.8g) 的混合物中逐滴添加 3,4-二氟苯甲酰氯 (1.5g)。在环境温度下搅拌所得反应混合物 2 小时直至反应完成。过滤产物, 并且用 CH_2Cl_2 洗涤两次并在真空烘箱中在 50°C 下干燥。1.3g, 呈白色固体状。产率 62%。HPLC 纯度: 96%。LC-MS, 计算值: 370.0, 测量值: $[\text{M}+1] = 371.0$ 。 ^1H NMR ($\text{DMSO}-d_6$, Broker Avance 400MHz) δ : 0.42 (2H, m), 0.49 (2H, m), 2.25-2.36 (1H, m), 7.45-7.48 (1H, t), 7.62-7.67 (1H, dd), 7.89 (1H, brs,), 8.05-8.11 (2H, m), 8.20-8.32 (2H, m), 10.62 (1H, s)

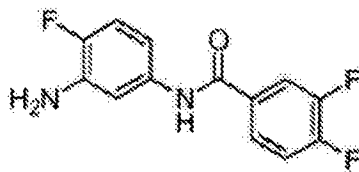
[1463] N-(3-(环丙烷亚磺酰氨基)-4-氟苯基)-3,4-二氟苯甲酰胺的合成:

[1464]



[1465] 3,4-二氟-N-(4-氟-3-硝基苯基)苯甲酰胺: 将 3,4-二氟苯甲酸 (1g) 溶解于 CH_2Cl_2 (10ml) 中。向溶液中添加草酰氯 (1ml)。在环境温度下搅拌反应混合物 30 分钟直至反应完成。汽提去除溶剂, 并且添加 CH_2Cl_2 (20ml), 冷却所得溶液至 -5°C , 接着添加 Et_3N (2ml), 随后添加 3-硝基-4-氟苯胺 (1g)。在环境温度下搅拌反应混合物 30 分钟直至反应完成。汽提去除溶剂, 并且获得 3g 呈固体状的 3,4-二氟-N-(4-氟-3-硝基苯基)苯甲酰胺。

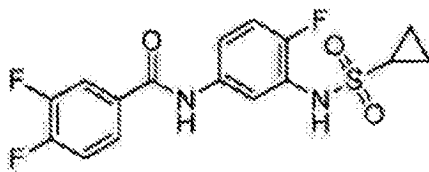
[1466]



[1467] N-(3-氨基-4-氟苯基)-3,4-二氟苯甲酰胺: 将 3,4-二氟-N-(4-氟-3-硝基苯

基) 苯甲酰胺 (2g) 溶解于 1, 4- 二噁烷 (40ml) 中, 接着添加 6N HCl (6ml) 和 SnCl_2 (8g)。在环境温度下搅拌反应混合物 4 小时直至反应完成。将反应混合物倾入 1N NaOH 溶液中, 并且用 EtOAc 萃取两次。有机层用盐水溶液洗涤, 并且通过旋转蒸发器来汽提去除溶剂并获得 1.24g 呈油状的 N-(3- 氨基 -4- 氟苯基)-3, 4- 二氟苯甲酰胺。粗产物不经进一步纯化即使用。

[1468]



[1469] N-(3-(环丙烷亚磺酰氨基)-4- 氟苯基)-3, 4- 二氟苯甲酰胺 : 将 N-(3- 氨基 -4- 氟苯基)-3, 4- 二氟苯甲酰胺 (12.4g) 溶解于吡啶 (15ml) 中, 接着添加 DMAP (100mg) 和环丙烷磺酰氯 (0.65g)。将反应混合物在环境温度下搅拌过夜直至反应完成。将反应混合物倾入水 (100ml) 中, 并且用 EtOAc 萃取两次。有机层用水洗涤, 并且用无水 Na_2SO_4 干燥。通过旋转蒸发器来汽提去除溶剂, 并且通过于 MTBE (20ml) 中浆化来纯化固体产物。获得 800mg 呈灰白色固体状的 N-(3-(环丙烷亚磺酰氨基)-4- 氟苯基)-3, 4- 二氟苯甲酰胺。 ^1H NMR (300MHz, CDCl_3): δ 7.8-7.10 (m, 6H), 6.6 (bs, 1H), 2.58 (m, 1H), 1.21 (m, 2H), 1.0 (m, 2H)。MS (ESI) (m/z) 观测值 : (M+1) = 371。HPLC 纯度 : 98%。LC-MS : 计算值 : 370.0 ; 测量值 : [M+1] = 371.0

