

**Use and Pharmaceutical Composition of Phenylisoxazolyl Methylene-Naphthalene-Ether
Derivatives**

Technical Field

5 The present invention relates to the field of pharmaceuticals for treating or preventing hepatitis B virus (HBV) infection. Specifically, the present invention relates to the use of phenylisoxazolyl methylene-naphthalene-ether derivatives for the treatment or prevention of HBV infection, pharmaceutical compositions comprising phenylisoxazolyl methylene-naphthalene-ether derivatives and other anti-HBV agents, and pharmaceutical use of
10 phenylisoxazolyl methylene-naphthalene-ether derivatives.

Background Art

 Hepatitis B virus (HBV) is a hepatotropic, enveloped, partially double-stranded DNA virus. It is most commonly spread from mother to child at birth (perinatal transmission) and
15 also can be transmitted by blood or body fluid.

 HBV generates a covalently closed circular DNA (cccDNA), secretes HBV surface antigen to suppress the immune system, and caused persistent (chronic) infection which is hard to eradicate. HBV infection is a major public health threat in the world with over 257 million people chronically infected and caused over 887000 deaths every year. (Revill, P.A.
20 et al, Lancet Gastroenterol. Hepatol. 2019, 4(7), 545-558). In the Asia-Pacific region, chronic hepatitis B virus (HBV) infection caused more than half of the deaths due to liver cirrhosis and about half the cases of hepatocellular carcinoma in the region (Sarin, S.K. et al Lancet Gastroenterol. Hepatol., 2020, 5(2):167-228). In a meta-analysis of 27 studies, it was reported that the pooled estimated prevalence of HBV infection in the general
25 population of China from 2013 to 2017 was 6.89% (Wang, H. et al BMC Infect Dis 2019, 19(1), 811).

 Currently, treatments for HBV infection are very limited. Approved treatments include nucleot(s)ide inhibitors, such as Tenofovir disoproxil (Viread), Tenofovir alafenamide (Vemlidy), Entecavir (Baraclude), Telbivudine (Tyzeka or Sebivo), Lamivudine
30 (Epivir-HBV, Zeffix, or Heptodin) and immunomodulators, such as pegylated Interferon alfa-2a (Pegasys). Thus, novel treatments are urgently needed. (Fanning, G.C, Nat. Rev. Drug Discov, 2019, 18(11), 827-844).

 Farnesoid X receptor (FXR) is a member of the nuclear receptor family, which

includes steroid receptors, retinoid receptors, and thyroid hormone receptors (Radreau P, Porcherot M, Ramière C, et al. Reciprocal regulation of farnesoid X receptor α activity and hepatitis B virus replication in differentiated HepaRG cells and primary human hepatocytes. FASEB J. 2016;30(9):3146-54). FXR is mainly expressed in the liver, kidney, small intestine and adrenal glands. After HBV infects cells, HBV cccDNA enters the nucleus and begins to transcribe a variety of HBV RNAs. The pregenomic RNA is reverse-transcribed to form HBV DNA, and the remaining RNAs are translated to form HBsAg, HBeAg, HBcAg, HBx, etc. These viral proteins and nucleic acids are assembled together in the endoplasmic reticulum, and then virus particles are formed and are released out of cells. In the life cycle of HBV, the transcription of HBV cccDNA can be regulated by nuclear receptors, such as HNF-4 α and FXR. In vitro experiments have confirmed that FXR agonists inhibit the formation of stable transcription complexes between cccDNA and HBx by activating FXR, thereby affecting the stability of cccDNA, inhibiting the transcriptional activity of cccDNA, and achieving the purpose of reducing viral DNA and HBsAg (Mouzannar K, Fusil F, Lacombe B, et al. Farnesoid X receptor- α is a proviral host factor for hepatitis B virus that is inhibited by ligands in vitro and in vivo. FASEB J. 2019; 33(2):2472-2483).

Disclosure of the Invention

The inventors of the present invention found that the phenylisoxazolyl methylene-naphthalene-ether derivatives represented by formula (I), as an efficient small molecule FXR agonist, has anti-HBV activity. In vitro primary human hepatocyte infection test results show that the phenylisoxazolyl methylene-naphthalene-ether derivatives represented by formula (I) can effectively inhibit HBV DNA, HBV RNA and HBsAg.

Thus, the present invention relates to the use of phenylisoxazolyl methylene-naphthalene-ether derivatives for the treatment or prevention of HBV infection, pharmaceutical compositions comprising phenylisoxazolylmethylene-naphthalene-ether derivatives and other anti-HBV agents, and pharmaceutical use of phenylisoxazolyl methylene-naphthalene-ether derivatives.

Definitions

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural, and vice versa.

As used herein, the term “C₁₋₆ alkyl” denotes an alkyl radical having from 1 up to 6, particularly up to 4 carbon atoms, the radicals being either linear or branched with single or multiple branching, for example, butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl; propyl, such as n-propyl or isopropyl; ethyl or methyl; more particularly, methyl, iso-propyl or
5 tert-butyl.

As used herein, “C₁₋₆ alkoxy” refers to “C₁₋₆ alkyl-O-”, and is particularly methoxy, ethoxy, isopropoxy or tert-butoxy.

As used herein, the term “C₃₋₆ cycloalkyl” refers to a cyclic alkyl radical having 3 to 6 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The C₃₋₆
10 cycloalkyl can be optionally substituted by C₁₋₆ alkyl and/or halogen.

As used herein, the term “C₄₋₇ alkylcycloalkyl” refers to a combination of alkyl and a cycloalkyl group such that the total number of carbon atoms is 4 to 7. For example, C₄ alkylcycloalkyl includes methylenecyclopropyl.

As used herein, the term “5-10 membered aryl” refers to a 5-10 membered monocyclic-
15 or bicyclic- or tricyclic-aromatic ring system. Typically, the aryl is a 5 or 6 membered ring system.

As used herein, the term “5-10 membered heteroaryl” refers to a 5-10 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system having 1 to 4 heteroatoms. Typically, the heteroaryl is a 5 or 6 membered ring system. Furthermore, the term “heteroaryl” as used
20 herein may encompass monovalent or divalent heteroaryls.

As used herein, the term “halogen” or “halo” refers to one or more of fluoro, chloro, bromo and iodo, and more particularly, fluoro or chloro.

As used herein, the term “C₁₋₆ haloalkyl” refers to an alkyl radical that is substituted by one or more halo radicals, and is particularly C₁₋₆ fluoroalkyl or C₁₋₆ chloroalkyl, such as
25 trifluoromethyl and 2,2,2-trifluoroethyl.

As used herein, the term “pharmaceutically acceptable salts” refers to salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

As used herein, the term “pharmaceutically acceptable auxilliary materials” may include
30 any or all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents and antifungal agents), isotonic agents, absorption delaying agents, salts, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents,

flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art. Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

As used herein, "hepatitis B virus" or "HBV" refers to a member of the Hepadnaviridae family having a small double-stranded DNA genome of approximately 3,200 base pairs and a tropism for liver cells. "HBV" includes hepatitis B virus that infects any of a variety of mammalian (e.g., human, non-human primate, etc.) and avian (duck, etc.) hosts. "HBV" includes any known HBV genotype, e.g., serotype A, B, C, D, E, F, and G; any HBV serotype or HBV subtype; any HBV isolate; HBV variants, e.g., HBeAg-negative variants, drug-resistant HBV variants (e.g., lamivudine-resistant variants; adefovir-resistant mutants; tenofovir-resistant mutants; entecavir-resistant mutants; etc.); and the like.

As used herein, the term "therapeutically effective amount" refers to an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors. The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and a nucleos(t)ide analogue, in a pharmaceutically acceptable carrier.

Unless specified otherwise, the term "compound of formula (I)" includes phenylisoxazolyl methylene-naphthalene-ether derivatives of the formula (I), prodrugs thereof, salts of the compound and/or prodrugs, hydrates or solvates of the compound, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers isotopically labeled compounds (including deuterium substitutions) and polymorphs of the compound.

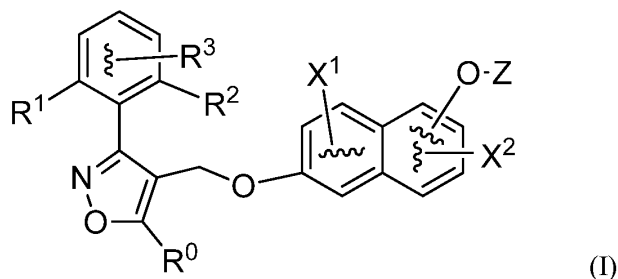
Salts of the compound of formula (I) may be made by methods known to a person skilled in the art. For example, treatment of a compound of formula (I) with an appropriate base or acid in an appropriate solvent will yield the corresponding salt.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compound of formula (I). Preferred are alkaline salts of the carboxylic acid, such as

sodium, potassium, lithium, calcium, magnesium, aluminium, zinc, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of formula (I) and these should be considered
5 to form a further aspect of the invention.

All starting materials, reagents, acids, bases, solvents and catalysts utilized to synthesize the compounds of formula (I) are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly
10 contradicted by context. The use of any and all examples, or exemplary language (e.g. such as) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

In one aspect, the present invention provides a method of treating or preventing
15 infection with hepatitis B virus in a human or animal, comprising administering to the human or animal in need thereof a therapeutically effective amount of a phenylisoxazolyl methylene-naphthalene-ether derivatives having a structure of formula (I), and a pharmaceutically acceptable salt, ester or stereoisomer thereof:



20 wherein:

R¹, R² and R³ are independently selected from H, halogen, and unsubstituted or halogen substituted C₁₋₆ alkyl and unsubstituted or halogen substituted C₁₋₆ alkoxy, provided that at least one of R¹, R² and R³ is not hydrogen, R⁰ is selected from unsubstituted or halogen substituted C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₄₋₇ alkylcycloalkyl;

25 X¹ and X² are independently selected from H and halogen;

moiety -O-Z (residue Z linked to the naphthalene ring via an oxygen atom) attaches to the naphthalene ring, wherein Z is a residue selected from 5-10 membered aryl or 5-10

membered heteroaryl optionally having one or more hetero atoms selected from N, O and S, wherein the 5-10 membered aryl or 5-10 membered heteroaryl is substituted by R⁴ and is optionally further substituted by R⁵;

5 wherein R⁴ is selected from -COOH, -CH₂COOH, -NHSO₂CF₃, -SO₂NH-C₁₋₆ alkyl, -SO₃H, -CONHSO₂-C₁₋₆alkyl, -CONHSO₂-C₃₋₆cycloalkyl, -CONHSO₂-5-10 membered aryl and -CONHSO₂-5-10 membered aryl substituted by C₁₋₆ alkyl at the aryl, and R⁵ is selected from H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, -O-(C₁₋₆ alkyl) and -NH-(C₁₋₆ alkyl).

In preferred embodiments of the present invention, R¹, R² and R³ are independently selected from H, halogen and C₁₋₃ perfluoroalkoxy, such as H, Cl, F and -O-CF₃. In one embodiment of the invention, both of R¹ and R² are Cl, and R³ is H. In another embodiment of the invention, both of R¹ and R² are Cl, and R³ is F. In still another embodiment of the invention, both of R¹ and R² are Cl, and R³ is -O-CH₃. In yet another embodiment of the invention, R¹ is -O-CF₃, and both of R² and R³ are H. In yet another embodiment of the invention, R⁰ is isopropyl or cyclopropyl.

15 In one embodiment of the present invention, Z is a phenyl, which is optionally substituted by 1-5 halogen atoms. In another embodiment of the present invention, Z is a 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S. In a preferred embodiment of the present invention, Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S. In yet another embodiment of the present invention, Z is a R⁴ and optionally R⁵ substituted pyridyl.

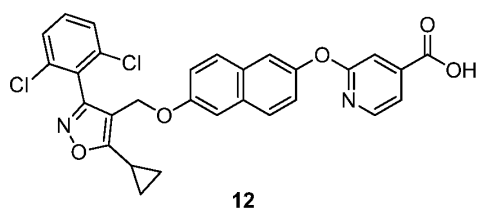
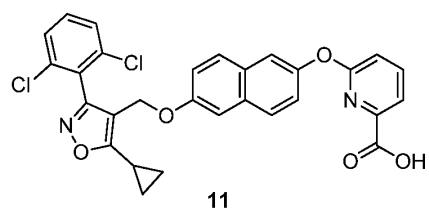
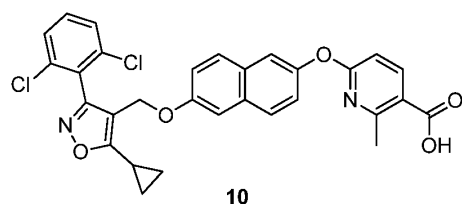
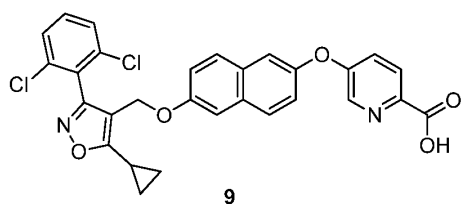
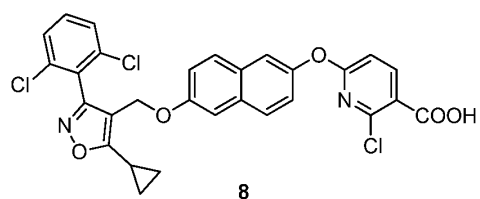
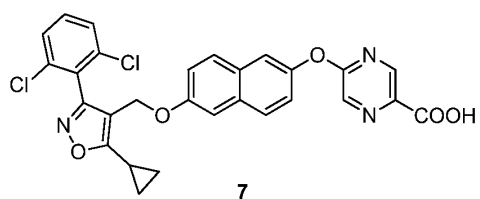
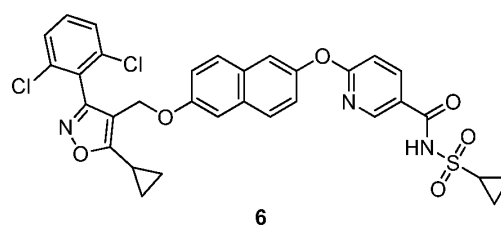
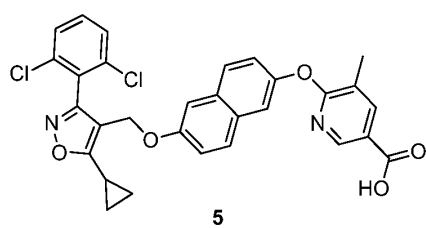
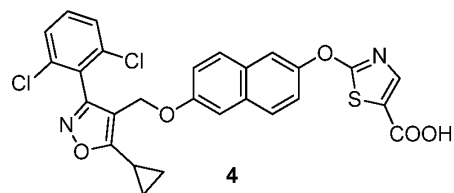
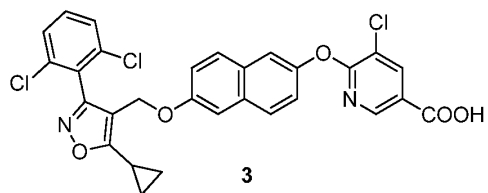
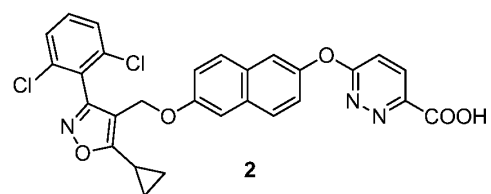
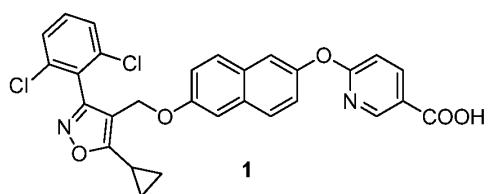
In preferred embodiments of the present invention, R⁴ is selected from -COOH, -CH₂COOH, -CONHSO₂-C₁₋₆ alkyl and -CONHSO₂-C₃₋₆ cycloalkyl. In more preferred embodiment of the present invention, R⁴ is -COOH or -CH₂COOH. In a most preferred embodiment of the present invention, R⁴ is -COOH.

25 Preferably, R⁵ is one selected from H, C₁₋₃ alkyl and halogen.

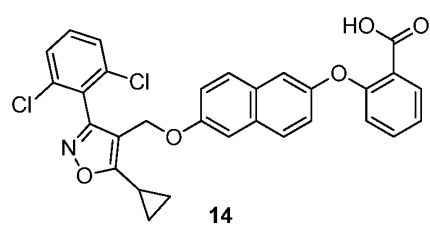
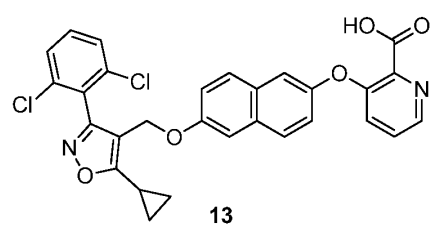
In a preferred embodiment of the present invention, Z is pyridyl; R⁴ is -COOH; and R⁵ is H or halogen.

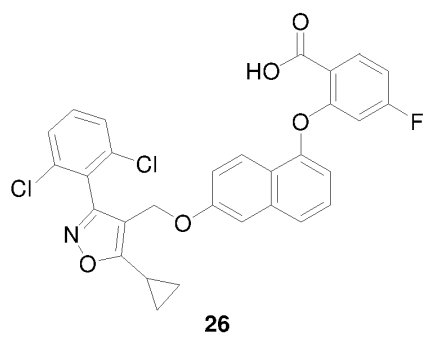
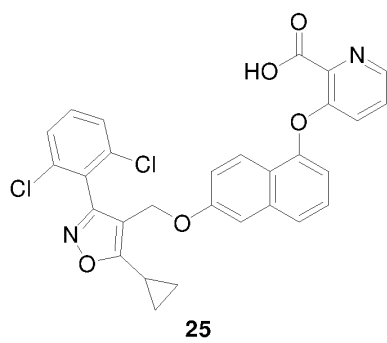
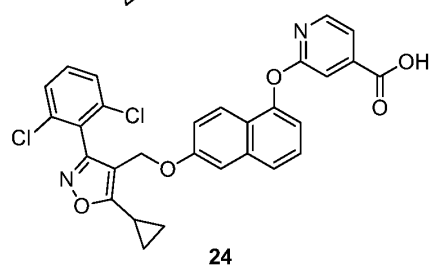
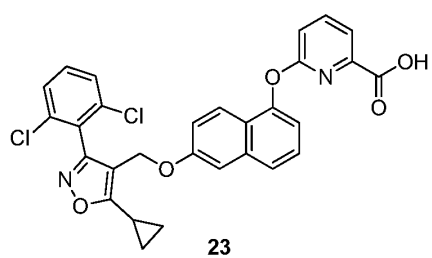
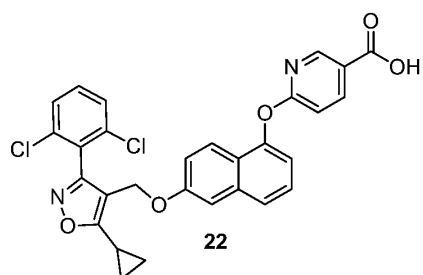
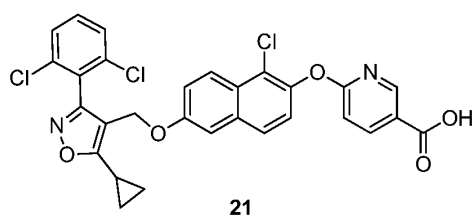
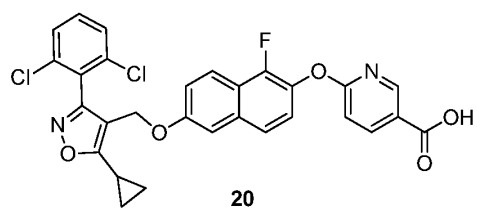
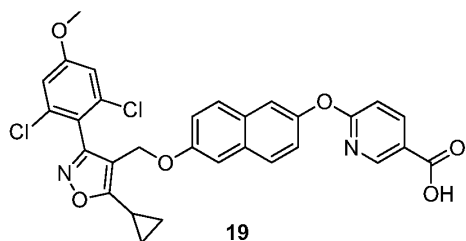
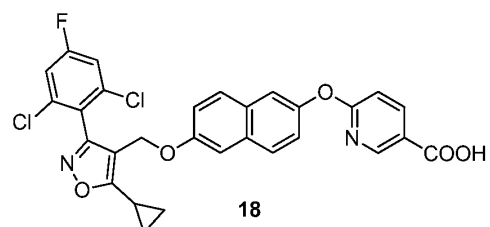
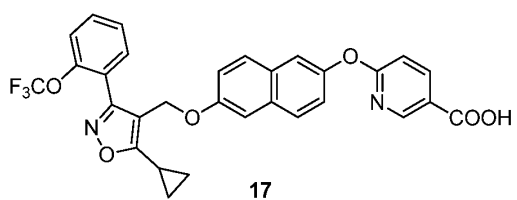
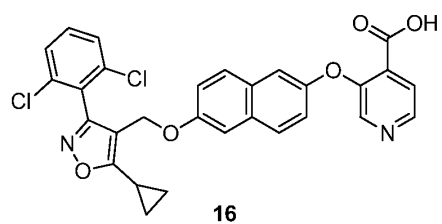
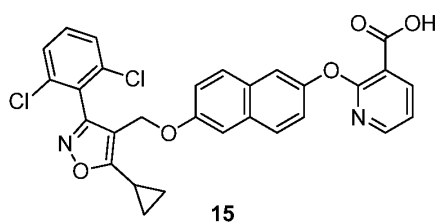
Preferably, the halogen in the aforesaid substituents is fluoro or chloro.