[1470] 程序

[1471] 以下程序可用于评估和选择作为 HBV 感染的抑制剂的化合物。

[1472] 本发明的 HBV 复制抑制剂能够治疗和预防与 HBV 感染相关的疾病。表 21 至 39 中呈现的结果证明通过使用标准 MTT 测定 (Promega), 直至 50 μM , 本发明化合物抑制永生化鼠类肝细胞 (AML12) 源性稳定细胞系 (AML12HBV10) 中的 HBV 复制而无可测量细胞毒性, 所述细胞系支持以四环素诱导性方式达成强力 HBV 复制。

[1473] 测定本公开的化合物在 AML12HBV10 细胞中的抗病毒功效, 如表 21 至 39 中所呈现。AML12HBV10 是一种永生化鼠类肝细胞 (AML12) 源性稳定细胞系, 其支持以四环素诱导性方式达成强力 HBV 复制 (Xu 等)。将细胞以每孔 2×10^4 个细胞的密度接种至 96 孔板中, 并且在具有 10% 胎牛血清的 DMEM/F12 培养基中不存在四环素下培养以允许 pgRNA 转录和 HBV DNA 复制。在接种之后一天, 使细胞不处理或用测试化合物的在 50 μM 至 0.39 μM 的范围内的连续稀释液处理 48 小时。接着通过添加 100 μl 含有 10mM Tris-HCl (pH 7.6)、1mM EDTA、100mM NaCl 和 1% NP-40 的裂解缓冲液至各孔中来裂解细胞, 并且在 37°C 下孵育 30 分钟。使来自各孔的一半量 (50 μl) 的细胞裂解物与相等体积的含有 0.5N NaOH 和 1.5M NaCl 的变性溶液合并。在孵育 5 分钟之后, 添加 100 μl 中和溶液 (1M Tris-HCl (pH 7.4)、1.5M NaCl) 至各孔中。使用 96 孔斑点印迹歧管 (Biorad) 将变性的细胞裂解物 (总计 200 μl) 施加于尼龙膜上。通过与 α - ^{32}P -UTP 标记的对 HBV 负链 DNA 具有特异性的核糖探针进行斑点印迹杂交来测定细胞裂解物中的 HBV DNA。本公开的化合物的抗病毒功效表示为使 HBV DNA 的量降低 50% 的浓度 (EC_{50})。

[1474] 测定本公开的化合物在 AML12HBV10 细胞中的细胞毒性 : 为测定化合物的细胞毒

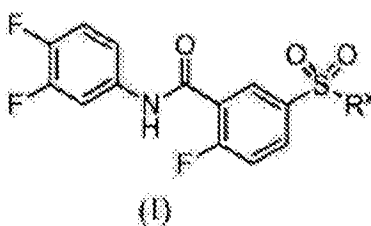
性,将 AML12HBV10 细胞以每孔 2×10^4 个细胞的密度接种至 96 孔板中,并且在具有 10% 胎牛血清的 DMEM/F12 培养基中不存在四环素下培养以允许 pgRNA 转录和 HBV DNA 复制。在接种之后一天,使细胞不处理或用测试化合物的在 $50 \mu\text{M}$ 至 $0.39 \mu\text{M}$ 的范围内的连续稀释液处理 48 小时。通过 MTT 测定,遵循由制造商 (Promega) 提供的程序测量细胞活力。化合物的细胞毒性表示为使细胞活力降低 50% 的化合物浓度 (CC_{50})。