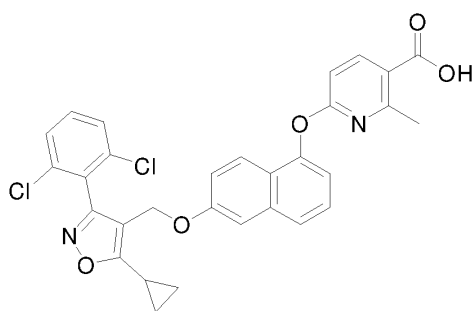
Specifically, in preferred embodiments of the present invention, the compound having the 30 formula (I) is of one of the following structures:



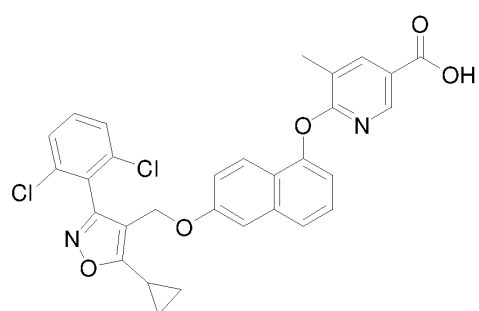
5



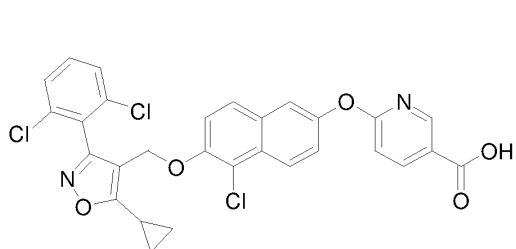




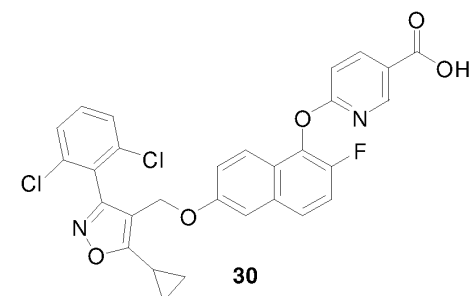
27



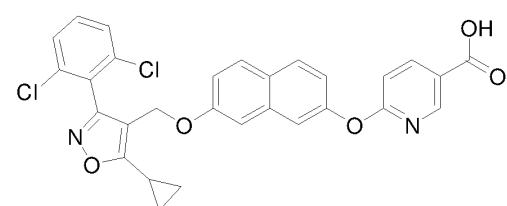
28



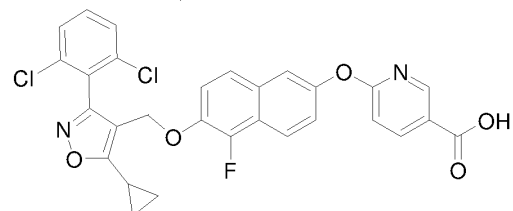
29



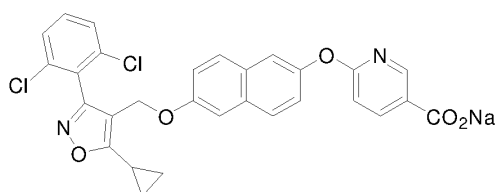
30



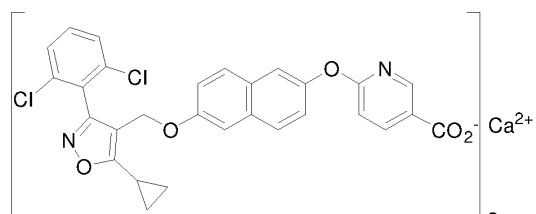
31



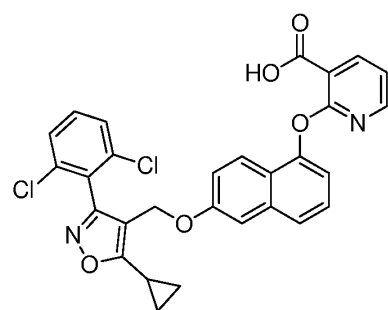
32



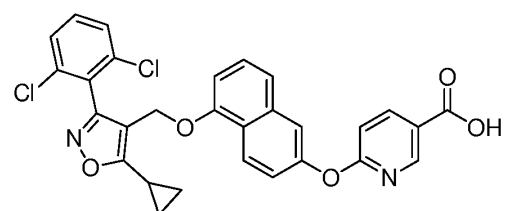
33



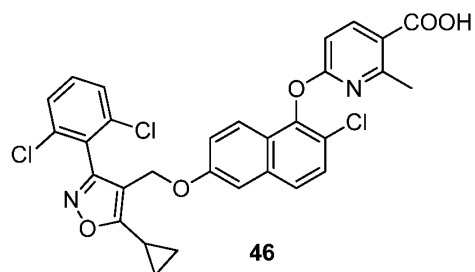
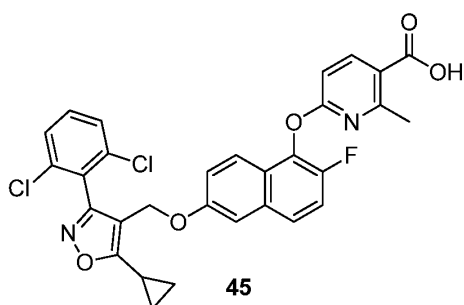
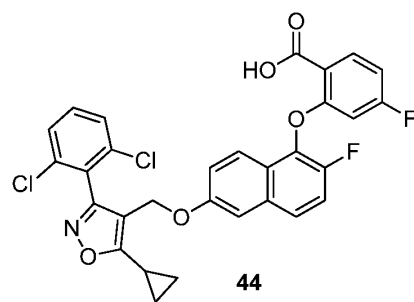
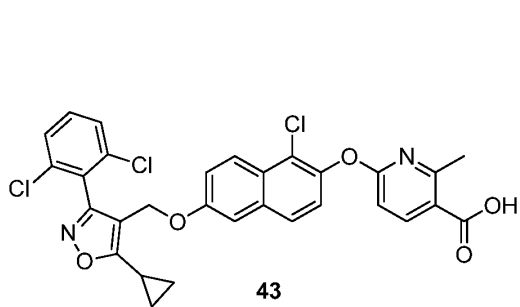
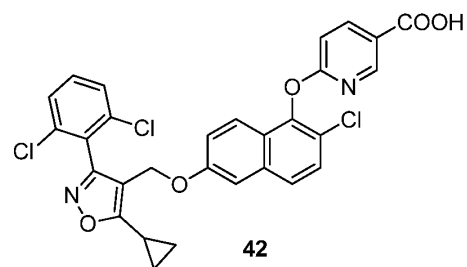
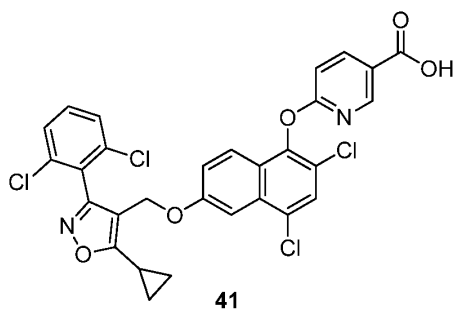
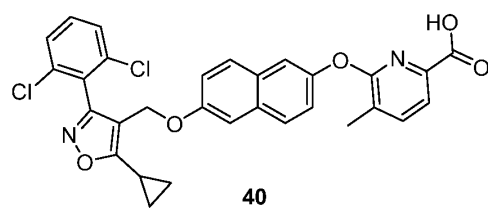
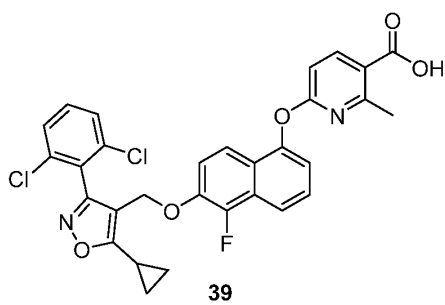
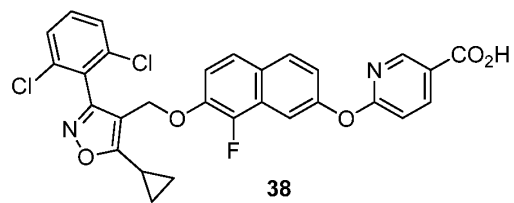
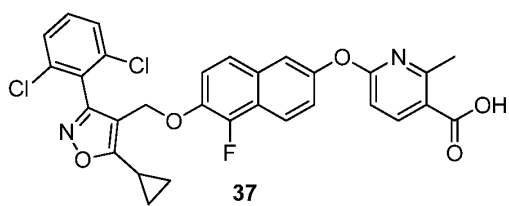
34

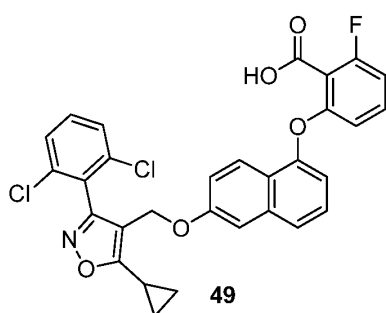
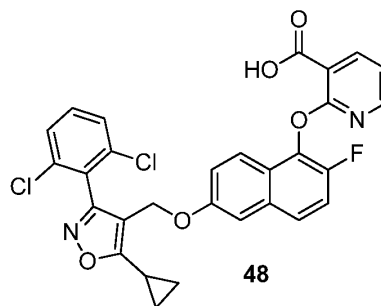
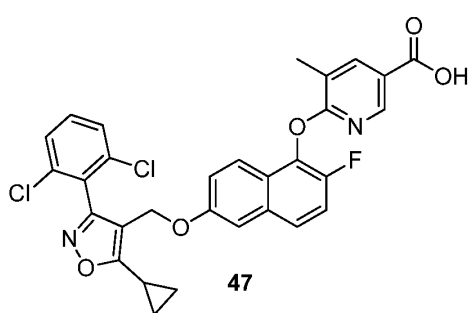


35



36

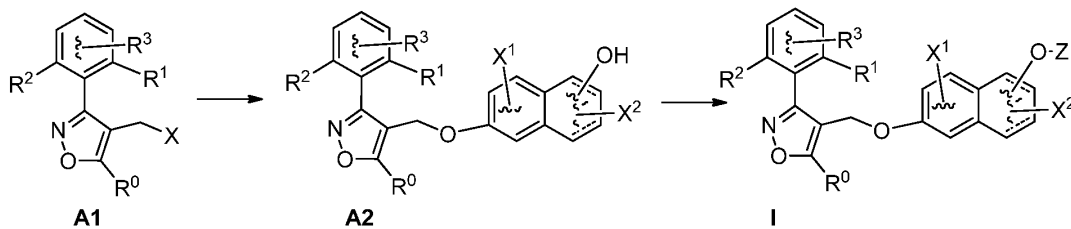




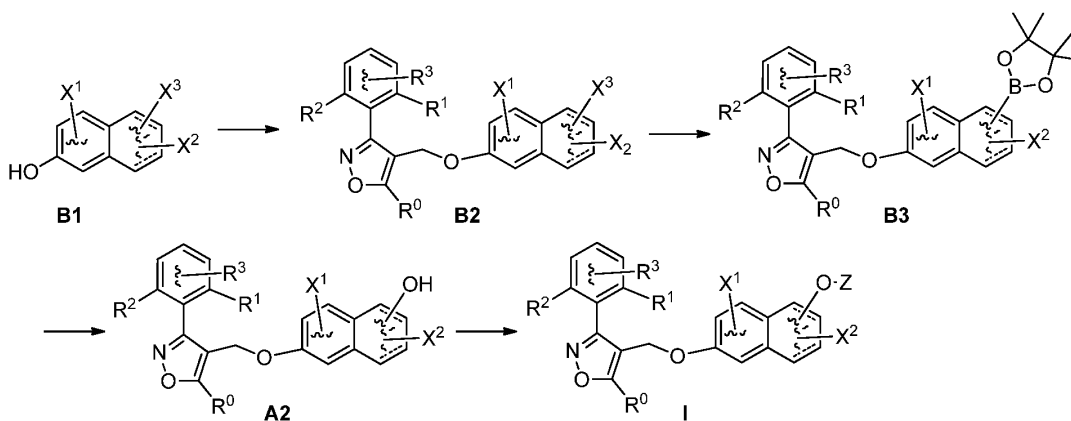
The method for preparing the compound of formula (I) can include the following four general routes (Route A, Route B, Route C, and Route D), among which:

5

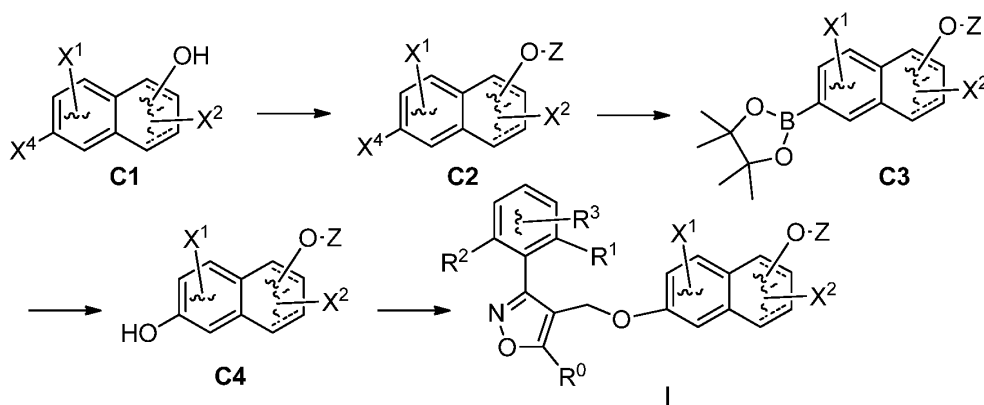
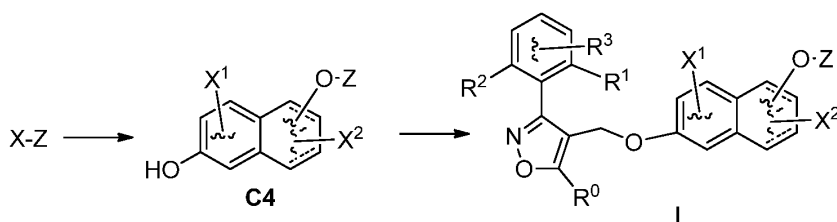
Route A:



Route B:



Route C:

**Route D:**

Hereinafter, the above-mentioned four general routes will be described in detail.

5 **Route A:**

(a) reacting a halogenated compound of the formula (A1) with a dinaphthol to give an ether of the formula (A2). The reaction is carried out in a polar solvent with a base, preferably, in DMF or acetonitrile or the like with cesium carbonate or potassium carbonate or similar bases.

10 wherein:

X is a halogen;

R^1 , R^2 and R^3 are independently selected from H, halogen, and unsubstituted or halogen substituted C_{1-6} alkyl and unsubstituted or halogen substituted C_{1-6} alkoxy, provided that at least one of R^1 , R^2 and R^3 is not hydrogen, R^0 is selected from
15 unsubstituted or halogen substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-7} alkylcycloalkyl;

(b) reacting the resulting ether of the formula (A2) with a halogenated compound X-Z to give a compound of formula (I),

wherein X is halogen, Z is a residue selected from 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S, wherein residue Z is substituted by R^4 and
20 optionally further substituted by R^5 ;

wherein R^4 is selected from $-\text{COOH}$, $-\text{CH}_2\text{COOH}$, $-\text{NHSO}_2\text{CF}_3$, $-\text{SO}_2\text{NH}-C_{1-6}$ alkyl,

–SO₃H, –CONHSO₂–C₁₋₆ alkyl, –CONHSO₂–C₃₋₆ cycloalkyl, –CONHSO₂–5-10 membered aryl and –CONHSO₂–5-10 membered aryl substituted by C₁₋₆ alkyl at the aryl, and R⁵ is selected from H, C₁₋₆ alkyl, halogen and C₁₋₆ haloalkyl; optionally

(c) reacting a compound of the formula (I) containing a –COOH substituent with an amide compound to give an amide compound of the formula (I) compound; and optionally

(d) when Z is substituted with R⁴ selected from –COOH and –CH₂COOH, ester precursors can be converted to free acids by hydrolysis using conditions well known to those skilled in the art,

wherein the compound of the formula (I) is as hereinabove defined.

According to the preparation method as provided by the present invention, X is preferably bromine or iodine, and more preferably bromine.

Route B:

(a) reacting a halogenated compound of the formula (A1) with a substituted naphthol (B1) to give an ether of the formula (B2). The reaction is carried out in a polar solvent with a base, preferably, in DMF or acetonitrile or the like, with cesium carbonate or potassium carbonate or similar bases;

(b) Compound (B2) is converted to boronic ester of the formula (B3), preferably, under Pd-catalyzed conditions;

(c) Compound (B3) is converted to naphthol (A2) by oxidation, with oxidants such as NaClO₂ or H₂O₂;

(d) Compound (A2) is converted to Compound (I) using condition outlined in Route A, wherein X³ is a halogen, preferably bromine or iodine, and more preferably bromine.

Route C:

(a) reacting a substituted naphthol (C1) with halogenated compound X–Z to give an ether of the formula (C2), wherein the reaction is carried out in a polar solvent with a base, preferably, in DMF or acetonitrile or the like, with cesium carbonate or potassium carbonate or similar bases;

(b) Compound (C2) is converted to boronic ester (C3), preferably, under Pd-catalyzed conditions;

(c) Compound (C3) is converted to naphthol (C4) by oxidation, with oxidants such as

NaClO₂ or H₂O₂;

(d) Compound (C4) is converted to Compound (I) using similar condition outlined in Route A;

wherein X⁴ is a halogen, preferably bromine or iodine, and more preferably bromine.

5

Route D:

(a) reacting a dinaphthol with halogenated compound X-Z to give an ether of the formula (C4) using similar condition outlined in Route C;

10 (b) Compound (C4) is converted to Compound (I) using similar condition outlined in Route C.

According to the method of treating or preventing infection with hepatitis B virus in a human or animal, the phenylisoxazolyl methylene-naphthalene-ether derivative having the structure of formula (I), or pharmaceutically acceptable salts, esters or stereoisomers thereof
15 (“compound of formula (I)” for short) can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

20 According to the method of the present invention, the compound of formula (I) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of formula (I), with any dose of other therapeutic agents. In one embodiment, the compound of formula (I) is co-administered with other anti-HBV agents, either as part of the same pharmaceutical composition or in separate pharmaceutical compositions. These agents
25 also can be administered at their own schedule and through different route. Co-administration includes administration of a unit dose of a compound of formula (I) before or after administration of a unit dose of one or more other anti-HBV agents. In some embodiments, the compound of formula (I) may be administered within seconds, minutes, or hours of administration of one or more other anti-HBV agents. In other embodiments, a unit dose of the
30 compound of formula (I) is administered first, followed by administration of one or more other anti-HBV agents within seconds, minutes, or hours.

In certain embodiments, when the compound of formula (I) is combined with one or more additional therapeutic agents as described herein, the components of the composition are

administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

In preferred embodiments of the present invention, the method of treating or preventing infection with hepatitis B virus in a human or animal comprises administering the
5 phenylisoxazolylmethylene-naphthalene-ether derivative having the structure of formula (I), its pharmaceutically acceptable salt, and ester or stereoisomer in combination with one or more other anti-HBV agents.

In the above embodiments, wherein the other anti-HBV agents may be selected from antisense oligonucleotide targeting viral mRNA (ASO), short interfering RNAs (siRNA), B-
10 and T-lymphocyte attenuator inhibitors, CCR2 chemokine antagonist, compounds targeting HBcAg, compounds targeting hepatitis B core antigen (HBcAg), covalently closed circular DNA (cccDNA) inhibitors, fatty acid synthase inhibitors, cyclophilin inhibitors, cytokines, Endonuclease modulator, epigenetic modifiers, gene modifiers or editors, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV antibodies, HBV DNA polymerase inhibitors,
15 HBV replication inhibitors, HBV RNase inhibitors, HBV vaccines, HBV viral entry inhibitors, HBx inhibitors, Hepatitis B structural protein modulator, hepatitis B surface antigen (HBsAg) inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, hepatitis B virus E antigen inhibitors, hepatitis B virus replication inhibitors, Hepatitis virus structural protein inhibitor, IL-2 agonist, IL-7 agonist, immunomodulators, inhibitors of ribonucleotide
20 reductase, Interferon agonist, Interferon alpha 1 ligand, Interferon alpha 2 ligand, Interferon alpha 5 ligand modulator, Interferon alpha ligand, Interferon alpha ligand modulator, interferon alpha receptor ligands, Interferon beta ligand, Interferon ligand, Interferon receptor modulator, Interleukin-2 ligand, ipi4 inhibitors, lysine demethylase inhibitors, microRNA (miRNA) gene therapy agents, modulators of B7-H3, modulators of B7-H4, modulators of CD 160,
25 modulators of CD161, modulators of CD27, modulators of CD47, modulators of CD70, modulators of GITR, modulators of TIGIT, modulators of Tim-4, Na^+ -taurocholate cotransporting polypeptide (NTCP) inhibitors, natural killer cell receptor 2B4 inhibitors, NOD2 gene stimulator, Nucleoprotein inhibitor, nucleoprotein modulators, PD-1 inhibitors, PD-L1 inhibitors, PEG-Interferon Lambda, Peptidylprolyl isomerase inhibitor, Retinoic acid-inducible gene 1 stimulator, Reverse transcriptase inhibitor, Ribonuclease inhibitor, RNA
30 DNA polymerase inhibitor, short synthetic hairpin RNAs (sshRNAs), stimulator of interferon gene (STING) agonists, stimulators of NOD 1, T cell surface glycoprotein CD28 inhibitor, TLR-3 agonist, TLR-7 agonist, TLR-8 agonist, TLR-9 agonist, TLR9 gene stimulator, toll-like

receptor (TLR) modulators, Viral ribonucleotide reductase inhibitor, zinc finger nucleases or synthetic nucleases (TALENs).

In the preferred solution of the present invention, the other anti HBV agents can be selected from HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators, toll-like
5 receptor (TLR) modulators, interferon alpha receptor ligands, hepatitis b surface antigen (HBsAg) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA) and ddRNAi endonuclease modulators, ribonucleotide reductase inhibitors, HBV E antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, fatty acid synthase inhibitors, HBV
10 antibodies, CCR2 chemokine antagonists, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, PD-1 inhibitors, PD-L1 inhibitors, KDM inhibitors, and HBV replication inhibitors.

In one embodiment, the other anti HBV agent is a nucleoside. Examples of HBV DNA polymerase inhibitors include adefovir (HEPSERA*), emtricitabine (EMTRIVA), tenofovir
15 disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir dipivoxil, tenofovir dipivoxil fumarate, tenofovir octadecyloxyethyl ester, CMX-157, besifovir, entecavir (BARACLUDE®), entecavir maleate, telbivudine (TYZEKA), pradefovir, devudine, ribavirin, lamivudine (EPIV R-V®), phosphazide, famciclovir, fusolin, metacavir, SNC-0 19754, FMCA,
20 AGX-1009, AR-II-04-26, HIP-1302, tenofovir disoproxil aspartate, tenofovir disoproxil orotate, and HS-10234. Further examples of HBV DNA polymerase inhibitors include filocilovir.

In a particular embodiment, the compound of formula (I) is administered in combination with entecavir or tenofovir.

25 In one embodiment, the other anti HBV agent is an immunomodulator. Examples of immunomodulators include TLR agonist RO7020531, GS-9620, GS-9688. Examples of immunomodulator also includes PD-1 inhibitors such as nivolumab, pembrolizumab, pidilizumab, BGB-108, camrelizumab (SHR-1210), PDR-001, PF-06801591, IBI-308, cemiplimab, camrelizumab, sintilimab, tislelizumab (BGB-A317), BCD-100, JNJ-63723283,
30 Zimberelimab (GLS-010, WBP-3055), Balstilimab (AGEN2034), and dostarlimab (TSR-042)

Examples of immunomodulator also include PD-L1 inhibitors such as atezolizumab (RG-7446), avelumab, BGB-A333, BMS-936559 (MDX-1105), durvalumab, CX-072, GX-P2 and envafolelimab (KN035, ASC022). PD-L1 inhibitors include small molecule inhibitors such

as GS-4224, INCB086550.