[1475] 测定本公开的化合物在人肝细胞瘤源性细胞系中的抗病毒活性,如表 21 至 39 中所呈现:为进一步确认本公开的化合物针对人肝细胞源性细胞中的 HBV 的抗病毒活性,将 HepDES19 细胞 (即支持以四环素诱导性方式达成 HBV 复制的人肝细胞瘤细胞系 (Guo 等, 2007) 以每孔 5×10^5 个细胞的密度接种至 12 孔板中,并且在具有 10% 胎牛血清和 $1 \mu\text{g/ml}$ 四环素的 DMEM/F12 培养基中培养。在接种之后两天,对细胞进行模拟处理,或用本公开的化合物的在 $10 \mu\text{M}$ 至 $0.018 \mu\text{M}$ 的范围内的连续稀释液不存在四环素下处理 6 天。在完成处理后,通过添加 0.5ml 裂解缓冲液至 12 孔板的各孔中并在 37°C 下孵育 10 分钟来裂解细胞,所述裂解缓冲液含有 10mM Tris-HCl (pH 8.0)、1mM EDTA、1% NP40 和 2% 蔗糖。通过离心来移除细胞碎片和核,并且使上清液与 $130 \mu\text{l}$ 含有 1.5M NaCl 的 35% 聚乙二醇 (PEG)8000 混合。在于冰中孵育 1 小时之后,通过在 4°C 下在 $6,000 \times g$ 下离心 5 分钟来沉淀病毒核衣壳,随后在 37°C 下于 $400 \mu\text{l}$ 消化缓冲液中消化 1 小时,所述消化缓冲液含有 0.5mg/ml 链霉蛋白酶 (Calbiochem)、0.5% SDS、150mM NaCl、25mM Tris-HCl (pH 8.0) 和 10mM EDTA。消化混合物用苯酚萃取两次,并且 DNA 用乙醇沉淀,溶解于 TE 缓冲液 (10mM Tris-HCl, pH 8.0 ; 0.1mM EDTA) 中。通过电泳至 1.5% 琼脂糖凝胶中来解析来自各孔的一半 DNA 样本。接着使凝胶经受于含有 0.5M NaOH 和 1.5M NaCl 的溶液中的变性,随后于含有 1M Tris-HCl (pH 7.4) 和 1.5M NaCl 的缓冲液中中和。接着在 20X SSC 缓冲液中将 DNA 印迹于 Hybond-XL 膜 (GE Health care) 上。通过 DNA 印迹杂交来测定细胞质 HBV 核心相关的 HBV DNA 的量,并且化合物的抗病毒功效表示为它的使 HBV DNA 的量降低 50% (EC_{50}) 或 90% (EC_{90}) 的浓度。

[1476] 测定本公开的化合物在人肝细胞瘤源性细胞系中的细胞毒性,将 HepDES19 细胞以每孔 6×10^4 个细胞的密度接种至 96 孔板中,并且在具有 10% 胎牛血清的 DMEM/F12 培养基中不存在四环素下培养。在接种之后一天,使细胞不处理或用测试化合物的在 $50 \mu\text{M}$ 至 $0.39 \mu\text{M}$ 的范围内的连续稀释液处理 6 天。通过 MTT 测定,遵循由制造商 (Promega) 提供的程序测量细胞活力。化合物的细胞毒性表示为使细胞活力降低 50% 的化合物浓度 (CC_{50})。

[1477] 表 21 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu\text{M}$; 1 = $5\text{--}10 \mu\text{M}$; 2 = $1\text{--}5 \mu\text{M}$; 3 = $<1 \mu\text{M}$ 。

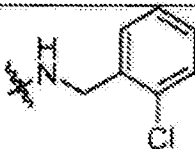
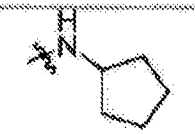
[1478]



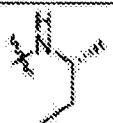
[1479]