In a particular embodiment, the compound of formula (I) is administered in combination with KN035 (ASC022).

In one embodiment, the other anti HBV agent is a HBV vaccine. HBV vaccines include both prophylactic and therapeutic vaccines. Examples of HBV prophylactic vaccines include Vaxelis, Hexaxim, Heplisav, Mosquirix, DTwP-HBV vaccine, Bio-Hep-B, D/T/P/F1BV7M (LBVP-0101; LBVW-0101), DTwP-Hepb-Flib-IPV vaccine, Heberpenta L, DTwP-HepB-Hib, V-419, CVI-HBV-001, Tetrabhay, hepatitis B prophylactic vaccine (Advax Super D), Hepatrol-07, GSK-223 192A, ENGERIX B®, recombinant hepatitis B vaccine (intramuscular, Kangtai Biological Products), recombinant hepatitis B vaccine (Hansenal polymorpha yeast, intramuscular, Hualan Biological Engineering), recombinant hepatitis B surface antigen vaccine, Bimmugen, Euforavac, Eutravac, anrix-DTaP-IPV-Hep B, HBAI-20, Infanrix-DT aP-IPV-Hep B-Hib, Pentabio Vaksin DTP-HB-Hib, Comvac 4, Twinrix, Euvax-B, Tritanrix HB, Infanrix Hep B, Comvax, DTP-Hib-HBV vaccine, DTP-HBV vaccine, Yi Tai, Heberbiovac HB, Trivac HB, GerVax, DTwP-Hep B-Hib vaccine, Bilive, HepavaxGene, SUPERVAX, Comvac5, Shanvac-B, Hebsulin, Recombivax HB, Revac B mcf, Revac B+, Fendrix, DTwP-HepB-Hib, DNA-001, Shan5, Shan6, rhHBsAG vaccine, HBI pentavalent vaccine, LBVD, Infanrix HeXa, and DTaP-rHB-Hib vaccine.

In a particular embodiment, the compound of formula (I) is administered in combination with ABX203, AIC 649, INO-1800, HB-110, TG1050, HepTcell, VR-CHB01, VBI-2601 or CARG-201.

In one embodiment, the other anti HBV agent is antisense oligonucleotide targeting viral mRNA (ASO). Examples of antisense oligonucleotide include Ionis-HBVRx and Ionis-HBV-LRx.

In one embodiment, the other anti HBV agent is short interfering RNAs (siRNA). Examples of short interfering RNAs include JNJ-3989 (ARO-HBV), Vir-2218 (ALN-HBV02), and DCR-HBVS.

In one embodiment, the other anti HBV agent is a hepatitis surface antigen (HBsAg) Inhibitor. Examples of HBsAg inhibitors include HBF-0259, PBHBV-001, PBHBV-2-15, PBHBV-2-1, REP-9AC, REP-9C, REP-9, REP-2139, REP-2139-Ca, REP-2165, REP-2055, REP-2163, REP-2165, REP-2053, REP-203 and REP-006, REP-9 AC, as well as inhibitors targeting the PAPD 57.

In one embodiment, the other anti HBV agent is a HB Viral Entry Inhibitor, such as

Myrcludex B, or an antibody targeting at preS.

In one embodiment, the other anti HBV agent is a fatty acid synthase inhibitor, such as TVB-2640, TVB-3150, TVB-3199, TVB-3166, TVB-3567 and TVB-3664.

In one embodiment, the other anti HBV agent is a capsid inhibitor. Examples of HBsAg inhibitors include ABI-H0731, ABI-H2158, ABI-H3733, CB-HBV-001, JNJ-6379, JNJ-0440, 5 QL-007, RG-7907 and RO7049389.

In yet another embodiment, the other anti-HBV agent is ordinary or long-acting interferon. The examples include Pegasys and PEG-INTRON.

In a specific embodiment, the compound of formula (I) of the present invention is 10 combined with Pegasys.

In another aspect, the present invention provides use of a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof in the preparation of a pharmaceutical composition for anti-hepatitis B virus. In this embodiment, the phenylisoxazolyl 15 methylene-naphthalene-ether derivative having the structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof are as defined above.

According to the use of the present invention, the anti-HBV pharmaceutical composition comprises as an active ingredient a phenylisoxazolylmethylene-naphthalene-ether derivative having a structure of formula (I), a pharmaceutically acceptable salt, ester or stereoisomer 20 thereof and one or more other anti-HBV agents. In this embodiment, the other anti-HBV agents are as defined above.

In still another aspect, the present invention provides an pharmaceutical composition for anti-hepatitis B virus comprising a therapeutically effective amount of a phenylisoxazolyl 25 methylene-naphthalene-ether derivative having a structure of formula (I), a pharmaceutically acceptable salt, ester or stereoisomer thereof and one or more other anti-HBV agents, and a pharmaceutically acceptable auxiliary material. In this embodiment, the phenylisoxazolyl methylene-naphthalene-ether derivative having the structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof are as defined above, and the 30 other anti-HBV agents are as defined above.

The pharmaceutical composition of the present invention are suitable for oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural)

administration, and the like, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well-known to those skilled in the art of
5 pharmacy.

The compositions include those suitable for various administration routes, including oral administration. The compositions may be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (e.g., a compound of the present
10 disclosure or a pharmaceutical salt thereof) with one or more pharmaceutically acceptable excipients. The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if necessary, shaping the product. Compositions described herein that are suitable for oral administration may be presented as discrete units (a unit dosage form)
15 including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient. In one embodiment, the pharmaceutical composition is a tablet.

The compound may be administered to an individual in an effective amount. The amount of active ingredient that may be combined with the inactive ingredients to produce
20 a dosage form may vary depending upon the intended treatment subject and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutically acceptable excipient varies from
25 about 5 to about 95% of the total compositions.

The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician. The frequency of dosage of the compound of the present disclosure are will be determined by the needs of the individual patient and can be, for example, once per day or
30 twice, or more times, per day. Administration of the compound continues for as long as necessary to treat the HBV infection.

Brief Description of the Drawings

In order to explain the embodiments of the present invention or the technical solutions in the prior art more clearly, drawings required for the description of the embodiments of the present invention will be briefly described below. Obviously, the drawings in the following description are only some embodiments of the present invention.

5 Fig. 1 is EC50 curves of inhibition HBV DNA in PHH Cells;

Fig. 2 is EC50 curves of HBsAg inhibition in PHH Cells;

Fig. 3 is EC50 curves of HBV RNA inhibition in PHH Cells.

Fig. 4 is HBV DNA level in AAV-HBV mouse serum before and after treatment of compound 33.

10 Fig. 5 is HBV RNA level in AAV-HBV mouse serum before and after treatment of compound 33.

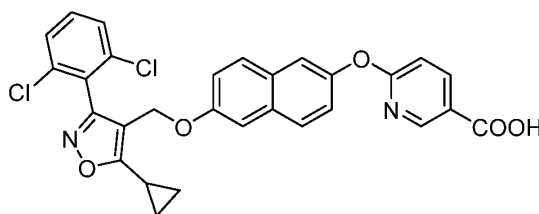
Fig. 6 is HBsAg level in AAV-HBV mouse serum before and after treatment of compound 33.

15 **Best Mode for Carrying Out the Invention**

The present invention will be further illustrated with reference to the examples below. It is necessary to state that, the examples below are only for illustration, but not for limitation of the present invention. Various alterations that are made by a person skilled in the art in accordance with teaching from the present invention should be within the scope
20 claimed by the claims of the present invention.

Example 1

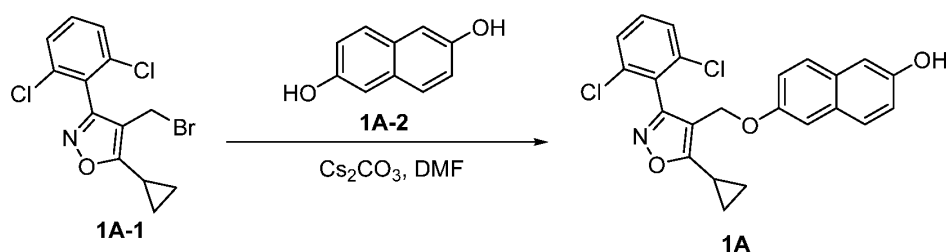
Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 1)



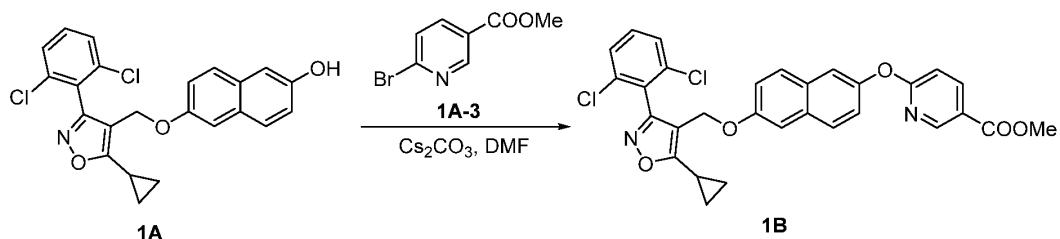
25

(a) Referring to the following reaction equation (Route A), Compound 1A-1 (1.0 g, 2.88 mmol, 1 eq.), Compound 1A-2 (0.46 g, 2.88 mmol, 1 eq.) and cesium carbonate (1.88 g, 5.76 mmol, 2 eq.) were dissolved in DMF (10 ml). The reaction was carried out at 65°C for 2 h. After cooling, 10 ml water and 10 ml EA (ethyl acetate) were added for extraction, and the

organic phase was washed with water and concentrated to dryness to give Compound 1A, 6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-ol, 0.8 g, yield: 65.0%. LCMS (ESI): calculated for $C_{23}H_{17}Cl_2NO_3$; $[M+H]^+$: 426.1, found: 426.1.



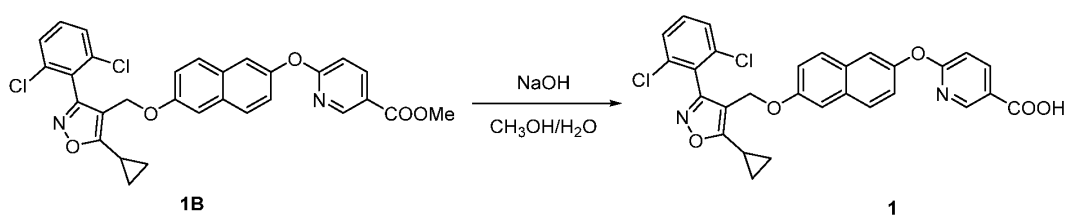
(b) Referring to the following reaction equation, Compound 1A (0.2 g, 0.47 mmol, 1 eq.), 6-bromonicotinic acid methyl ester (0.1 g, 0.47 mmol, 1 eq.) and cesium carbonate (0.306 g, 0.94 mmol, 2 eq.) were dissolved in DMF (10 ml). The reaction was carried out at 65°C for 2 h. After cooling, 10 ml water and 10 ml EA were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 1B, methyl 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinate, 0.21 g, yield: 80.0%. LCMS (ESI): calculated for $C_{30}H_{22}Cl_2N_2O_5$; $[M+H]^+$: 561.1, found: 561.1.



(c) Referring to the following reaction equation, compound 1B (100 mg) was dissolved in methanol (2 ml), then 10% NaOH aqueous solution (1 ml) was added, the temperature was raised to 60°C, and the reaction was carried out for 1 h. The pH of the reaction solution was adjusted to 2 to 4 by adding 1N HCl solution, and 10 ml EA (ethyl acetate) was added for extraction. The organic phase was concentrated and purified on a column (PE/EA/AcOH = 1/1/0.01 elution, wherein PE is petroleum ether) to give the title compound 1 (36 mg, yield: 37.0%).

1H NMR (400 MHz, $DMSO-d_6$) δ 8.57 (s, 1H), 8.23 (d, $J = 7.2$ Hz, 1H), 7.74 (dd, $J = 2.0, 8.8$ Hz, 2H), 7.60 (d, $J = 7.6$ Hz, 2H), 7.56 (s, 1H), 7.51 (dd, $J = 8.8, 7.2$ Hz, 1H), 7.33 (s, 1H), 7.26 (d, $J = 8.8$ Hz, 1H), 7.02 (d, $J = 8.0$ Hz, 1H), 6.93 (d, $J = 6.4$ Hz, 1H), 4.98 (s, 2H), 2.57-2.50 (m, 1H), 1.19-1.11 (m, 4H). LCMS (ESI): calculated for $C_{29}H_{20}Cl_2N_2O_5$;

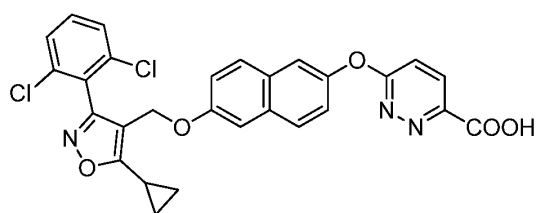
[M+H]⁺: 547.1, found: 547.1. ¹³C NMR (400 MHz, DMSO-*d*₆) δ 7.79, 8.87, 8.87, 59.31, 107.74, 110.05, 110.97, 117.64, 119.43, 122.52, 127.55, 128.64, 128.89, 128.89, 129.18, 129.67, 131.73, 131.79, 132.94, 135.10, 135.10, 141.20, 149.11, 150.73, 155.79, 159.68, 163.82, 167.81, 172.61. IR (cm⁻¹): major stretches at 1591.94 (C=O stretch), 1412.27, 1556.70 (C-C stretch), 1364.37, 1389.89 (C-H deformation), 1218.41, 1250.94 (C=N stretch), 791.88 (C-Cl stretch).



10

Example 2

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)pyridazine-3-carboxylic acid (Compound 2)



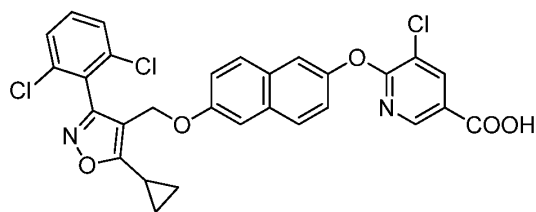
Following the procedure of Example 1, the title Compound 2 was obtained by substituting methyl 6-bromopyridazine-3-carboxylate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (s, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 7.74 (dd, *J* = 2.0, 8.8 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.52 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.34 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 6.4 Hz, 1H), 4.98 (s, 2H), 2.59-2.50 (m, 1H), 1.21-1.11 (m, 4H). LCMS (ESI): calculated for C₂₈H₁₉Cl₂N₃O₅; [M+H]⁺: 548.1, found: 548.1.

20

Example 3

Preparation of 5-chloro-6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 3)

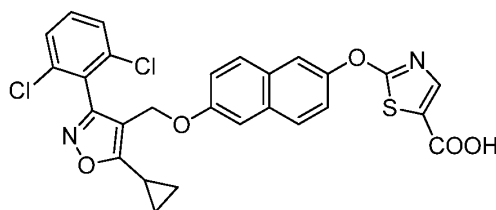


Following the procedure of Example 1, the title Compound 3 was obtained by substituting methyl 5,6-dichloronicotinate for 6-bromonicotinic acid methyl ester.

^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (s, 1H), 7.73 (dd, J = 2.0, 8.8 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.51 (dd, J = 8.8, 7.2 Hz, 1H), 7.33 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 6.4 Hz, 1H), 5.00 (s, 2H), 1.26-1.12 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 581.0, found: 581.0.

Example 4

10 Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)thiazole-5-carboxylic acid (Compound 4)

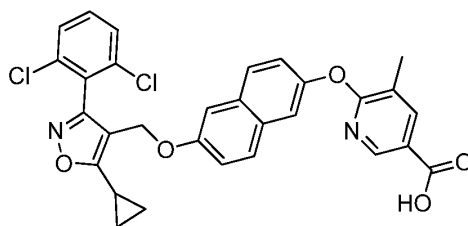


Following the procedure of Example 1, the title Compound 4 was obtained by substituting methyl 2-bromothiazole-5-carboxylate for 6-bromonicotinic acid methyl ester.

15 ^1H NMR (400 MHz, DMSO- d_6) δ 8.80 (s, 1H), 7.69 (dd, J = 2.0, 8.8 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.53 (dd, J = 8.8, 7.2 Hz, 1H), 7.32 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 6.4 Hz, 1H), 5.00 (s, 2H), 1.25-1.12 (m, 5H). LCMS (ESI): calculated for $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_5\text{S}$; $[\text{M}+\text{H}]^+$: 553.0, found: 553.0.

Example 5

20 Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)-5-methylnicotinic acid (Compound 5)

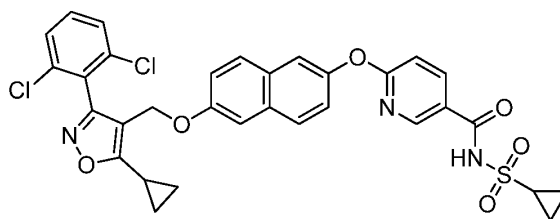


Following the procedure of Example 1, the title Compound 5 was obtained by substituting methyl 6-bromo-5-methylnicotinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 8.35 (d, *J* = 1.5 Hz, 1H), 8.12-7.90 (m, 1H), 7.72-7.61 (m, 2H), 7.54 (s, 3H), 7.28 (m, 2H), 7.15-7.10 (m, 1H), 7.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.41 (s, 2H), 2.99-2.70 (m, 1H), 2.28 (s, 3H), 2.12-1.56 (m, 4H). LCMS (ESI): calculated for C₃₀H₂₂Cl₂N₂O₅; [M+H]⁺: 561.1, found: 561.1.

Example 6

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)-N-(cyclopropylsulfonyl)nicotinamide (Compound 6)

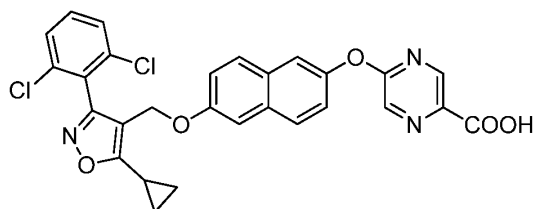


Compound 1 (70 mg) as prepared in Example 1 and cyclopropylsulfonamide (23 mg) were dissolved in 2 ml DCM (dichloromethane), then 40 mg EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) and 26 mg DMAP (dimethylaminopyridine) were added. After completion of the reaction, 10 ml DCM and 10 ml water was added for extraction. The organic phase was washed with water and concentrated to dryness. The crude product is purified by column (PE/EA/AcOH=2/1/0.01) to give the title Compound 6 (8 mg, yield: 9.6%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 1.5 Hz, 1H), 8.30 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.59-7.62 (m, 3H), 7.49-7.53 (m, 1H), 7.35 (s, 1H), 7.26-7.29 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.93-6.96 (m, 1H), 4.98 (s, 2H), 1.02-1.20 (m, 10H). LCMS (ESI): calculated for C₃₂H₂₅Cl₂N₃O₆S; [M+H]⁺: 650.1, found: 650.1.

Example 7

Preparation of 5-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)pyrazine-2-carboxylic acid (Compound 7)

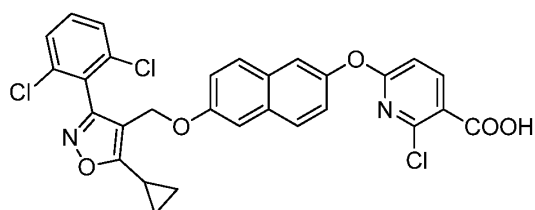


5 Following the procedure of Example 1, the title Compound 7 was obtained by substituting methyl 5-chloro-pyridine-2-carboxylate for 6-bromonicotinic acid methyl ester.

^1H NMR (400 MHz, DMSO- d_6) δ 8.63 (s, 1H), 8.30 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.58-7.63 (m, 4H), 7.49-7.53 (m, 1H), 7.34 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 4.98 (s, 2H), 1.11-1.22 (m, 5H). LCMS (ESI): calculated for $\text{C}_{28}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_5$; $[\text{M}+\text{H}]^+$: 548.1, found: 548.1.

Example 8

Preparation of 2-chloro-6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 8)



15

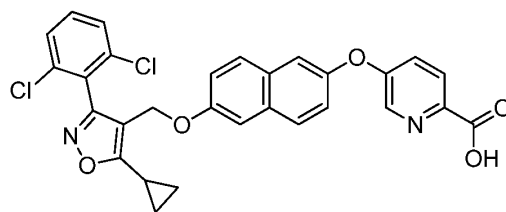
Following the procedure of Example 1, the title Compound 8 was obtained by substituting methyl 2,6-dichloronicotinate for 6-bromonicotinic acid methyl ester.

^1H NMR (400 MHz, DMSO- d_6) δ 7.98 (br s, 1H), 7.70-7.79 (m, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.47-7.55 (m, 2H), 7.18-7.33 (m, 2H), 6.90-6.95 (m, 2H), 4.98 (s, 2H), 1.11-1.22 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 581.0, found: 581.0.

20

Example 9

Preparation of 5-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)picolinic acid (Compound 9)

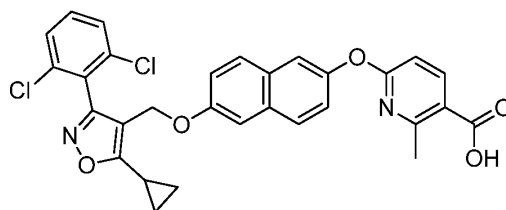


Following the procedure of Example 1, the title Compound 9 was obtained by substituting methyl 5-bromopicolinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (d, *J* = 3.1 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.55 (dt, *J* = 28.7, 8.3 Hz, 4H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.39 – 7.24 (m, 2H), 6.95 (d, *J* = 8.9 Hz, 1H), 4.98 (s, 2H), 1.23 – 1.02 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

10 **Example 10**

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)-2-methylnicotinic acid (Compound 10)

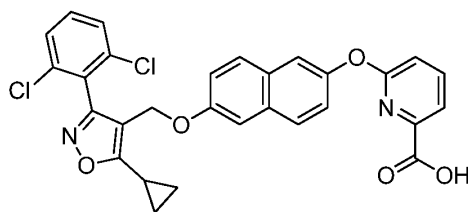


Following the procedure of Example 1, the title Compound 10 was obtained by substituting methyl 6-chloro-2-methylnicotinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.21 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.55 (m, 3H), 7.51 (dd, *J* = 9.0, 7.1 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.27 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.94 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 4.98 (s, 2H), 2.52 (s, 3H), 1.24 – 1.07 (m, 5H). LCMS (ESI): calculated for C₃₀H₂₂Cl₂N₂O₅; [M+H]⁺: 561.1, found: 561.1.

Example 11

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)picolinic acid (Compound 11)

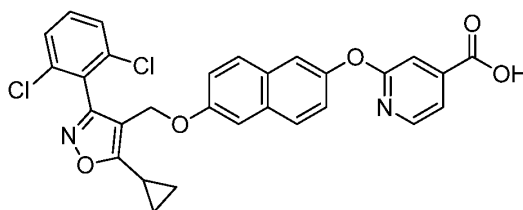


Following the procedure of Example 1, the title Compound 11 was obtained by substituting methyl 2,6-dichloronicotinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99 (t, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.45 (m, 4H), 7.33 (s, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 4.98 (s, 2H), 1.26 – 1.01 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

10 **Example 12**

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)isonicotinic acid (Compound 12)



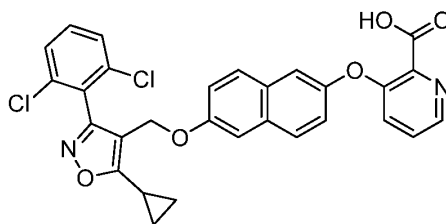
Following the procedure of Example 1, the title Compound 12 was obtained by substituting methyl 2-fluoroisonicotinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 3H), 7.52 (m, 2H), 7.34 (s, 2H), 7.29 (s, 1H), 4.98 (s, 2H), 1.31-1.06 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

20

Example 13

Preparation of 3-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)picolinic acid (Compound 13)

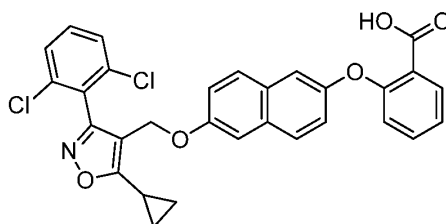


Following the procedure of Example 1, the title Compound 13 was obtained by substituting methyl 3-fluoropicolinate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (d, *J* = 4.4 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.43 (m, 3H), 7.30 (d, *J* = 2.8 Hz, 2H), 7.26 – 7.16 (m, 1H), 6.95 – 6.85 (m, 1H), 4.95 (s, 2H), 1.24 – 1.06 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

10 **Example 14**

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)benzoic acid (Compound 14)



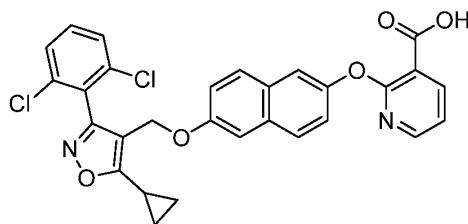
Following the procedure of Example 1, the title Compound 14 was obtained by substituting methyl 2-fluorobenzoate for 6-bromonicotinic acid methyl ester.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.55 – 7.45 (m, 2H), 7.26 (d, *J* = 10.6 Hz, 2H), 7.21 – 7.11 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.94 (s, 2H), 1.27 – 1.06 (m, 5H). LCMS (ESI): calculated for C₃₀H₂₁Cl₂NO₅; [M+H]⁺: 546.1, found: 546.1

20

Example 15

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 15)

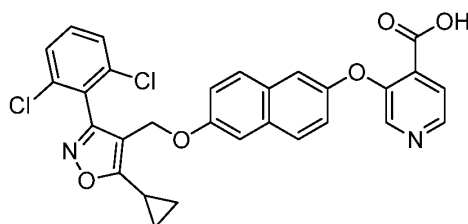


Following the procedure of Example 1, the title Compound 15 was obtained by substituting methyl 2-chloronicotinate for 6-bromonicotinic acid methyl ester.

^1H NMR (400 MHz, DMSO- d_6) δ 8.30 – 8.19 (m, 2H), 7.73 (dd, J = 19.2, 9.0 Hz, 2H), 7.60 (d, J = 7.9 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.32 (d, J = 2.5 Hz, 1H), 7.26 – 7.18 (m, 2H), 6.92 (dd, J = 8.9, 2.5 Hz, 1H), 4.98 (s, 2H), 1.23 – 1.10 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 547.1, found: 547.1.

Example 16

Preparation of 3-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)isonicotinic acid (Compound 16)

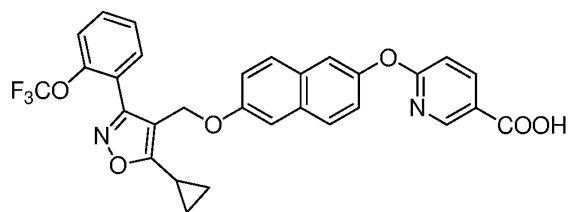


Following the procedure of Example 1, the title Compound 16 was obtained by substituting methyl 3-fluoroisonicotinate for 6-bromonicotinic acid methyl ester.

^1H NMR (400 MHz, DMSO- d_6) δ 8.52 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 4.9 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.50 (dd, J = 9.0, 7.0 Hz, 1H), 7.32 – 7.15 (m, 4H), 6.89 (dd, J = 8.9, 2.5 Hz, 1H), 4.95 (s, 2H), 1.27 – 1.09 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 547.1, found: 547.1.

Example 17

Preparation of 6-((6-((5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 17)

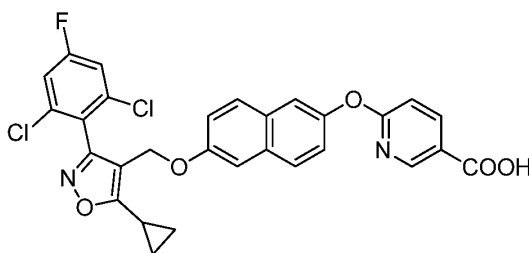


Following the procedure of Example 1, the title Compound 17 was obtained by substituting 4-(chloromethyl)-5-cyclopropyl-3-(2-(trifluoromethoxy)phenyl) isoxazole for 1A-1.

- 5 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.62 (s, 1H), 8.27 (d, $J = 8.1$ Hz, 1H), 7.75 (dt, $J = 31.9, 15.9$ Hz, 2H), 7.61 (s, 2H), 7.56-7.43 (m, 2H), 7.36 (s, 1H), 7.29 (d, $J = 8.6$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 5.03 (s, 2H), 2.44-2.37 (m, 1H), 1.20-1.05 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_6$; $[\text{M}+\text{H}]^+$: 563.1, found: 563.1.

10 **Example 18**

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichloro-4-fluorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 18)



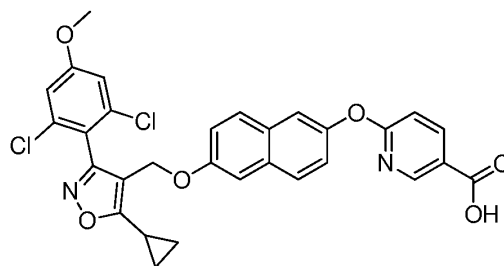
Following the procedure of Example 1, the title Compound 18 was obtained by substituting 4-(chloromethyl)-5-cyclopropyl-3-(2,6-dichloro-4-fluorophenyl) isoxazole for 1A-1.

- 15 ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.63 (s, 1H), 8.27 (d, $J = 7.9$ Hz, 1H), 7.87-7.63 (m, 4H), 7.60 (s, 1H), 7.40-7.24 (m, 2H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 8.6$ Hz, 1H), 4.98 (s, 2H), 2.47-2.40 (m, 1H), 1.23-1.08 (m, 4H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 565.1, found: 565.1.
- 20

Example 19

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichloro-4-methoxyphenyl)

isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 19)



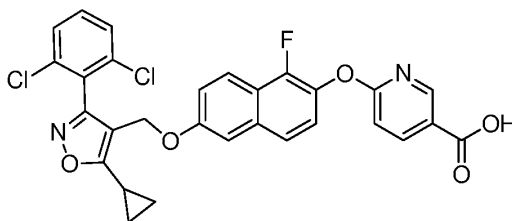
Following the procedure of Example 1, the title Compound 19 was obtained by substituting 4-(chloromethyl)-5-cyclopropyl-3-(2,6-dichloro-4-methoxyphenyl) isoxazole for

5 1A-1.

LCMS (ESI): calculated for $C_{30}H_{22}Cl_2N_2O_6$; $[M+H]^+$: 577.1, found: 577.1.

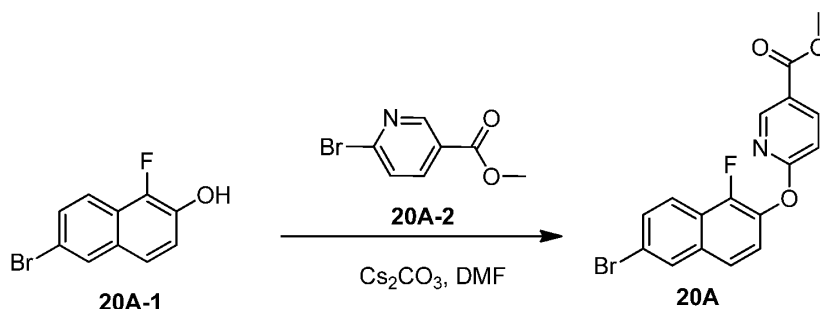
Example 20

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-1-fluoronaphthalen-2-yl)oxy)nicotinic acid (Compound 20)

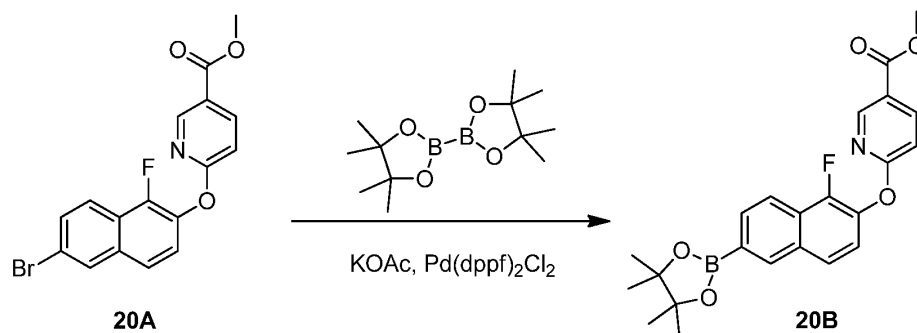


(a) Referring to the following reaction equation (Route C), Compound 20A-1 (1.0 g, 4.15 mmol, 1 eq.), Compound 20A-2 (0.90 g, 4.15 mmol, 1 eq.) and cesium carbonate (2.70 g, 8.30 mmol, 2 eq.) were dissolved in DMF (10 ml). The reaction was carried out at 65°C for 2 h.

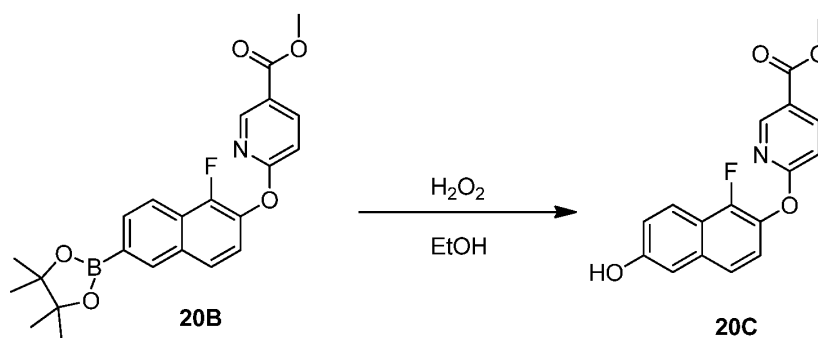
15 After cooling, 10 ml water and 10 ml EA (ethyl acetate) were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 20A, methyl 6-((6-bromo-1-fluoronaphthalen-2-yl)oxy)nicotinate, 1.2 g, yield: 77.0%. LCMS (ESI): calculated for $C_{17}H_{11}BrFNO_3$; $[M+H]^+$: 376.0, found: 376.0.



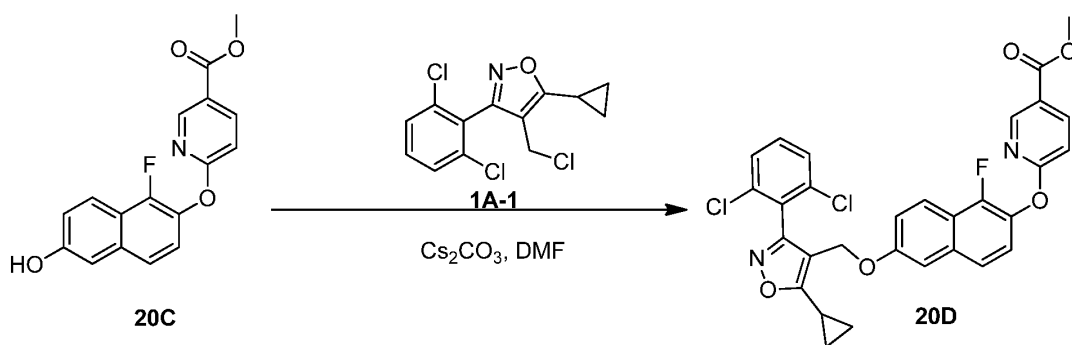
(b) Referring to the following reaction equation, compound 20A (200 mg, 0.53 mmol, 1 eq) was dissolved in dry THF (2 ml), then KOAc (104 mg, 1.06 mmol, 2 eq), $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (39 mg, 0.053 mmol, 0.1 eq), and bis(pinacolato)diboron (135 mg, 0.53 mmol, 1 eq) were added under N_2 , and the reaction mixture was heated to reflux for 2 h. After cooling, 10 ml water and 10 ml EtOAc were added for extraction, and the organic phase was washed with water and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum Ether:EtOAc = 3:1) to give Compound 20B, methyl 6-((1-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)nicotinate, 151 mg, yield: 67.1%. LCMS (ESI): calculated for $\text{C}_{23}\text{H}_{23}\text{BFNO}_5$; $[\text{M}+\text{H}]^+$: 424.2, found: 424.2.



(c) Referring to the following reaction equation, compound 20B (100 mg) was dissolved in EtOH (2 ml), then 30% H_2O_2 aqueous solution (1 ml) were added. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous Na_2SO_3 , and extracted with EA. The organic phase was concentrated and purified on a column (PE/EA = 3/1) to give the compound 20C (36 mg, yield: 37.0%). LCMS (ESI): calculated for $\text{C}_{17}\text{H}_{12}\text{FNO}_4$; $[\text{M}+\text{H}]^+$: 314.1, found: 314.1.



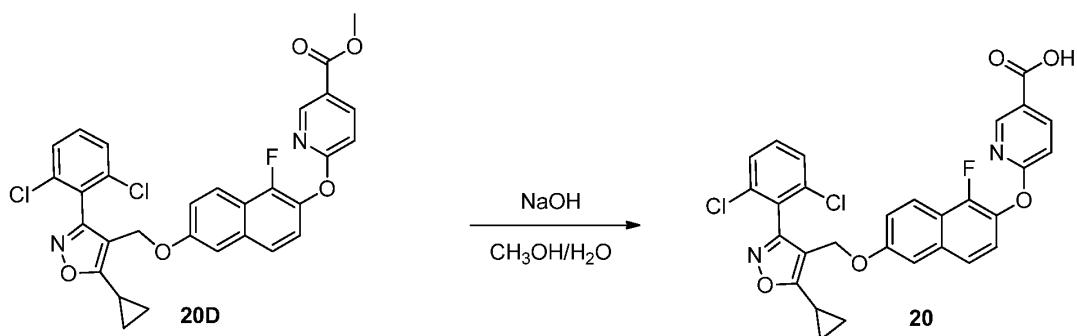
(d) Referring to the following reaction equation, Compound 20C (0.2 g, 0.47 mmol, 1 eq.), 1A-1 (0.1 g, 0.47 mmol, 1 eq.) and cesium carbonate (0.306 g, 0.94 mmol, 2 eq.) were dissolved in DMF (10 ml) for reacting. The reaction was carried out at 65°C for 2 h. After cooling, 10 ml water and 10 ml EtOAc were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 20D, 0.21 g, yield: 80.0%. LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 579.1, found: 579.1.



10

(e) Referring to the following reaction equation, compound 20D (100 mg) was dissolved in dry THF (2 ml), then 10% NaOH aqueous solution (1 ml) were added under N_2 , and the reaction mixture was heated to reflux for 1 h. The pH of the reaction solution was adjusted to 3 to 4 by adding 1N HCl solution, and 10 ml EA was added for extraction. The organic phase was concentrated and purified on a column (PE/EA/AcOH = 1/1/0.01 elution) to give the title compound 20 (36 mg, yield: 37.0%).

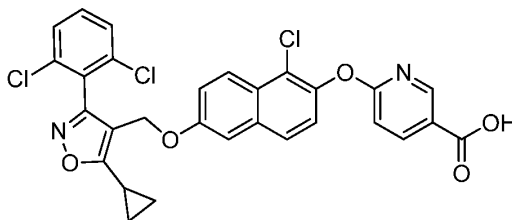
15



¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 5.3 Hz, 1H), 7.60 (d, *J* = 6.4 Hz, 1H), 7.57 (d, *J* = 4.3 Hz, 2H), 7.42-7.36 (m, 2H),
 5 7.17 (d, *J* = 8.6 Hz, 1H), 5.09 (s, 2H), 1.22 – 1.06 (m, 5H). LCMS (ESI):
 calculated for C₂₉H₁₉Cl₂FN₂O₅; [M+H]⁺: 565.1, found: 565.1.

Example 21

10 Preparation of 6-((1-chloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 21)

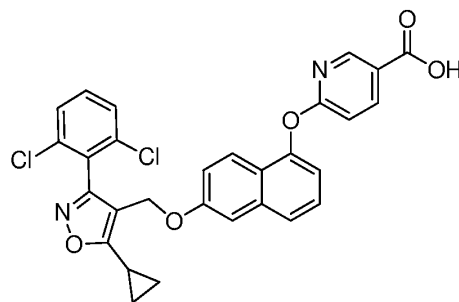


Following the procedure of Example 20, the title Compound 21 was obtained by substituting 6-bromo-1-chloronaphthalen-2-ol for 20A-1.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.87-7.63 (m, 4H), 7.60 (s, 1H), 7.40-7.24 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.98 (s, 2H), 2.47-2.40 (m, 1H), 1.23-1.08 (m, 4H). LCMS (ESI): calculated for C₂₉H₁₉Cl₃N₂O₅; [M+H]⁺: 581.0, found: 581.0.

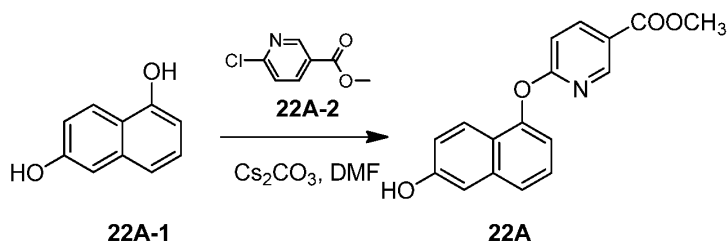
Example 22

20 Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)nicotinic acid (Compound 22)

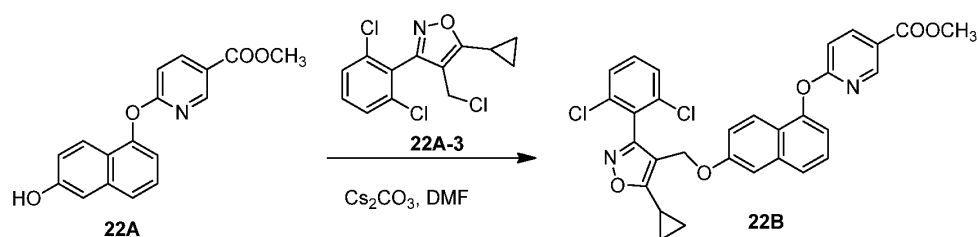


(a) Referring to the following reaction equation (Route D), Compound 22A-1 (2.0 g, 12.49 mmol, 1 eq.), Compound 22A-2 (1.71 g, 9.99 mmol, 0.8 eq.) and cesium carbonate (6.09 g, 18.74 mmol, 1.5 eq.) were dissolved in DMF (20 ml) for reacting. The reaction was carried out at 65°C for 3 h. After cooling, 30 ml water and 30 ml EA (ethyl acetate) were added for extraction, and the organic phase was washed with water and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum:AcOEt = 5:1) to give Compound 22A, methyl 6-((6-hydroxynaphthalen-1-yl)oxy)nicotinate, 1.1 g, yield: 37.3%. LCMS (ESI): calculated for $C_{17}H_{13}NO_4$; $[M+H]^+$: 296.1, found: 296.1.

10

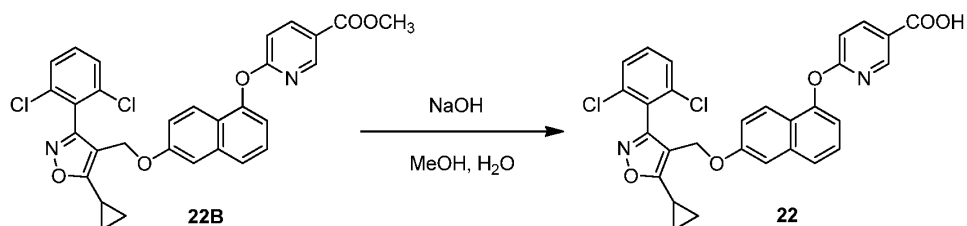


(b) Referring to the following reaction equation, Compound 22A (0.2 g, 0.68 mmol, 1 eq.), 22A-3 (0.2 g, 0.68 mmol, 1 eq.) and cesium carbonate (0.44 g, 1.36 mmol, 2 eq.) were dissolved in DMF (5 ml) for reacting. The reaction was carried out at 40°C for 2 h. After cooling, 10 ml water and 10 ml EA were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 22B, methyl 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)nicotinate, 0.31 g, yield: 81.2%. LCMS (ESI): calculated for $C_{30}H_{22}Cl_2N_2O_5$; $[M+H]^+$: 561.1, found: 561.1.



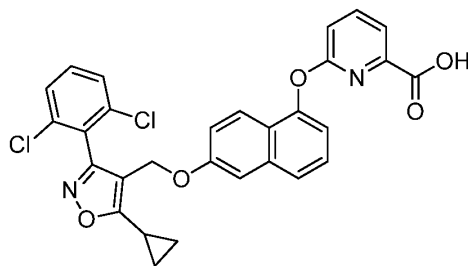
(c) Referring to the following reaction equation, compound 22B (100 mg) was dissolved in methanol (2 ml), then 10% NaOH aqueous solution (1 ml) was added, the temperature was raised to 60°C, and the reaction was carried out for 0.5 h. The pH of the reaction solution was adjusted to 2 to 4 by adding 1N HCl solution, and 10 ml EA was added for extraction. The organic phase was concentrated on a column (PE/EA/AcOH = 1/1/0.01 elution) to give the title compound 22 (42 mg, yield: 43.2%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.11 (br s, 1H), 8.56 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.56-7.61 (m, 3H), 7.45-7.53 (m, 2H), 7.39 (s, 1H), 7.15 (t, *J* = 9.6 Hz, 2H), 6.9 (d, *J* = 9.2 Hz, 2H), 4.98 (s, 2H), 1.09-1.28 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.