R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}

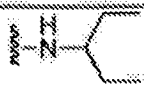
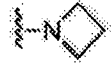
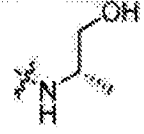
[1480]

	2	3
	2	3
	2	3
	3	3
	3	3
	3	3

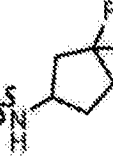
[1481]

R ^s	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	1	-
	2	-
	3	3
	3	3
	3	-

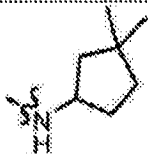
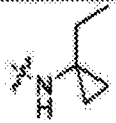
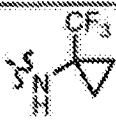
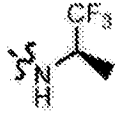
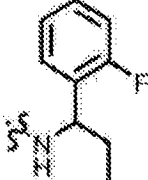
[1482]

	3	3
	1	-
	3	3
	0	-
	2	-
	1	-
	0	-
	3	2
	3	-
	2	-
	1	-
	3	3
	3	3

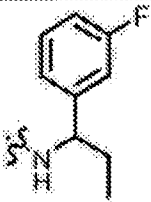
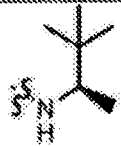
[1483]

	2	2
	3	3
	2	-
	3	3
	2	-
	3	3
	3	3
	3	-
	3	-

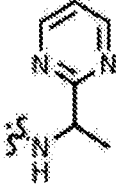
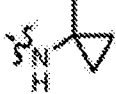
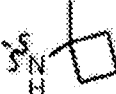
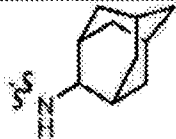
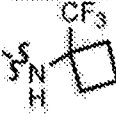
[1484]

	3	-
	3	3
	3	-
	3	3
	3	-
	3	-
	3	-
	3	-

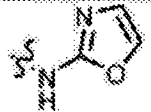
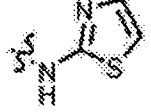
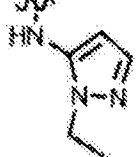
[1485]

	3	-
	3	-
	3	3
	3	3
	3	3
	3	3
	3	3

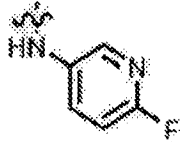
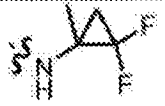
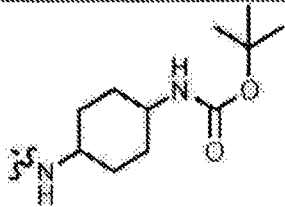
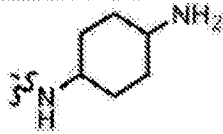
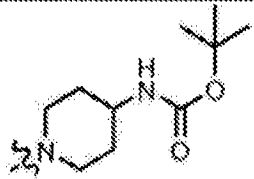
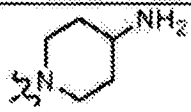
[1486]

	3	-
	2	-
	3	3
	3	3
	3	3
	3	3
	3	2
	3	3

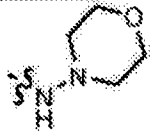
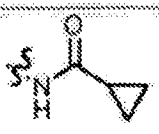
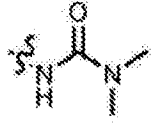
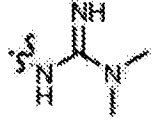
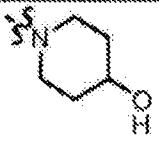
[1487]

	2	-
	0	-
	0	-
	0	-
	1	-
	3	3
	3	-
	0	-

[1488]

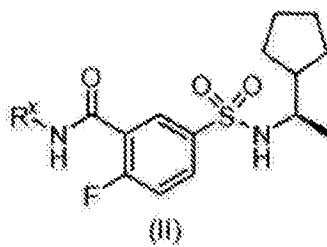
	0	-
	2	-
	3	-
	0	-
	0	-
	0	-
	3	-
	2	-

[1489]