Example 23

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)picolinic acid (Compound 23)

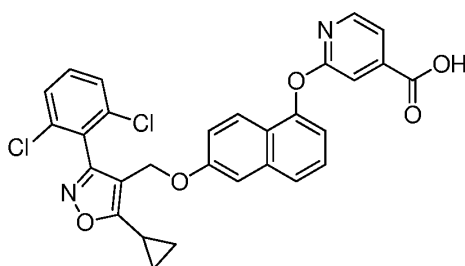


Following the procedure of Example 22, the title Compound 23 was obtained by substituting methyl 6-fluoropicolinate for 22A-2.

^1H NMR (400 MHz, DMSO- d_6) δ 7.99 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.52 – 7.44 (m, 2H), 7.40 – 7.37 (m, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.94 – 6.90 (m, 1H), 4.99 (s, 2H), 1.23 – 1.09 (m, 5H). LCMS (ESI):
 5 calculated for $\text{C}_{29}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 547.1, found: 547.1.

Example 24

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)isonicotinic acid (Compound 24)



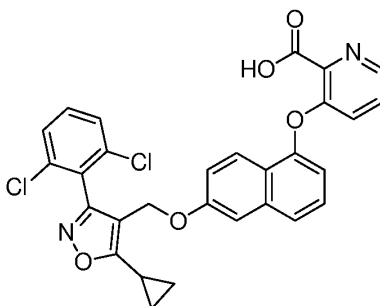
10

Following the procedure of Example 22, the title Compound 24 was obtained by substituting methyl 2-fluoroisonicotinate for 22A-2.

^1H NMR (400 MHz, DMSO- d_6) δ 8.22 (d, J = 5.1 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.53 – 7.42 (m, 3H), 7.38 (s, 2H), 7.11 (d, J = 7.5 Hz, 1H), 6.89 (dd, J = 9.2, 2.4 Hz, 1H), 4.98 (s, 2H), 1.22 – 1.07 (m, 5H). LCMS
 15 (ESI): calculated for $\text{C}_{29}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 547.1, found: 547.1.

Example 25

Preparation of 3-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)picolinic acid (Compound 25)



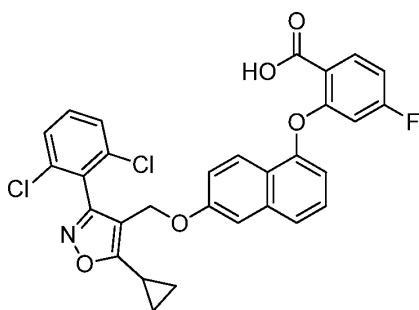
20

Following the procedure of Example 22, the title Compound 25 was obtained by substituting methyl 3-fluoropicolinate for 22A-2.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 – 8.37 (m, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.53 – 7.47 (m, 2H), 7.43 – 7.35 (m, 2H), 7.35 – 7.30 (m, 1H), 6.99 – 6.94 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.00 (s, 2H), 1.21 – 1.10 (m, 5H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

Example 26

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)-4-fluorobenzoic acid (Compound 26)

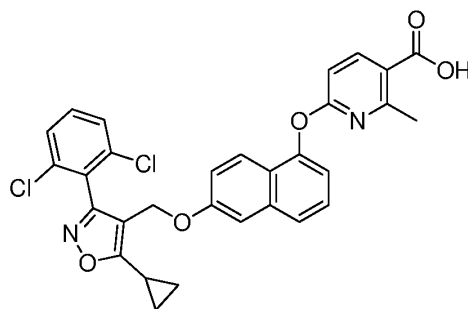


Following the procedure of Example 22, the title Compound 26 was obtained by substituting methyl 2,4-difluorobenzoate for 22A-2.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.22 (d, *J* = 5.1 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.57 (s, 2H), 7.52 – 7.43 (m, 3H), 7.38 (s, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.90 (s, 0H), 4.98 (s, 2H), 1.20 – 1.06 (m, 5H). LCMS (ESI): calculated for C₃₀H₂₀Cl₂FNO₅; [M+H]⁺: 564.1, found: 564.1.

Example 27

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)-2-methylnicotinic acid (Compound 27)

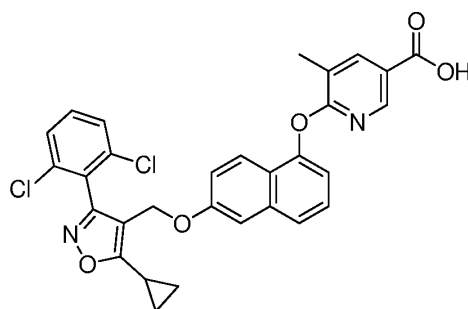


Following the procedure of Example 22, the title Compound 27 was obtained by substituting methyl 6-chloro-2-methylnicotinate for 22A-2.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.20 (d, $J = 8.5$ Hz, 1H), 7.63 (dd, $J = 8.8$, 4.5 Hz, 2H), 7.57 (s, 1H), 7.52 – 7.43 (m, 1H), 7.38 (d, $J = 2.7$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 6.90 (dd, $J = 9.2$, 2.5 Hz, 1H), 6.81 (d, $J = 8.6$ Hz, 1H), 4.98 (s, 2H), 2.48 (s, 3H), 1.23 – 1.00 (m, 5H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 561.1, found: 561.1.

10 **Example 28**

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)-5-methylnicotinic acid (Compound 28)

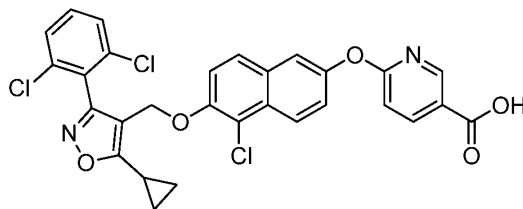


Following the procedure of Example 22, the title Compound 28 was obtained by substituting methyl 6-chloro-5-methylnicotinate for 22A-2.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.31 (d, $J = 2.3$ Hz, 1H), 8.19 (d, $J = 2.3$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 1H), 7.61 – 7.55 (m, 3H), 7.53 – 7.44 (m, 2H), 7.38 (d, $J = 2.7$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 6.88 (dd, $J = 9.1$, 2.5 Hz, 1H), 4.98 (s, 2H), 2.47 (s, 3H), 1.20 – 1.08 (m, 5H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 561.1, found: 561.1.

Example 29

Preparation of 6-((5-chloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 29)

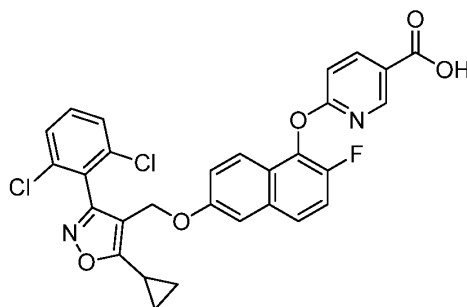


5

Following the procedure of Example 32, the title Compound 29 was obtained by substituting 6-bromo-1-chloronaphthalen-2-ol for 32A-1.

^1H NMR (400 MHz, DMSO- d_6) δ 8.63 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 8.9 Hz, 1H), 7.70 (s, 1H), 7.65 – 7.46 (m, 4H), 7.38 (s, 2H), 7.17 (d, J = 8.5 Hz, 1H), 5.09 (s, 2H), 1.21 – 1.02 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 581.0, found: 581.0.

Example 30
Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)nicotinic acid (Compound 30)



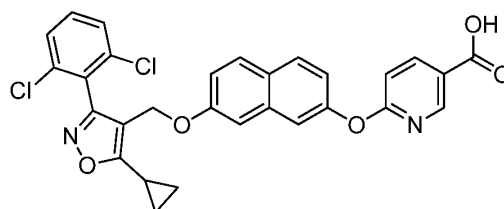
Following the procedure of Example 20, the title Compound 30 was obtained by substituting 6-bromo-2-fluoronaphthalen-1-ol for 20A-1.

^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 8.6, 2.4 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.66 (d, J = 6.9 Hz, 1H), 7.59 (s, 1H), 7.56 (dd, J = 5.7, 3.3 Hz, 1H), 7.51 (dd, J = 9.0, 7.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.25 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 9.2, 2.4 Hz, 1H), 5.02 (s, 2H), 1.28 –

1.08 (m, 5H). LCMS (ESI): calculated for $C_{29}H_{19}Cl_2FN_2O_5$; $[M+H]^+$: 565.1, found: 565.1.

Example 31

Preparation of 6-((7-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)nicotinic acid (Compound 31)

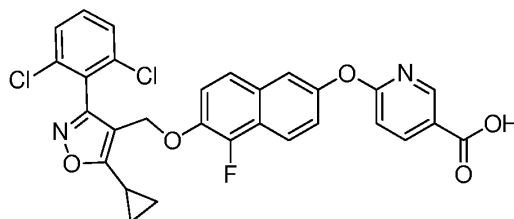


Following the procedure of Example 1, the title Compound 31 was obtained by substituting naphthalene-2,7-diol for 1A-2.

1H NMR (400 MHz, DMSO- d_6) δ 8.64 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.55 – 7.43 (m, 2H), 7.27 (s, 1H), 7.13 (t, J = 9.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 1H), 4.95 (s, 2H), 1.29 – 1.06 (m, 5H). LCMS (ESI): calculated for $C_{29}H_{20}Cl_2N_2O_5$; $[M+H]^+$: 547.1, found: 547.1.

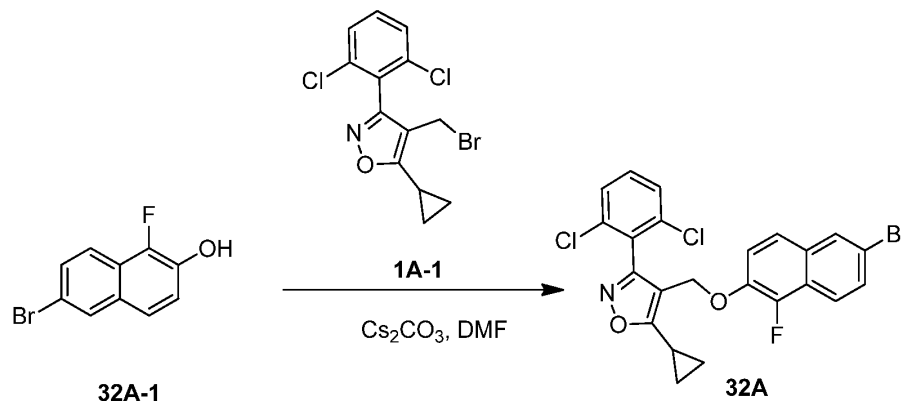
Example 32

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-5-fluoronaphthalen-2-yl)oxy)nicotinic acid (Compound 32)

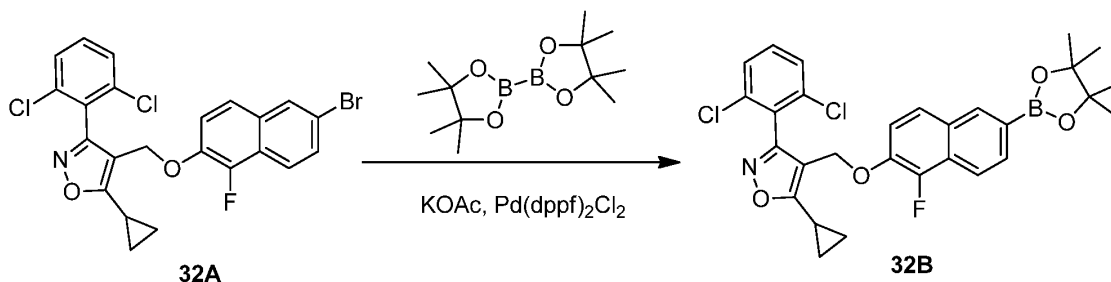


(a) Referring to the following reaction equation (Route B), Compound 32A-1 (1.0 g, 4.15 mmol, 1 eq.), Compound 1A-1 (1.44 g, 4.15 mmol, 1 eq.) and cesium carbonate (2.70 g, 8.30 mmol, 2 eq.) were dissolved in DMF (10 ml) for reacting. The reaction was carried out at 65°C for 2 h. After cooling, 10 ml water and 10 ml EA (ethyl acetate) were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 32A, 4-(((6-bromo-1-fluoronaphthalen-2-yl)oxy)methyl)-5-cyclopropyl-3-

(2,6-dichlorophenyl)isoxazole, 1.51 g, yield: 71.9%. LCMS (ESI): calculated for $C_{23}H_{15}BrCl_2FNO_2$; $[M+H]^+$: 506.0, found: 506.0.



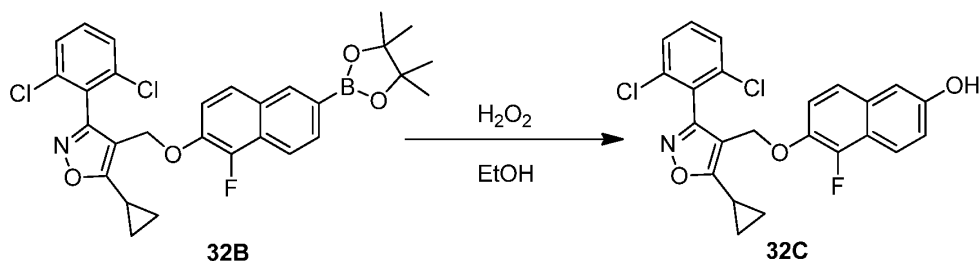
(b) Referring to the following reaction equation, compound 32A (200 mg, 0.39 mmol, 1 eq) was dissolved in dry THF (2 ml), then KOAc (76 mg, 0.78 mmol, 2 eq), $Pd(dppf)_2Cl_2$ (28 mg, 0.039 mmol, 0.1 eq), and bis(pinacolato)diboron (100 mg, 0.39 mmol, 1 eq) were added under N_2 , and the reaction mixture was heated to reflux for 2 h. After cooling, 10 ml water and 10 ml EA were added for extraction, and the organic phase was washed with water and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum:AcOEt = 3:1) to give Compound 32B, 5-cyclopropyl-3-(2,6-dichlorophenyl)-4-(((1-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)methyl)isoxazole, 137 mg, yield: 62.8%. LCMS (ESI): calculated for $C_{29}H_{27}BCl_2FNO_4$; $[M+H]^+$: 554.1, found: 554.1.



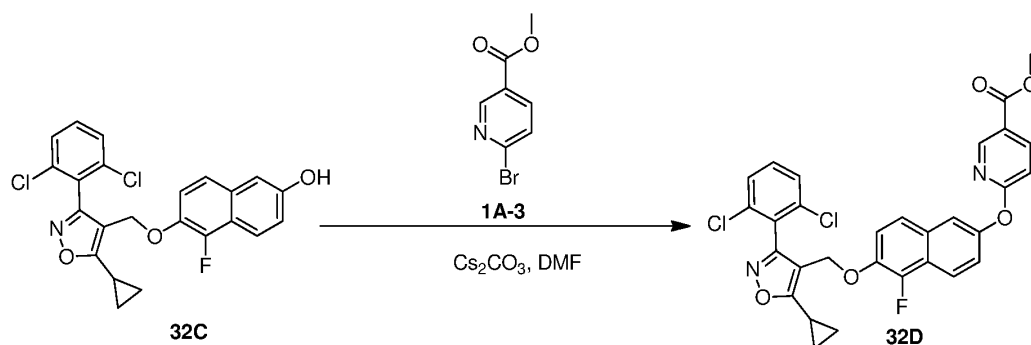
15

(c) Referring to the following reaction equation, compound 32B (100 mg) was dissolved in EtOH (2 ml), then 30% H_2O_2 aqueous solution (1 ml) were added. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous Na_2SO_3 , and extracted with EA. The organic phase was concentrated and purified on a column (PE/EA = 3/1) to give the compound 32C (61 mg, yield: 76.2%). LCMS (ESI): calculated for $C_{23}H_{16}Cl_2FNO_3$;

$[M+H]^+$: 444.1, found: 444.1.



(d) Referring to the following reaction equation, Compound 32C (50 mg, 0.11 mmol, 1 eq.), 1A-3 (24.3 mg, 0.11 mmol, 1 eq.) and cesium carbonate (71.5 mg, 0.22 mmol, 2 eq.) were dissolved in DMF (1 ml) for reacting. The reaction was carried out at 65°C for 2 h. After cooling, 5 ml water and 5 ml EA were added for extraction, and the organic phase was washed with water and concentrated to dryness to give Compound 32D, 40 mg, yield: 61.5%. LCMS (ESI): calculated for $C_{30}H_{21}Cl_2FN_2O_5$; $[M+H]^+$: 579.1, found: 579.1.



10

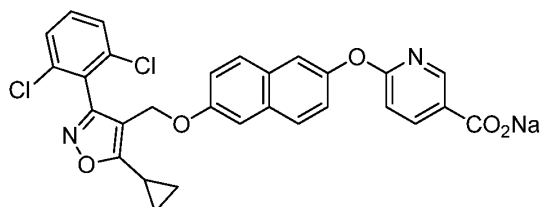
(e) Referring to the following reaction equation, compound 32D (30 mg) was dissolved in MeOH (1 ml), then 10% NaOH aqueous solution (0.5 ml) were added under N_2 , and the reaction mixture was heated to reflux for 1 h. The pH of the reaction solution was adjusted to 3 to 4 by adding 1N HCl solution, and 5 ml EA was added for extraction. The organic phase was concentrated and purified on a column (PE/EA/AcOH = 1/1/0.01 elution) to give the title compound 32 (21 mg, yield: 71.7%).

1H NMR (400 MHz, $DMSO-d_6$) δ 8.59 (d, J = 2.3 Hz, 1H), 8.31 (dd, J = 8.6, 2.4 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.62 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.56 (dd, J = 5.7, 3.3 Hz, 1H), 7.51 (dd, J = 9.0, 7.1 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.25 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 5.7, 4.3 Hz, 1H), 5.02 (s, 2H), 1.26 – 1.09 (m, 5H). LCMS (ESI): calculated for $C_{29}H_{19}Cl_2FN_2O_5$; $[M+H]^+$: 565.1, found: 565.1.

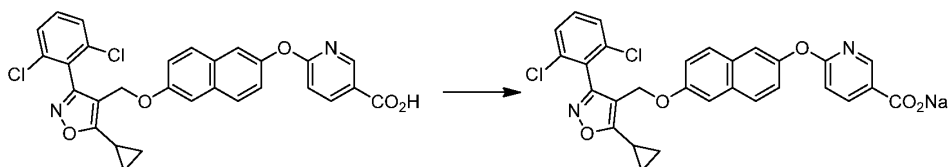
20



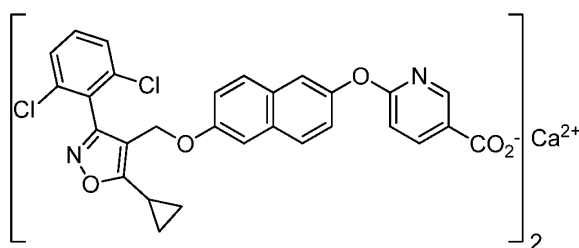
Preparation of Sodium 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl) 5 methoxy) naphthalen-2-yl)oxy)nicotinate.



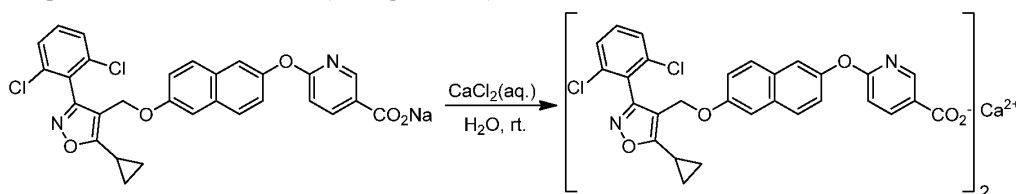
An aq. solution of NaOH (30%, 1.44 g, 1.2 eq) was added to a solution of Compound 1 (4.99 g, 9.12 mmol) in EtOH at r.t. After the reaction mixture was heated at reflux for 6 h, it was cooled to r.t. The solid was collected by filtration, washed with EtOH (10 ml), and dried to give a gray solid (4.07 g, yield: 78.3%).



Preparation of Calcium 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-15 4-yl)methoxy) naphthalen-2-yl)oxy)nicotinate.

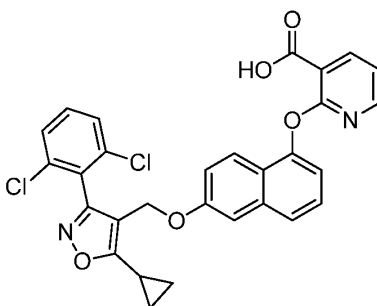


To a solution of Compound 35 (1.00 g, 1.76 mmol) in water (10 ml) was added a solution of CaCl_2 (1.0 g, 20%) in water. White precipitates formed. After the reaction mixture was stirred at r.t. for 4 h, the solid was collected by filtration, washed with water (2.0 ml) to give the product as a white solid (0.80 g, 76.7%).



Example 35

Preparation of 2-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)nicotinic acid



10

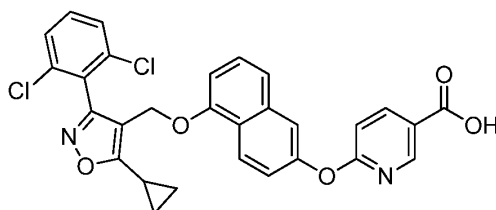
The title compound 35 was prepared according to Route D, following the procedure of Example 22. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.31 (s, 1H), 8.29–8.24 (m, 1H), 8.15–8.10 (m, 1H), 7.67 (d, $J = 9.1$ Hz, 1H), 7.64–7.56 (m, 3H), 7.53–7.47 (m, 1H), 7.47–7.42 (m, 1H), 7.36 (d, $J = 2.6$ Hz, 1H), 7.22–7.17 (m, 1H), 7.06 (d, $J = 7.4$ Hz, 1H), 6.92–6.87 (m, 1H), 4.98 (s, 2H), 1.24–1.08 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 547.1, found: 547.1.

15

Example 36

Preparation of 6-((5-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)

naphthalen-2-yl)oxy)nicotinic acid

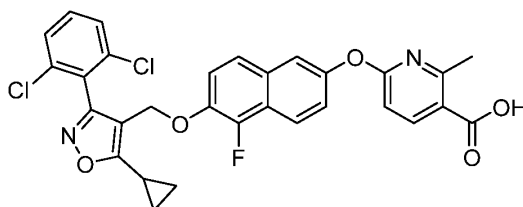


The title compound 36 was prepared according to Route B, following the procedure of
 5 Example 32. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.19 (s, 1H), 8.65 (d, *J* = 2.4 Hz, 1H), 8.29 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.77 (d, *J* = 9.1 Hz, 1H), 7.65–7.54 (m, 3H), 7.51–7.44 (m, 1H), 7.44–7.34 (m, 2H), 7.19 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 5.09 (s, 2H), 1.31–1.07 (m, 6H). LCMS (ESI): calculated for C₂₉H₂₀Cl₂N₂O₅; [M+H]⁺: 547.1, found: 547.1.