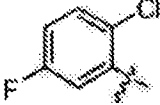
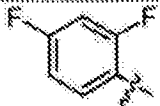
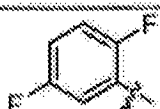
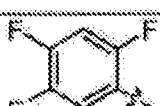
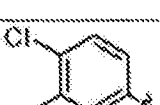
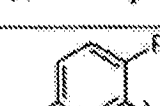
	0	-
	0	-
	2	-
	3	-
	0	-
	0	-
	0	-
	0	-

[1490] 表 22 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1491]

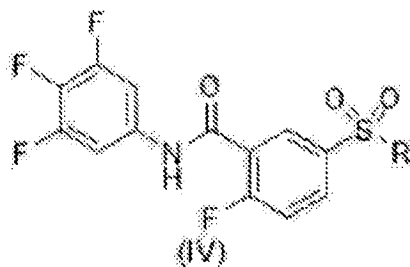


[1492]

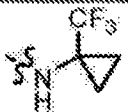
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	0	-
	1	-
	2	-
	2	-
	2	-
	1	-
	3	-
	0	-

[1493] 表 23 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀ 关键值 : 0 = >10 μM ; 1 = 5-10 μM ; 2 = 1-5 μM ; 3 = <1 μM。

[1494]

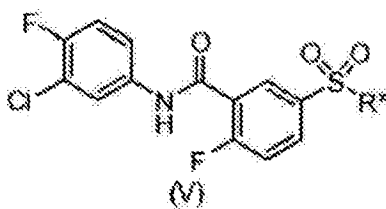


[1495]

R	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	3	-
	3	-
	3	-

[1496] 表 24 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀ 关键值 : 0 = >10 μM ; 1 = 5-10 μM ; 2 = 1-5 μM ; 3 = <1 μM。

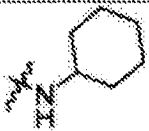
[1497]



[1498]

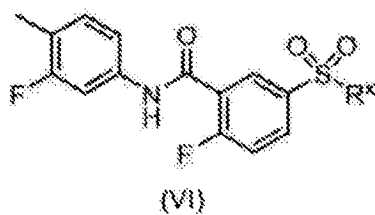
R ^x	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	2

[1499]

	2	-
	1	-
	3	3
	3	-

[1500] 表 25 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值: 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

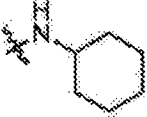
[1501]



[1502]

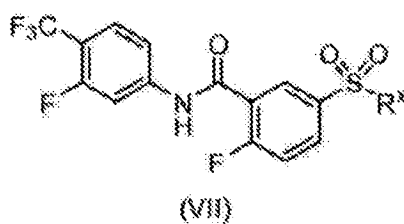
R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	1	-
	0	-
	0	-

[1503]

	0	-
	0	-
	0	-

[1504] 表 26 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1505]

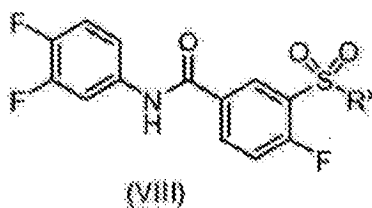


[1506]

R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	0	-

[1507] 表 27 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

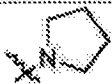
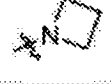
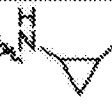
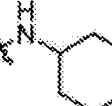
[1508]



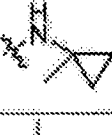
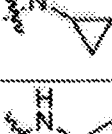
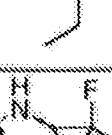
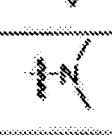
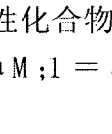
[1509]

R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}

[1510]

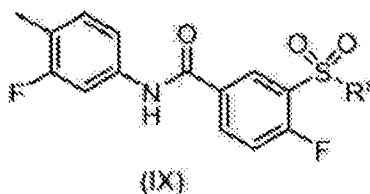
	3	2
	3	2
	3	2
	3	3
	3	3
	2	3
	3	-
	2	-
	3	-
	3	-
	3	3
	2	-

[1511]

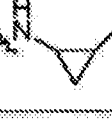
	0	-
	3	-
	3	2
	2	-
	0	-
	2	-

[1512] 表 28 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1513]

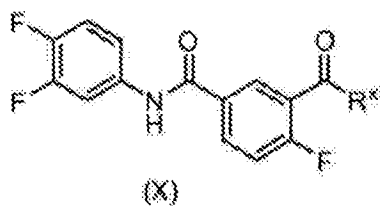


[1514]

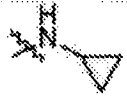
R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	0	-

[1515] 表 29 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1516]

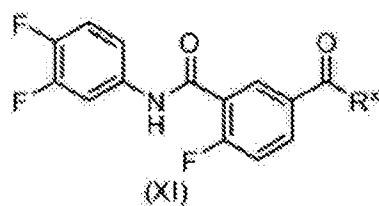


[1517]

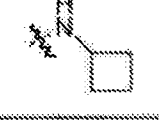
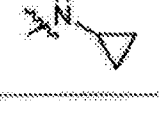
R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	2	~

[1518] 表 30 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1519]

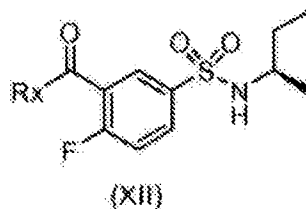


[1520]

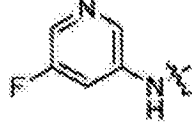
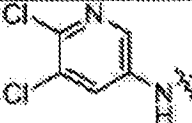
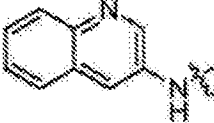
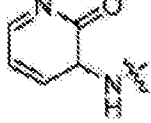
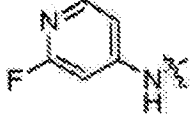
R^x	AML12HBV10	HepDES19
	EC_{50}	EC_{50}
	2	~
	0	~
	0	~
	0	~

[1521] 表 31 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

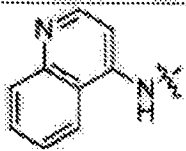
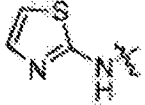
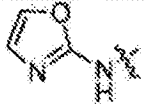
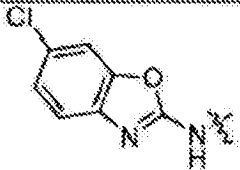
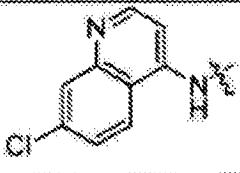
[1522]



[1523]

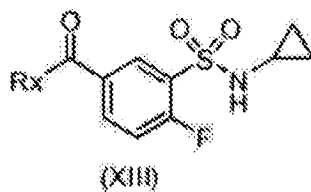
Rx	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	2	-
	2	-
	0	-
	0	-
	0	-
	0	-
	0	-

[1524]

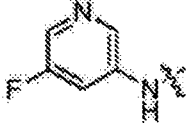
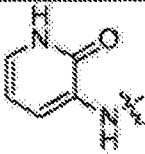
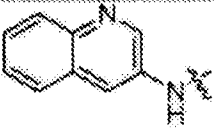
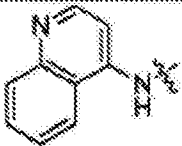
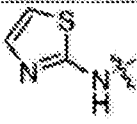
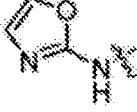
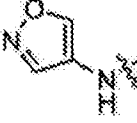
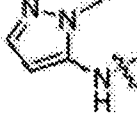
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-

[1525] 表 32 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性, 在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