10

Example 37

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-5-fluoronaphthalen-2-yl)oxy)-2-methylnicotinic acid



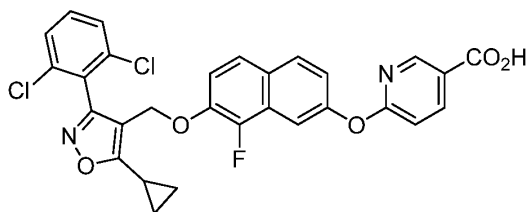
15

The title compound 37 was prepared according to Route B, following the procedure of
 Example 32. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.68 (s, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.55–7.51 (m, 1H), 7.43–7.34 (m, 2H), 6.92 (d, *J* = 8.6 Hz, 1H),
 20 5.09 (s, 2H), 2.52 (s, 3H), 1.19 – 1.08 (m, 4H). LCMS (ESI): calculated for C₃₀H₂₁Cl₂FN₂O₅; [M+H]⁺: 579.1, found: 579.1.

Example 38

Preparation of 6-((7-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-8-fluoronaphthalen-2-yl)oxy)nicotinic acid

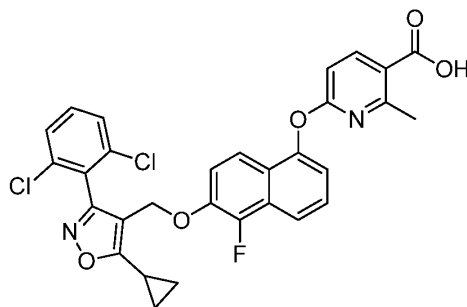
25



The title compound 38 was prepared according to Route B, following the procedure of Example 32. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.64 (s, 1H), 8.30 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.96 (d, $J = 8.9$ Hz, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.64–7.48 (m, 3H),
 5 7.37 (t, $J = 8.8$ Hz, 1H), 7.27 (d, $J = 9.2$ Hz, 1H), 7.19 (d, $J = 8.6$ Hz, 1H), 6.85 (s, 1H), 5.10 (s, 2H), 2.07–1.89 (m, 1H), 0.94–0.76 (m, 4H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 565.1, found: 565.1.

Example 39

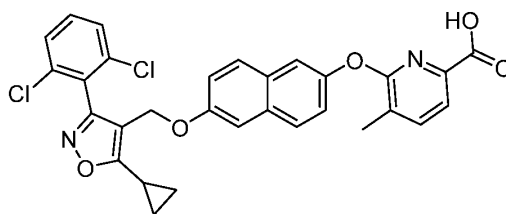
10 Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-5-fluoronaphthalen-1-yl)oxy)-2-methylnicotinic acid



The title compound 39 was prepared according to Route B, following the procedure of Example 32. ^1H NMR (400 MHz, CDCl_3) δ 7.94 (dd, $J = 7.9, 5.0$ Hz, 1H), 7.83
 15 (d, $J = 8.1$ Hz, 1H), 7.72–7.59 (m, 2H), 7.58–7.49 (m, 2H), 7.49–7.38 (m, 2H), 7.25–6.97 (m, 1H), 6.67 (d, $J = 7.9$ Hz, 1H), 5.52 (d, $J = 16.9$ Hz, 1H), 5.24 (d, $J = 16.9$ Hz, 1H), 2.70–2.96 (M, 1H), 2.61 (s, 3H), 1.05–0.89 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 579.1, found: 579.1.

20 Example 40

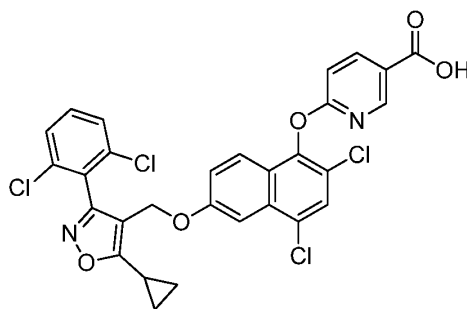
Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)-5-methylpicolinic acid



The title compound 40 was prepared according to Route D, following the procedure of Example 22. ^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.65–7.55 (m, 2H), 7.54–7.49 (m, 2H), 7.50–7.40 (m, 2H), 7.22 (t, $J = 2.3$ Hz, 1H), 7.03–6.93 (m, 2H), 5.44 (s, 2H), 2.95–2.58 (m, 1H), 2.22 (s, 3H), 1.01 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 561.1, found: 561.1.

Example 41

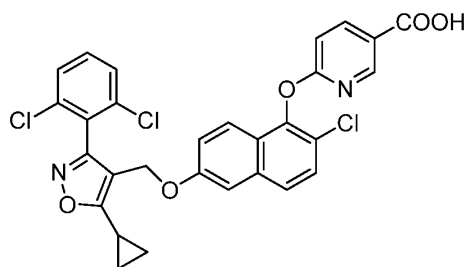
10 Preparation of 6-((2,4-dichloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)nicotinic acid



The title compound 41 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.17 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.34 (dd, $J = 8.6, 2.4$ Hz, 1H), 7.84–7.78 (m, 2H), 7.70–7.65 (m, 2H), 7.64–7.56 (m, 2H), 7.38 (dd, $J = 9.1, 2.3$ Hz, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 4.92 (s, 2H), 2.45–2.41 (m, 1H), 1.22–1.10 (m, 4H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{18}\text{Cl}_4\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 615.0, found: 615.0.

20 Example 42

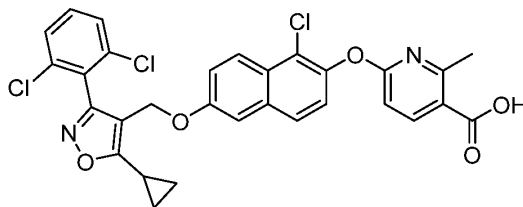
Preparation of 6-((2-chloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)nicotinic acid



The title compound 42 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.15 (s, 1H), 8.65 (d, $J = 2.4$ Hz, 1H), 8.31 (dd, $J = 8.6, 2.4$ Hz, 1H), 7.76 (d, $J = 2.4$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 3H), 7.66–7.59 (m, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.44 (d, $J = 9.1$ Hz, 1H), 7.22 (dd, $J = 9.1, 2.4$ Hz, 1H), 7.19 (d, $J = 8.6$ Hz, 1H), 4.87 (s, 2H), 2.46–2.40 (m, 1H), 1.30–1.09 (m, 4H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 581.0, found: 581.0.

10 **Example 43**

Preparation of 6-(((1-chloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-2-yl)oxy)-2-methylnicotinic acid

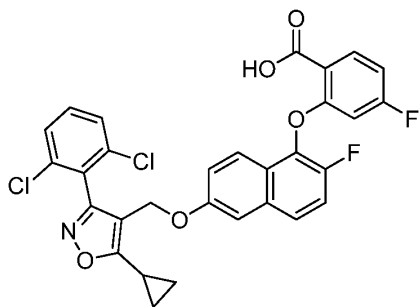


The title compound 43 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.97 (s, 1H), 8.24 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.80 (d, $J = 8.9$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.55–7.49 (m, 1H), 7.47 (s, 1H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.12 (dd, $J = 9.2, 2.5$ Hz, 1H), 6.95 (d, $J = 8.6$ Hz, 1H), 5.02 (s, 2H), 2.47 (s, 3H), 1.23–1.11 (m, 5H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 595.1, found: 595.1.

20

Example 44

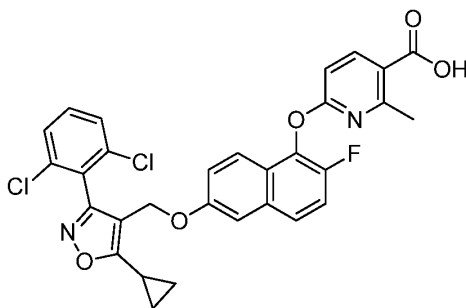
Preparation of 2-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)-4-fluorobenzoic acid



The title compound 44 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.04 (s, 1H), 7.82 (t, $J = 8.6$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.57 (d, $J = 7.8$ Hz, 2H), 7.52–7.46 (m, 1H), 7.39 (d, $J = 2.4$ Hz, 1H), 7.37–7.31 (m, 1H), 7.15–7.10 (m, 1H), 7.01 (dd, $J = 9.3, 2.4$ Hz, 1H), 6.88 (dd, $J = 12.3, 2.4$ Hz, 1H), 6.73 (dd, $J = 8.7, 2.3$ Hz, 1H), 5.08 (s, 2H), 1.28–1.05 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{19}\text{Cl}_2\text{F}_2\text{NO}_5$; $[\text{M}+\text{H}]^+$: 582.1, found: 582.1.

10 **Example 45**

Preparation of 6-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)-2-methylnicotinic acid

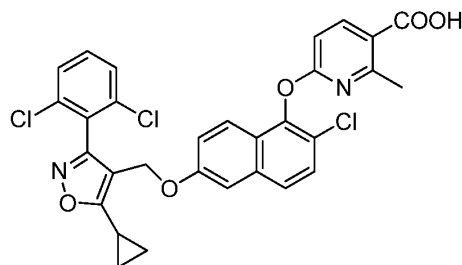


The title compound 45 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.98 (s, 1H), 8.21 (d, $J = 8.6$ Hz, 1H), 7.65 (dd, $J = 9.3, 1.7$ Hz, 1H), 7.57 (d, $J = 7.7$ Hz, 2H), 7.51–7.44 (m, 1H), 7.37 (d, $J = 2.5$ Hz, 1H), 7.35–7.29 (m, 1H), 7.16–7.11 (m, 1H), 6.98 (dd, $J = 9.2, 2.5$ Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 1H), 5.08 (s, 2H), 1.22–1.09 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 579.1, found: 579.1.

20

Example 46

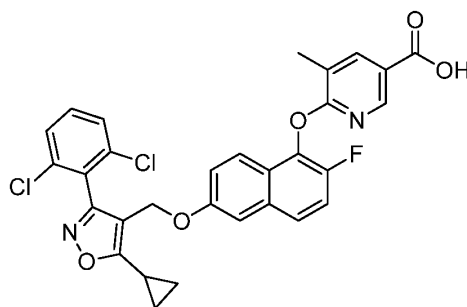
Preparation of 6-((2-chloro-6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)naphthalen-1-yl)oxy)-2-methylnicotinic acid



The title compound 46 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.03 (s, 1H), 8.25 (d, $J = 8.6$ Hz, 1H), 7.76 (d, $J = 9.2$ Hz, 1H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.49–7.44 (m, 1H), 7.18 (d, $J = 8.2$ Hz, 1H), 7.04 (dd, $J = 9.2, 2.4$ Hz, 1H), 6.95 (d, $J = 8.6$ Hz, 1H), 5.13 (s, 2H), 2.59–2.54 (m, 1H), 2.48 (s, 3H), 1.27–1.15 (m, 4H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_3\text{N}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 595.1, found: 595.1.

Example 47

Preparation of 6-((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)-5-methylnicotinic acid



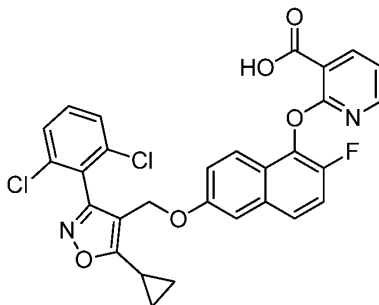
15

The title compound 47 was prepared according to Route C, following the procedure of Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.09 (s, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 7.67–7.55 (m, 3H), 7.55–7.45 (m, 1H), 7.39 (s, 1H), 7.37–7.30 (m, 1H), 7.20–7.09 (m, 1H), 7.03–6.93 (m, 1H), 5.09 (s, 2H), 2.48 (s, 3H), 1.41–1.00 (m, 5H). LCMS (ESI): calculated for $\text{C}_{30}\text{H}_{21}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 579.1, found: 579.1.

20

Example 48

Preparation of 2-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)nicotinic acid

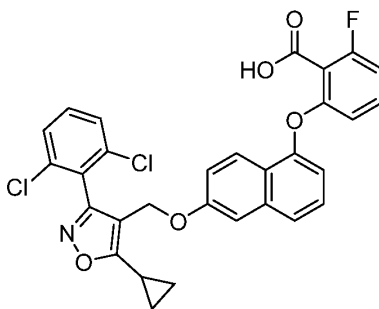


The title compound 48 was prepared according to Route C, following the procedure of
 5 Example 20. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.29–8.27 (m, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.09–8.06 (m, 1H), 7.53–7.47 (m, 3H), 7.46–7.42 (m, 1H), 7.30–7.25 (m, 2H), 7.08–7.05 (m, 1H), 6.96 (dd, J = 8.4, 2.4 Hz, 1H), 5.44 (s, 2H), 2.79 (p, J = 6.4 Hz, 1H), 1.20–1.09 (m, 5H). LCMS (ESI): calculated for $\text{C}_{29}\text{H}_{19}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 565.1, found: 565.1.

10

Example 49

Preparation of 2-(((6-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methoxy)-2-fluoronaphthalen-1-yl)oxy)-4-fluorobenzoic acid



15 The title compound 49 was prepared according to Route D, following the procedure of Example 22. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.62 (s, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.63–7.55 (m, 3H), 7.54–7.49 (m, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.40–7.32 (m, 2H), 7.06 (t, J = 8.8 Hz, 1H), 6.96 (dd, J = 9.1, 2.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 4.99 (s, 2H), 1.23–1.09 (m, 4H). LCMS
 20 (ESI): calculated for $\text{C}_{30}\text{H}_{20}\text{Cl}_2\text{FN}_2\text{O}_5$; $[\text{M}+\text{H}]^+$: 564.1, found: 564.1.

Biology Examples

Compound of formula (I) in HBV Cell-Based Assay

PHH (primary human hepatocyte) Assay: Cell line and compound treatment

The PHH cells were seeded into the 48-well plates at the density of 1.32×10^5 cells/well.

- 5 The PHH cells seeding date was defined as day 0. The PHH cells were infected with HBV (D type) at 1600GE/cell on day 1. The culture medium containing compounds was refreshed on day 2, 4, 6 and day 8. On day 9, the cells were treated with CCK8 and culture supernatant and cells were collected.

- 10 FXR Compounds were tested at 10000.0, 3000.0, 1000.0, 300.0, 100.0, 30.0, and 10.0 nM, and ETV was tested at 0.2000, 0.0667, 0.0222, 0.0074, 0.0025, 0.0008, and 0.0003 nM. 1% DMSO was used as non-treatment control. The supernatants on day 9 were collected, and analyzed for HBV DNA by qPCR, HBV RNA by RT-qPCR, HBsAg and HBeAg by ELISA.

HBV DNA, RNA and antigen assay

- 15 DNA in the culture supernatants was isolated with the QIAamp 96 DNA Blood Kit according to the manual and quantified by the qPCR. 80 μ l of the culture supernatants sample was used to extract DNA. The elution volume was 120 μ l. The PCR mix (8 μ l/well) and the samples (2 μ l/well) or plasmid standards (2 μ l/well) were added to the 384-well optical reaction plate and performed using the following program: 95°C for 10 min, then cycling at 95°C 15 sec, 60°C 1 min for 40 cycles.

- 20 RNA in the culture supernatants was isolated with the PureLink™ Pro 96 Viral RNA Kit according to the manual. 35 μ l of the culture supernatants sample was used to extract RNA. The elution volume was 100 μ l. HBV RNA was quantified by RT-qPCR.

- For HepG2-NTCP Assay, HBsAg and HBeAg in the samples harvested on day 9 were measured by the HBsAg ELISA kit (Autobio) and HBeAg ELISA kit (Autobio) according to the manual. For PHH assay, Chemiluminescence Apparatu was used to measure HBsAg according to the Antu HBsAg ELISA kit manual.

- After collecting culture supernatants at the terminal day for each plate, CCK-8 working solution (diluted with fresh culture medium at ratio of 1:9) was added to the cell plates. The plates were incubated at 37°C, 5% CO₂ incubator for approximate 30 min. The ODs were measured by microplate reader (OD450nm/OD630nm).

Dose Response Curves

% HBV DNA inhibition= (1-HBV DNA copy number of test sample/ avg. HBV DNA

copy number of 1% DMSO control) $\times 100\%$

% HBV RNA inhibition = (1-HBV RNA copy number of test sample/ avg. HBV RNA copy number of 1% DMSO control) $\times 100\%$

% HBsAg inhibition = (1-HBsAg quantity of sample/ HBsAg quantity of 1% DMSO control) $\times 100\%$

% HBeAg inhibition = (1-HBeAg quantity of sample/ HBeAg quantity of 1% DMSO control) $\times 100\%$

% Cell viability = value of sample/ avalue of 1% DMSO $\times 100\%$.

The EC50 and CC50 values were determined by dose-response curves fitted by GraphPad Prism using "log (agonist) vs. response - variable slope".

Results

As shown in in Figure 1, 2 and 3, in PHH assay, Compound 1, 22, and 27 had dose-dependent inhibition of extracellular HBV DNA HBsAg and HBV RNA. As control, ETV showed significant inhibition of HBV DNA, but no significant inhibition of HBV HBsAg and HBV RNA.

Compound of formula (I) in AAV/HBV Animal Model

AAV/HBV mouse model and compound treatment

Male C57BL/6 mice of 5-week old (obtained from Shanghai Jihui Laboratory Animal Care Co., Ltd) were given rAAV8-1.3HBV (1×10^{11} v.g.) via tail vein to establish infection on Day -28. After 14 days, 21 days, and on Day -4, blood was drawn from submandibular vein to determine the level of HBV DNA, and HBsAg. On Day-4, 40 mice were chosen based on HBV DNA, and HBsAg results, and were randomly assigned to 5 groups. After the mice were infected with HBV virus for 28 days, treatment was given orally once per day, for 4 weeks. Group 1 was given vehicle (0.5% CMC-Na, 10 ml/kg), Group 2 was given positive control ETV (0.1 mg/kg). Groups 3, 4, and 5 were given Compound 33 at 10 mg/kg, 30 mg/kg, and 60 mg/kg, respectively. Blood was drawn from submandibular vein every week to determine the concentration of HBV DNA, HBV RNA, and HBsAg. On Day 28, blood was taken from the heart.

Blood sample analysis

HBV DNA determination by qPCR. DNA in the mice plasma was isolated with the

QIAamp 96 DNA Blood Kit according to the manual and quantified by the qPCR, and performed using the following program: 95°C for 10 min, then cycling at 95°C 15 sec, 60°C 1 min for 40 cycles.

HBV RNA determination by qPCR. RNA in the mice plasma was isolated with the
5 PureLink™ Pro 96 Viral RNA/DNA Kit according to the manual. 20 µl of the plasma was used to extract RNA

HBsAg determination by ELISA. HBsAg in the samples was measured by the HBsAg ELISA kit (Autobio) according to the manual. Briefly, after the plasma was diluted 1200x in a coated plate, and incubate with the enzyme conjugated (37°C, 60min), and the plate was
10 washed 5 time. Substrate was added, and it was kept from light at room temperature for 10 min and intensity was measured by a plated reader.

Data analysis

Average $\pm$ Standard deviation was calculated for each group, and analyzed with Student's t-test.

15 Results

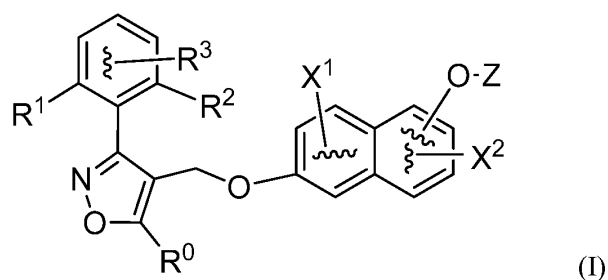
As shown in Figure 4, after Compound 33 was given to the mice for 28 days, the HBV DNA in the high dose group (60 mg/kg) was significantly lower than that of the vehicle group. On average, the log₁₀[DNA copy/uL] of the high dose group was 0.77-1.12 lower than the vehicle group (p<0.05).

20 As shown in Figure 5, after Compound 33 was given to the mice for 28 days, the HBV RNA in the high dose group (60 mg/kg) was significantly lower than that of the vehicle group. On average, the log₁₀[RNA copy/uL] of the high dose group was 0.60-0.66 lower than the vehicle group (p<0.01). ETV treatment showed no significant effect on HBV RNA as compared to the vehicle group.

25 As shown in Figure 6, after Compound 33 was given to the mice for 28 days, the HBsAg in the high dose group (60 mg/kg) was lowered by 0.38 log₁₀ [IU/ml] as compared to the vehicle group. ETV treatment showed no significant effect on HBsAg as compared to the vehicle group.

CLAIMS

1. A method of treating or preventing infection with hepatitis B virus in a human or animal, comprising administering to the human or animal in need thereof a therapeutically effective amount of a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), and a pharmaceutically acceptable salt, ester or stereoisomer thereof:



wherein:

- R^1 , R^2 and R^3 are independently selected from H, halogen, unsubstituted or halogen substituted C_{1-6} alkyl and unsubstituted or halogen substituted C_{1-6} alkoxy, provided that at least one of R^1 , R^2 and R^3 is not hydrogen, R^0 is selected from unsubstituted or halogen substituted C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{4-7} alkylcycloalkyl;

X^1 and X^2 are independently selected from H and halogen;

- moiety $-O-Z$ attaches to the naphthalene ring, wherein Z is a residue selected from 5-10 membered aryl or 5-10 membered heteroaryl optionally having one or more hetero atoms selected from N, O and S, wherein the 5-10 membered aryl or 5-10 membered heteroaryl is substituted by R^4 and is optionally further substituted by R^5 ; and

- wherein R^4 is selected from $-COOH$, $-CH_2COOH$, $-NHSO_2CF_3$, $-SO_2NH-C_{1-6}$ alkyl, $-SO_3H$, $-CONHSO_2-C_{1-6}$ alkyl, $-CONHSO_2-C_{3-6}$ cycloalkyl, $-CONHSO_2-5-10$ membered aryl and $-CONHSO_2-5-10$ membered aryl substituted by C_{1-6} alkyl at the aryl, and wherein R^5 is selected from H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, $-O-(C_{1-6}$ alkyl) and $-NH-(C_{1-6}$ alkyl).