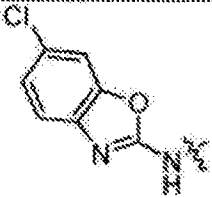
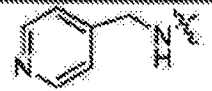
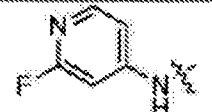
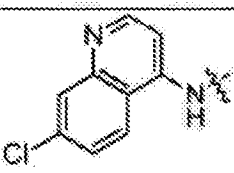
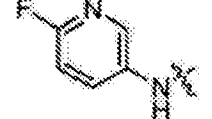
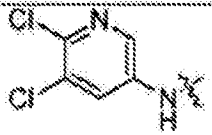
[1526]



[1527]

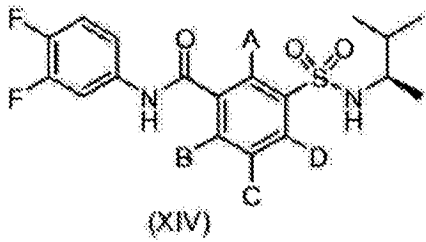
Rx	AML12HBV10	HepDES19
	EC ₅₀	EC ₅₀
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-
	0	-

[1528]

	0	~
	0	~
	0	~
	0	~
	0	~
	0	~
	0	~

[1529] 表 33 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀ 关键值 : 0 = >10 μ M ; 1 = 5-10 μ M ; 2 = 1-5 μ M ; 3 = <1 μ M。

[1530]

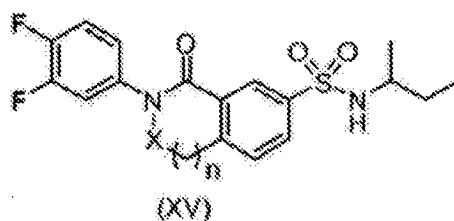


[1531]

A	B	C	D	AML12HBV10	HepDES19
				EC ₅₀	EC ₅₀
H	Cl	H	H	3	-
H	OMe	H	H	3	3
H	F	H	F	2	-
H	Me	H	H	3	3

[1532] 表 34 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀ 关键值 : 0 = >10 μM ; 1 = 5-10 μM ; 2 = 1-5 μM ; 3 = <1 μM。

[1533]

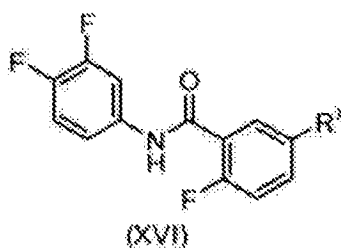


[1534]

X	n	AML12HBV10	HepDES19
		EC ₅₀	EC ₅₀
CH ₂	1	0	-

[1535] 表 35 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀ 关键值 : 0 = >10 μM ; 1 = 5-10 μM ; 2 = 1-5 μM ; 3 = <1 μM。

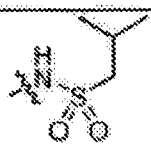
[1536]



[1537]

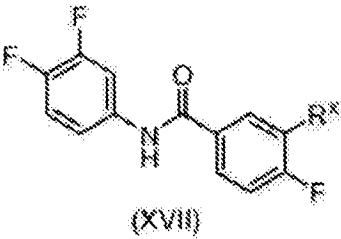
R _x	AML12HBV10	HepDES19
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[1538]

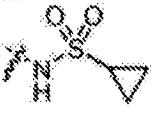
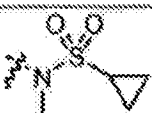
	EC50	EC50
-NO ₂	1	~
-NH ₂	1	~
	2	0
	2	~

[1539] 表 36 :示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC₅₀关键值 :0 = >10 μ M ;1 = 5-10 μ M ;2 = 1-5 μ M ;3 = <1 μ M。

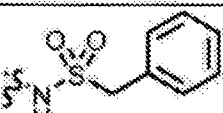
[1540]



[1541]