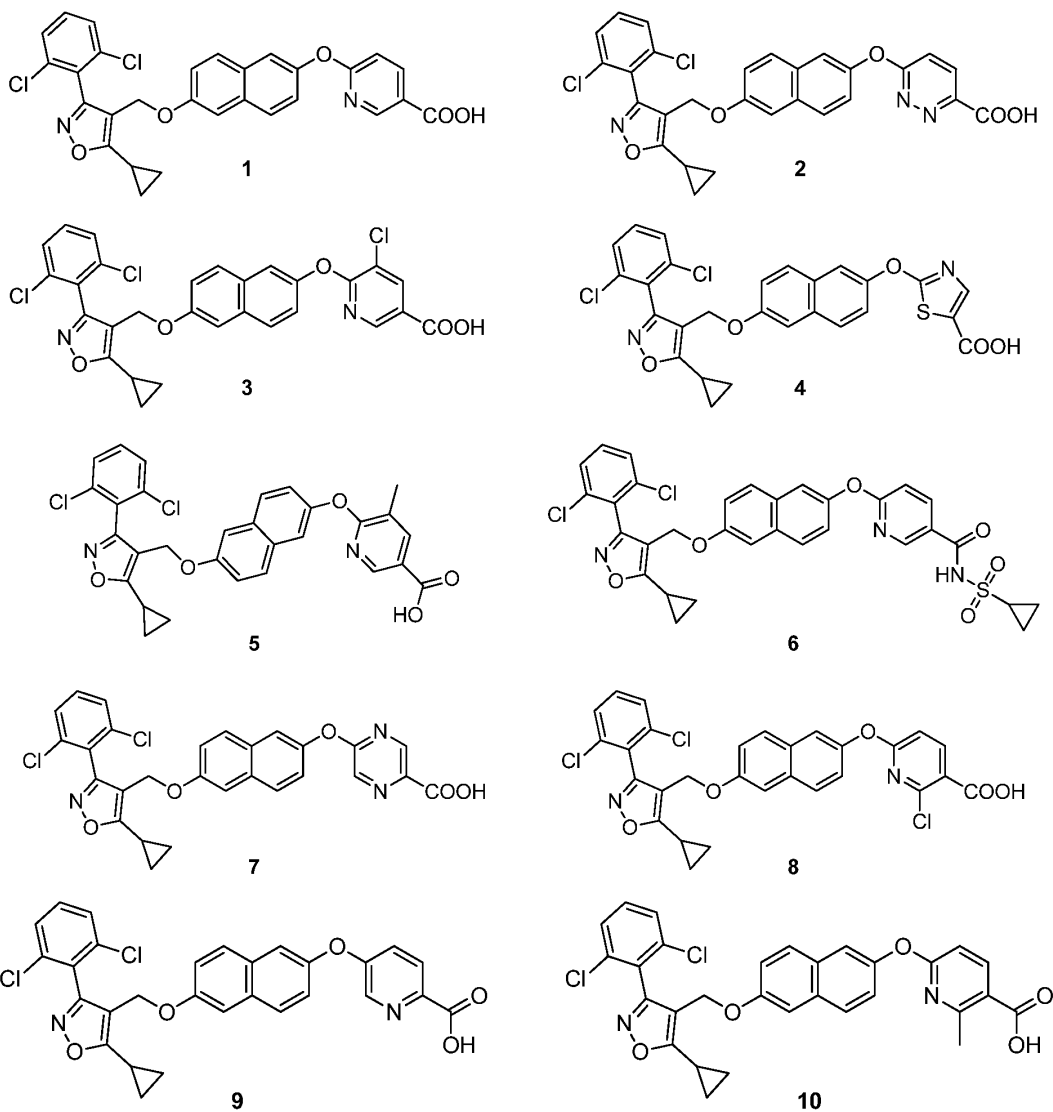
2. The method according to claim 1, wherein R^1 , R^2 and R^3 are independently selected from H, halogen and C_{1-3} perfluoroalkoxy, and R^0 is selected from isopropyl or cyclopropyl;
- wherein Z is a phenyl which is substituted by R^4 and is optionally substituted by R^5 ; or Z is a 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5 ; and
- wherein the halogen is fluoro or chloro.

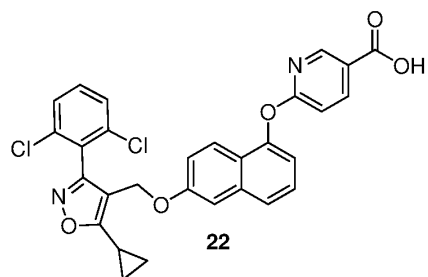
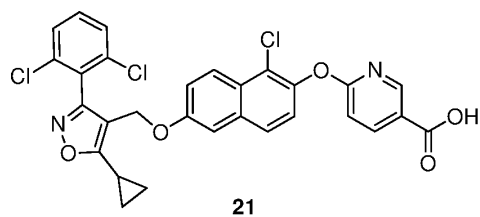
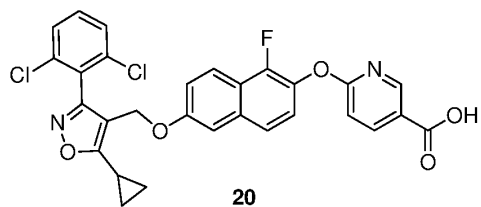
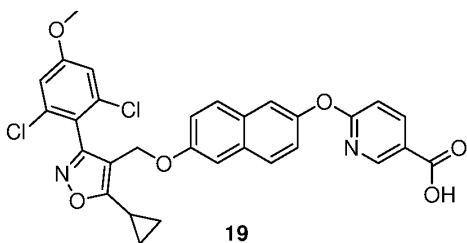
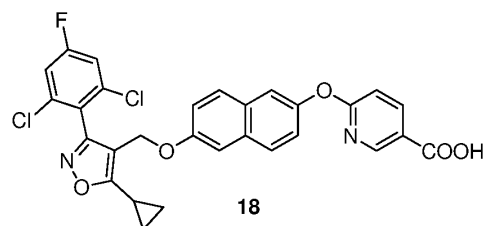
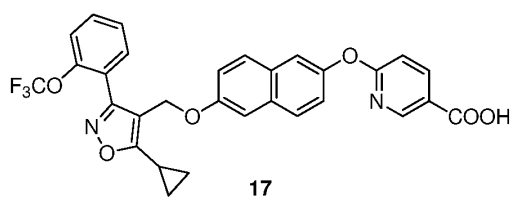
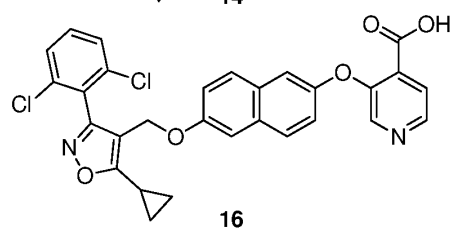
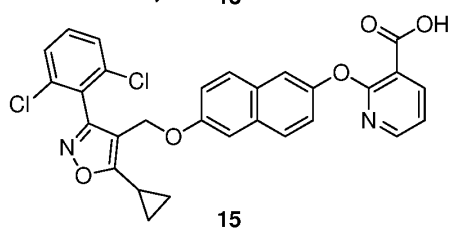
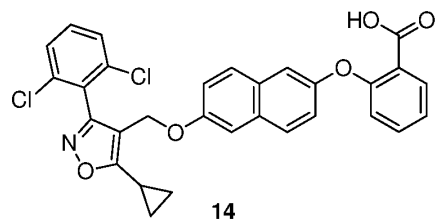
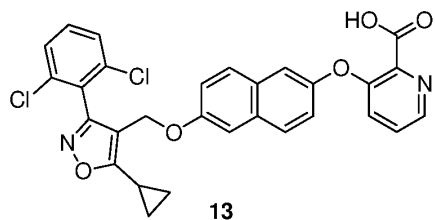
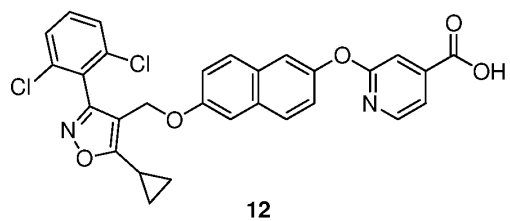
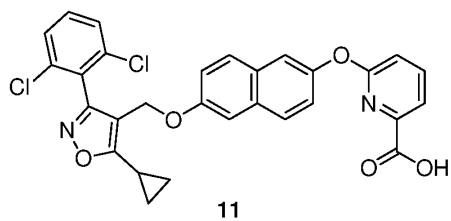
3. The method according to claim 2, wherein R^1 , R^2 and R^3 are independently selected from H, Cl, F and $-O-CF_3$; and

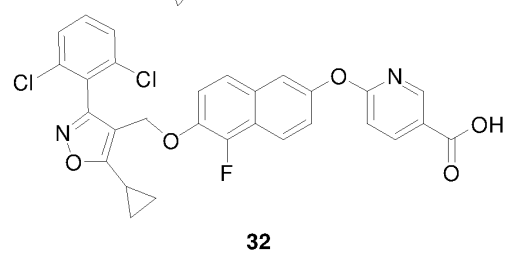
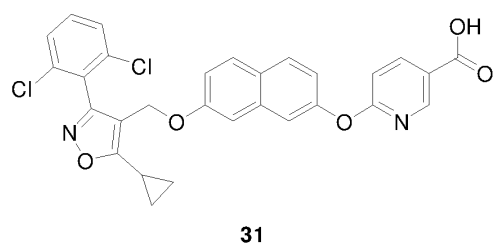
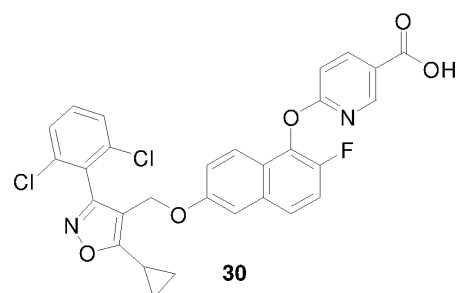
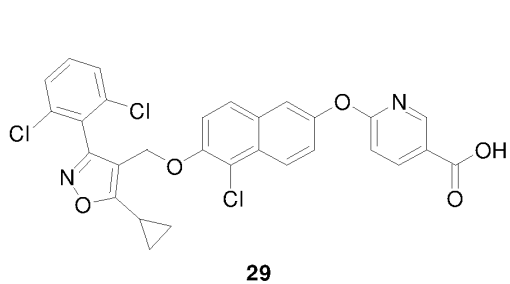
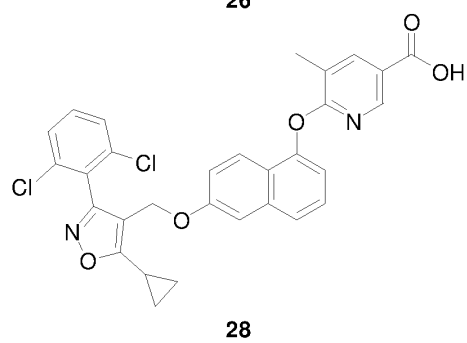
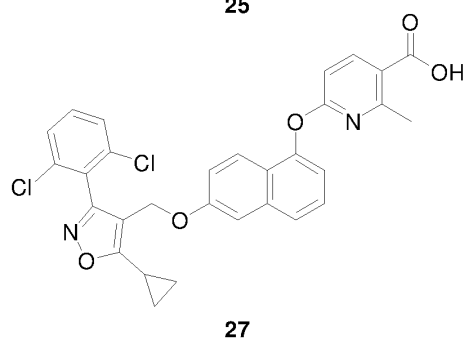
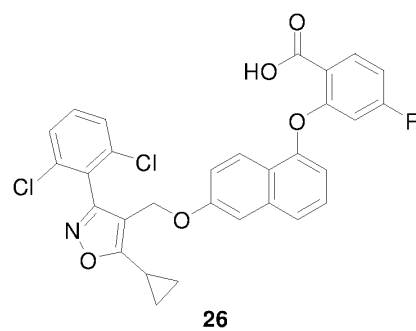
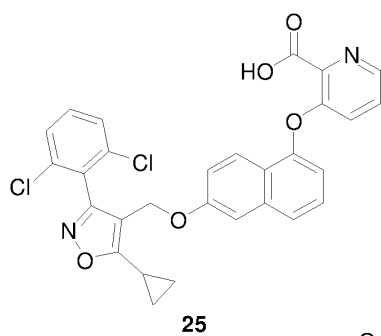
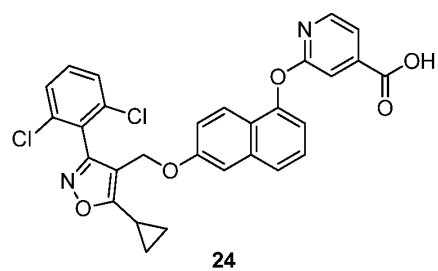
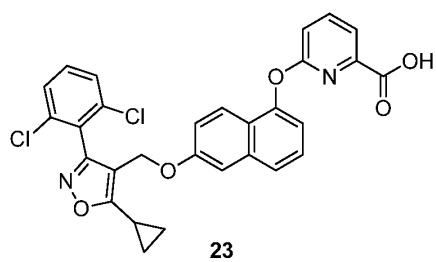
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5 , wherein R^4 is selected from $-COOH$, $-CH_2COOH$, $-CONHSO_2-C_{1-6}$ alkyl and $-CONHSO_2-C_{3-6}$ cycloalkyl, R^5 is selected from H, C_{1-3} alkyl and halogen.

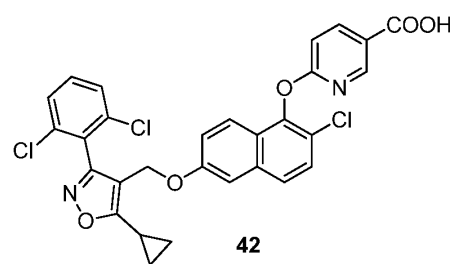
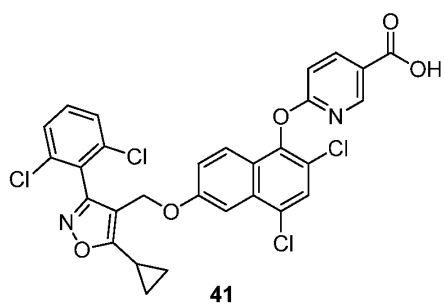
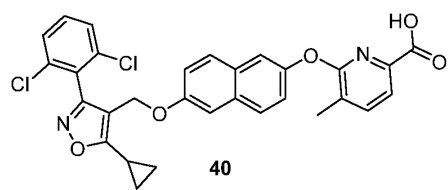
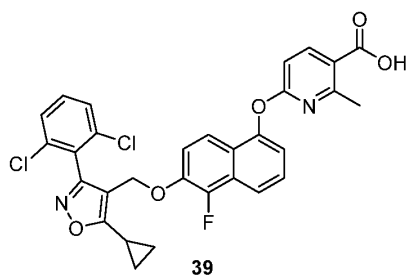
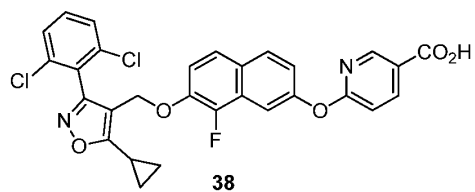
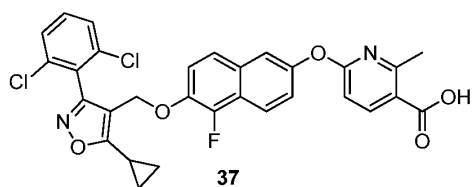
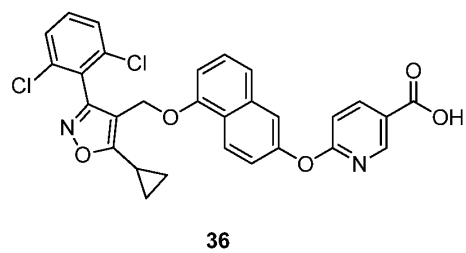
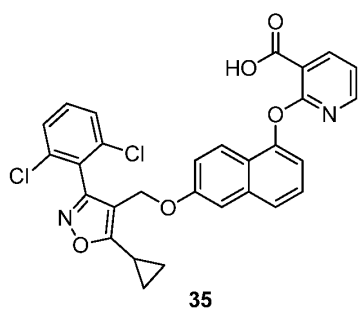
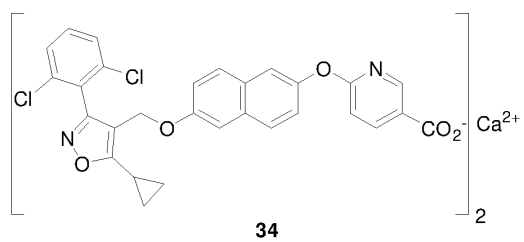
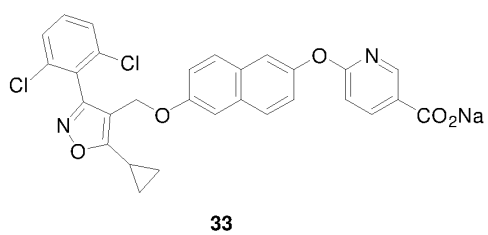
4. The method according to claim 3, wherein Z is pyridyl; R^4 is $-COOH$; and R^5 is H or halogen.

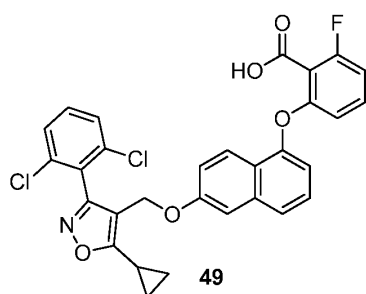
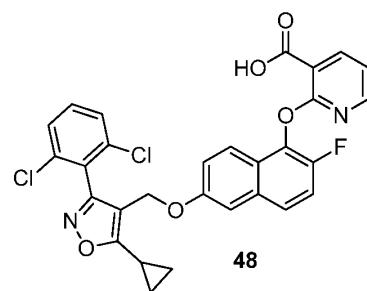
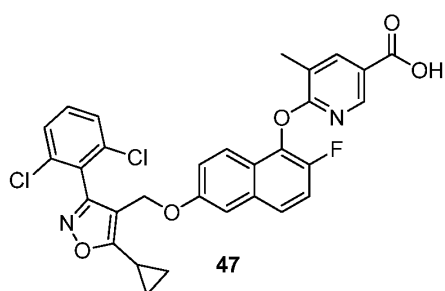
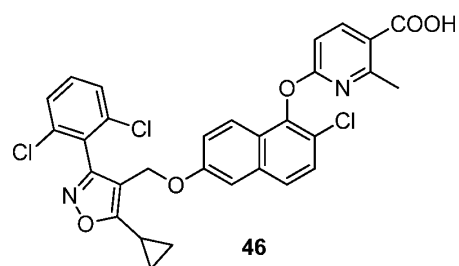
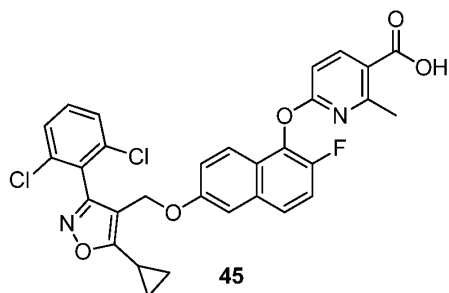
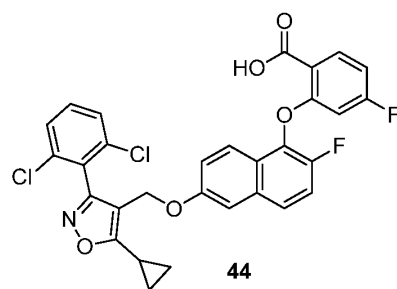
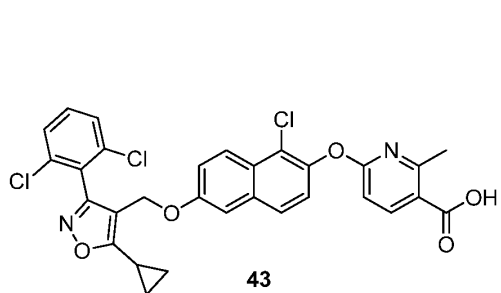
5. The method according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



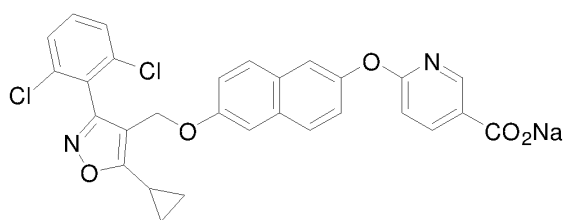








5 6. The method according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



33

7. The method according to claim 1, wherein the method comprises administering the phenylisoxazolymethylene-naphthalene-ether derivative having the structure of formula (I), its pharmaceutically acceptable salt, and ester or stereoisomer in combination with one or more
5 other anti-HBV agents.

8. The method of claim 7, wherein the other anti-HBV agents are selected from HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators, toll-like receptor (TLR) modulators, interferon alpha receptor ligands, hepatitis b surface antigen (HBsAg) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral
10 mRNA, short interfering RNAs (siRNA) and ddRNAi endonuclease modulators, ribonucleotide reductase inhibitors, HBV E antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, fatty acid synthase inhibitors, HBV antibodies, CCR2 chemokine antagonists, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, PD-1 inhibitors, PD-L1 inhibitors, KDM inhibitors, and HBV replication inhibitors.

15 9. The method of claim 8, wherein the HBV DNA polymerase inhibitor is entecavir or tenofovir;

the PD-1 inhibitor is one or more selected from nivolumab, pembrolizumab, pidilizumab, BGB-108, SHR-1210, PDR-001, PF-06801591, IBI-308, cemiplimab, camrelizumab, sintilimab, tislelizumab (BGB-A317), BCD-100, JNJ-63723283, Zimberelimab (GLS-010,
20 WBP-3055), Balstilimab (AGEN2034) and dostarlimab (TSR-042);

the PD-L1 inhibitors is one or more selected from atezolizumab (RG-7446), avelumab, BGB-A333, BMS-936559 (MDX-1105), durvalumab, CX-072, GX-P2, KN035 (ASC022), GS-4224 and INCB086550;

the antisense oligonucleotide is Ionis-HBVRx or Ionis-HBV-LRx

25 the short interfering RNA is JNJ-3989, or Vir-2218, or DCR-HBVS

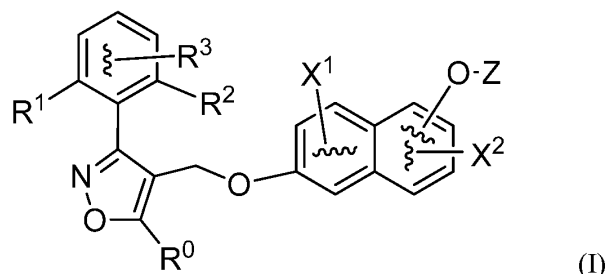
the fatty acid synthase inhibitor is TVB-2640 and/or TVB-3567;

the interferon is Pegasys; and

the capsid inhibitor is one or more selected from ABI-H0731, ABI-H2158, ABI-H3733,

CB-HBV-001, JNJ-6379, JNJ-0440, QL-007, RG-7907 and RO7049389.