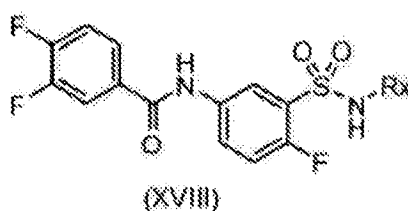
Rx	AML12HBV10 EC50	HepDES19 EC50
-NO ₂	0	~
-NH ₂	0	~
	3	2
	0	0

[1542]

	0	0
	0	0

[1543] 表 37 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1544]

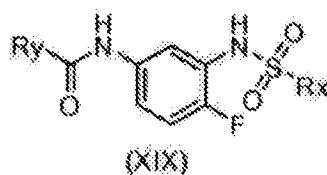


[1545]

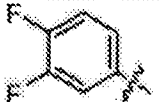
Rx	AML12HBV10 EC50	HepDES19 EC50
	0	-

[1546] 表 38 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1547]

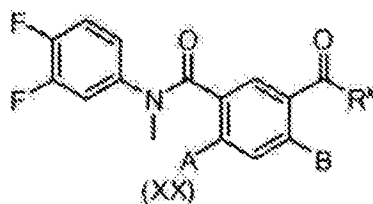


[1548]

Rx	Ry	AML12HBV10 EC50	HepDES19 EC50
		0	-

[1549] 表 39 : 示例性化合物在 AML12HBV10 和 HepDES19 细胞中的抗病毒活性。在表中, EC_{50} 关键值 : 0 = $>10 \mu M$; 1 = $5-10 \mu M$; 2 = $1-5 \mu M$; 3 = $<1 \mu M$ 。

[1550]



[1551]

R ^x	A	B	AML12HBV10	HepDES19
			EC ₅₀	EC ₅₀
	F	H	2	-
	H	F	0	-

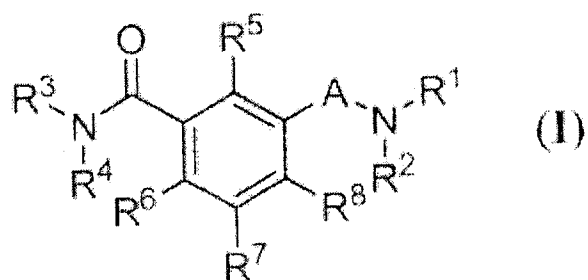
[1552] 应了解,尽管本发明已连同其优选特定实施方案一起加以描述,但前述描述和随后实施示意图说明而非限制本发明的范围。本领域技术人员将了解,可在不脱离本发明的范围下进行各种变化,并且可用等效物进行替换,并且此外其它方面、优势和修改将为本发明所属领域技术人员显而易见。除本文所述的实施方案之外,本发明涵盖和要求保护由组合本文引用的本发明特征和所引用现有技术参考文献的补充本发明特征的那些特征所产生的那些发明物。类似地,应了解,任何所述物质、特征或物品都可与任何其它物质、特征或物品组合使用,并且所述组合被视为在本发明的范围内。

[1553] 本文件中引用或所述的各专利、专利申请和出版物的公开内容都据此出于所有目的以引用的方式各自整体并入本文。

NOVEL ANTIVIRAL AGENTS AGAINST HBV INFECTION

Abstract

The present invention is directed toward novel compounds and novel methods of use of said compounds of the formula (I), useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions. (Formula (I)) Including hydrates, solvates, pharmaceutically acceptable salts, prodrugs and complexes thereof, wherein A, R1, R2, R3, R4, R5, R6, R7, and R8 are defined herein.



针对 HBV 感染的新型抗病毒剂

摘要

本发明涉及式(I)的新型化合物和使用所述化合物的新型方法，所述化合物用作作用于处理病毒的核衣壳装配抑制剂，尤其但不限于包括用于治疗乙型肝炎病毒(HBV)感染和相关病状的 HBV 前基因组 RNA 衣壳化抑制剂。(式(I))包括其水合物、溶剂合物、药学上可接受的盐、前药和复合物，其中 A、R1、R2、R3、R4、R5、R6、R7 和 R8 在本文中定义。