10. Use of a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof in the preparation of a pharmaceutical composition for anti-hepatitis B virus:



wherein:

R^1 , R^2 and R^3 are independently selected from H, halogen, unsubstituted or halogen substituted C_{1-6} alkyl and unsubstituted or halogen substituted C_{1-6} alkoxy, provided that at least one of R^1 , R^2 and R^3 is not hydrogen, R^0 is selected from unsubstituted or halogen substituted C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{4-7} alkylcycloalkyl;

X^1 and X^2 are independently selected from H and halogen;

moiety $-O-Z$ attaches to the naphthalene ring, wherein Z is a residue selected from 5-10 membered aryl or 5-10 membered heteroaryl optionally having one or more hetero atoms selected from N, O and S, wherein the 5-10 membered aryl or 5-10 membered heteroaryl is substituted by R^4 and is optionally further substituted by R^5 ; and

wherein R^4 is selected from $-COOH$, $-CH_2COOH$, $-NHSO_2CF_3$, $-SO_2NH-C_{1-6}$ alkyl, $-SO_3H$, $-CONHSO_2-C_{1-6}$ alkyl, $-CONHSO_2-C_{3-6}$ cycloalkyl, $-CONHSO_2-5-10$ membered aryl and $-CONHSO_2-5-10$ membered aryl substituted by C_{1-6} alkyl at the aryl, and wherein R^5 is selected from H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, $-O-(C_{1-6}$ alkyl) and $-NH-(C_{1-6}$ alkyl).

11. The use according to claim 10, wherein R^1 , R^2 and R^3 are independently selected from H, halogen and C_{1-3} perfluoroalkoxy, and R^0 is selected from isopropyl or cyclopropyl; and

wherein Z is a phenyl which is substituted by R^4 and is optionally substituted by R^5 ; or Z is a 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5 ; and

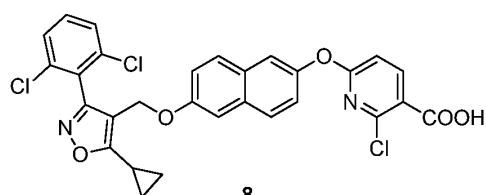
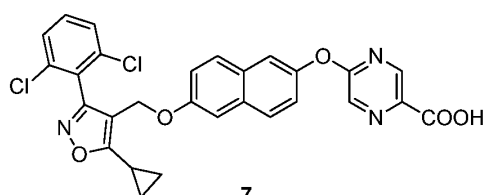
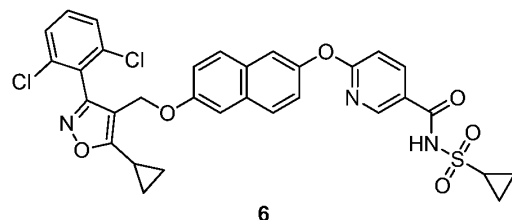
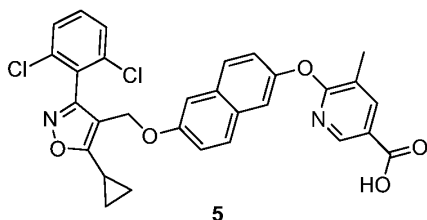
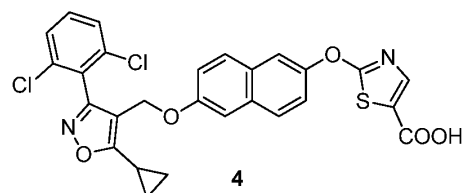
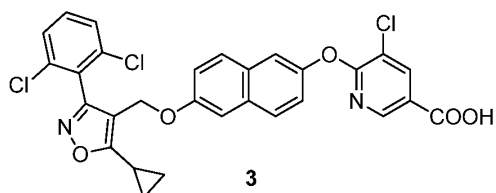
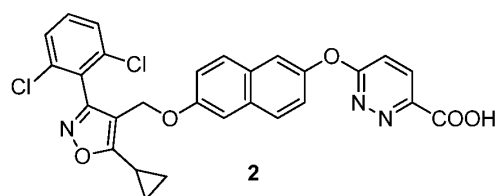
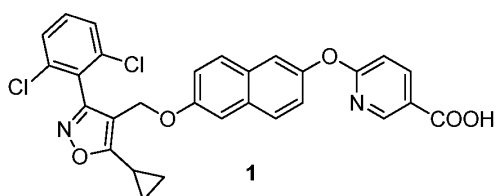
wherein the halogen is fluoro or chloro.

12. The use according to claim 11, wherein R^1 , R^2 and R^3 are independently selected from H, Cl, F and $-O-CF_3$; and

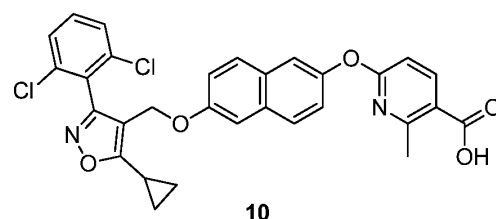
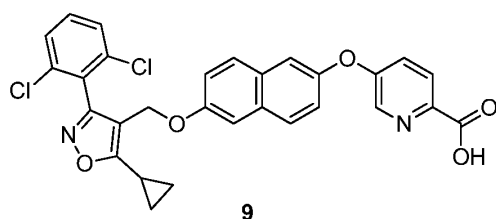
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵, wherein R⁴ is selected from -COOH, -CH₂COOH, -CONHSO₂-C₁₋₆ alkyl and -CONHSO₂-C₃₋₆ cycloalkyl, R⁵ is selected from H, C₁₋₃ alkyl and halogen.

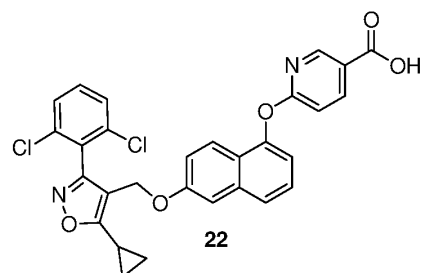
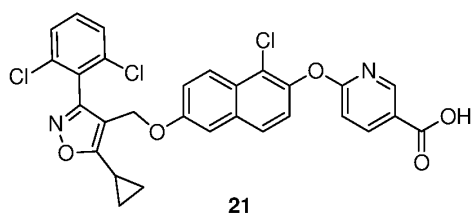
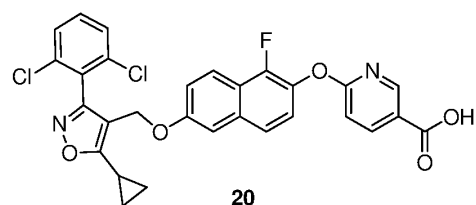
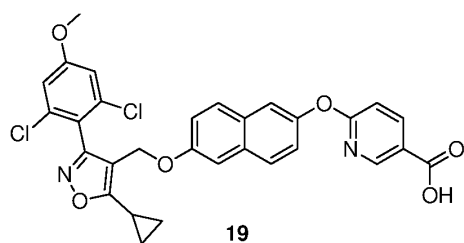
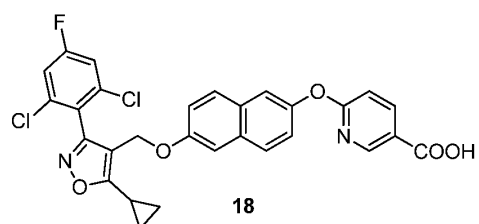
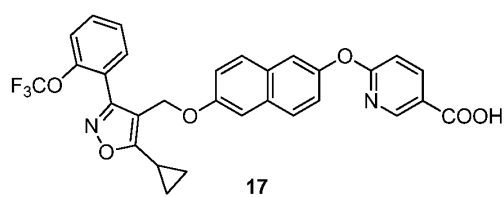
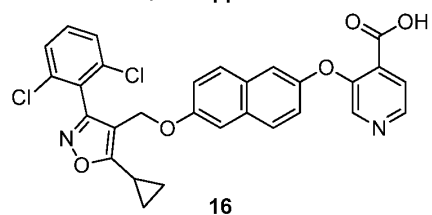
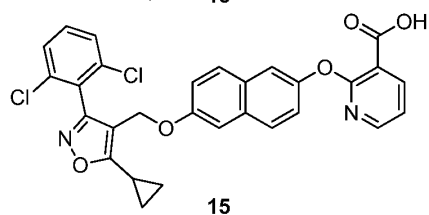
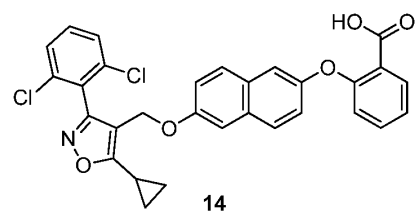
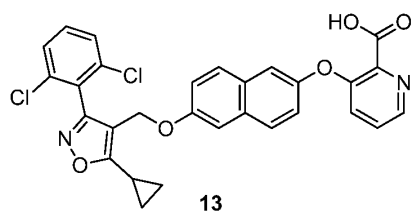
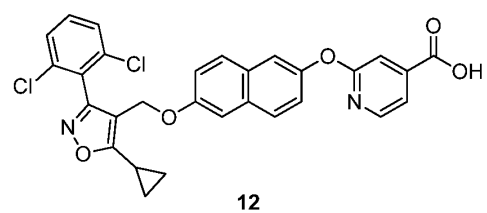
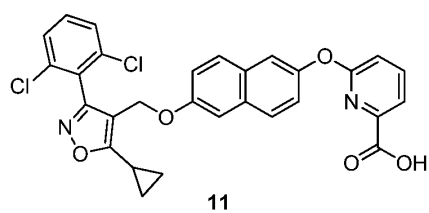
5 13. The use according to claim 12, wherein Z is pyridyl; R⁴ is -COOH; and R⁵ is H or halogen.

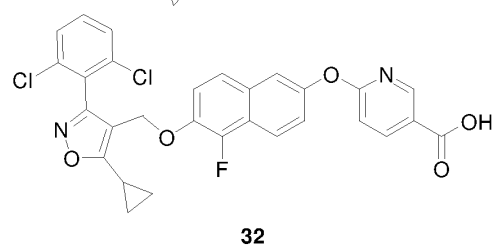
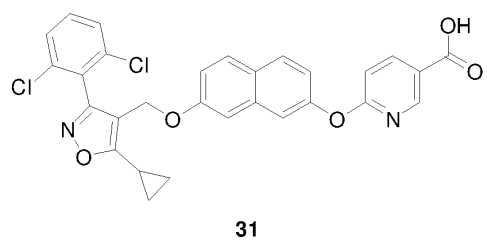
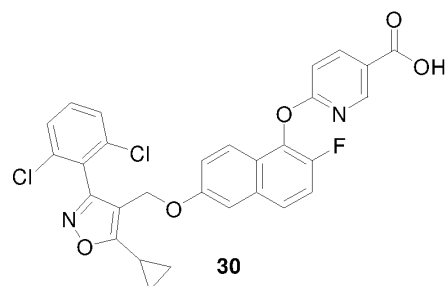
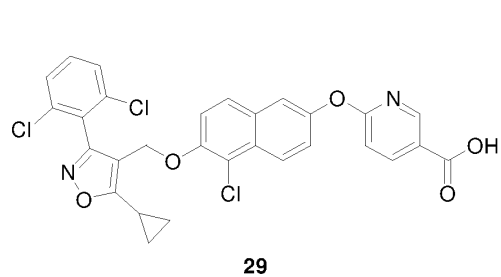
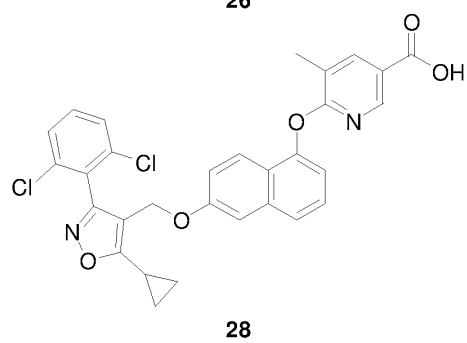
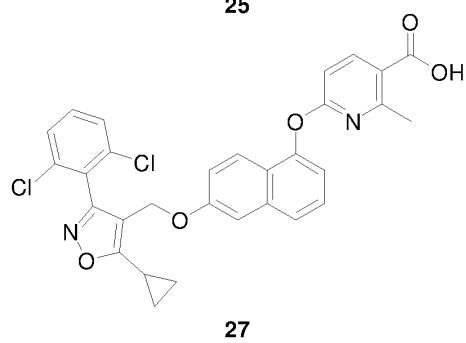
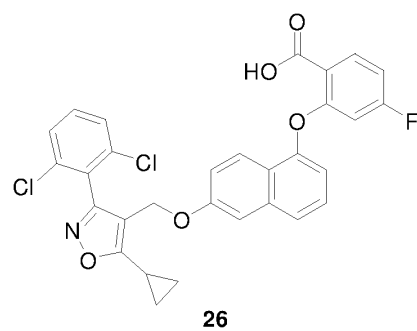
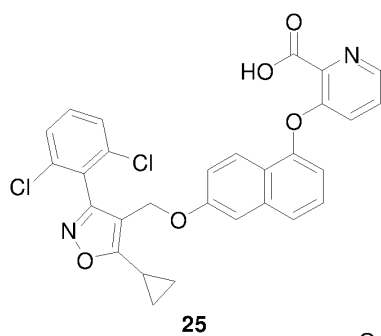
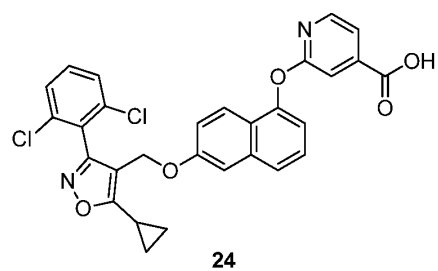
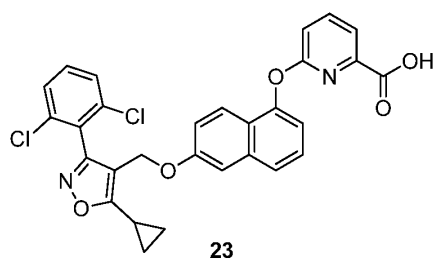
14. The use according to claim 10, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:

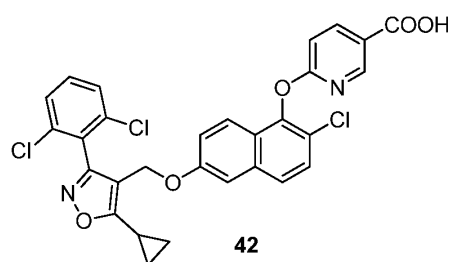
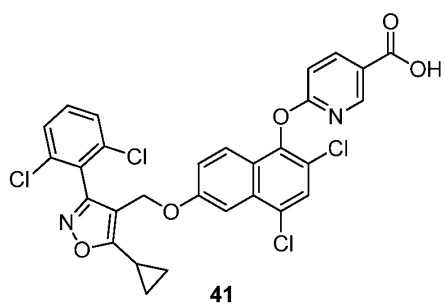
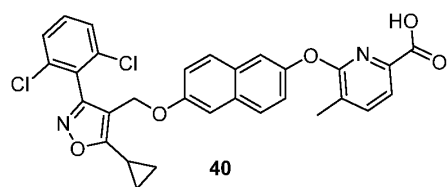
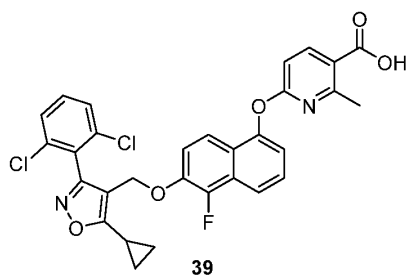
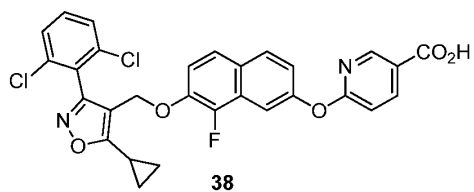
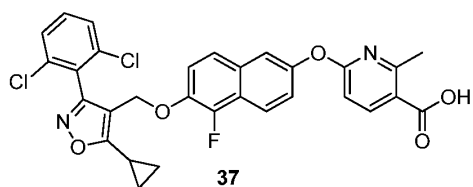
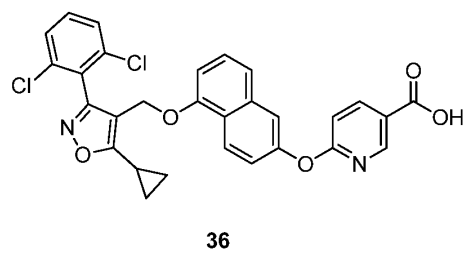
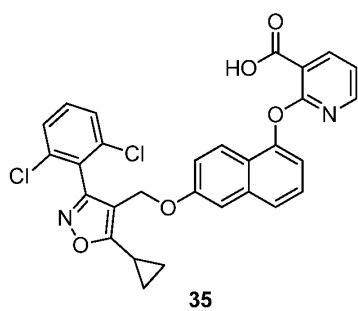
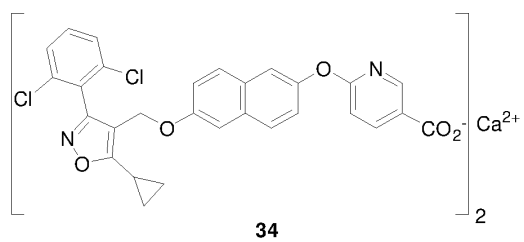
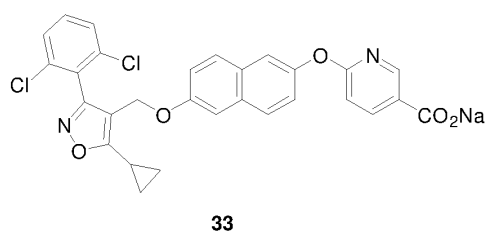


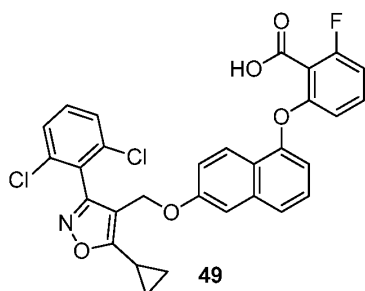
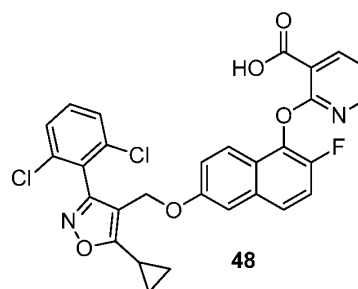
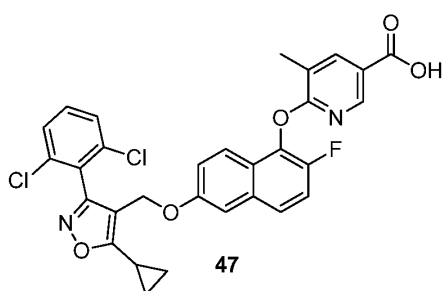
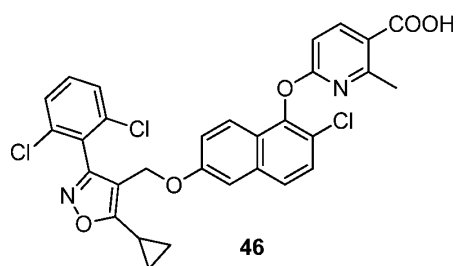
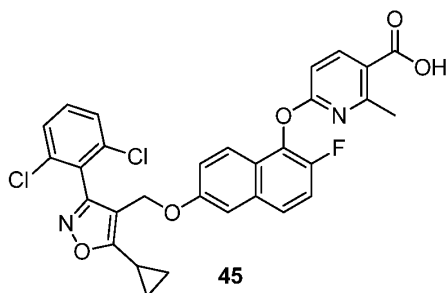
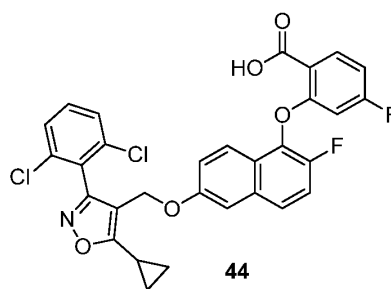
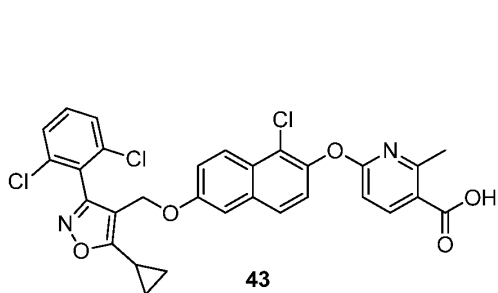
10



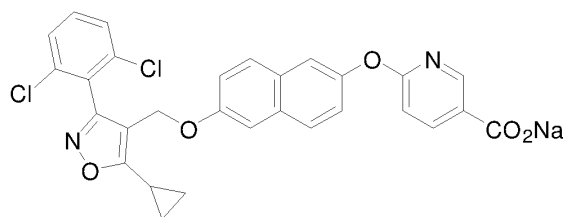






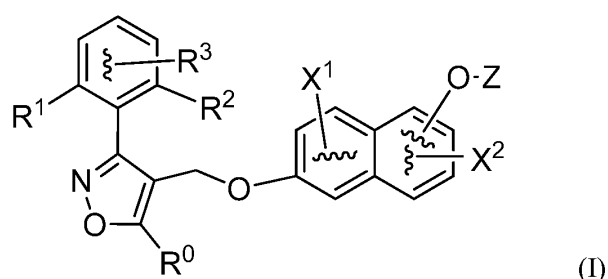


5 15. The use according to claim 10, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



33

16. A pharmaceutical composition for anti-hepatitis B virus, comprising a therapeutically effective amount of a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof or a pharmaceutically acceptable salt, an ester or a stereoisomer thereof and one or more other anti-HBV agents, and a pharmaceutically acceptable auxiliary material,



wherein:

- R^1 , R^2 and R^3 are independently selected from H, halogen, unsubstituted or halogen substituted C_{1-6} alkyl and unsubstituted or halogen substituted C_{1-6} alkoxy, provided that at least one of R^1 , R^2 and R^3 is not hydrogen, R^0 is selected from unsubstituted or halogen substituted C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{4-7} alkylcycloalkyl;

X^1 and X^2 are independently selected from H and halogen;

- moiety $-O-Z$ attaches to the naphthalene ring, wherein Z is a residue selected from 5-10 membered aryl or 5-10 membered heteroaryl optionally having one or more hetero atoms selected from N, O and S, wherein the 5-10 membered aryl or 5-10 membered heteroaryl is substituted by R^4 and is optionally further substituted by R^5 ; and

- wherein R^4 is selected from $-COOH$, $-CH_2COOH$, $-NHSO_2CF_3$, $-SO_2NH-C_{1-6}$ alkyl, $-SO_3H$, $-CONHSO_2-C_{1-6}$ alkyl, $-CONHSO_2-C_{3-6}$ cycloalkyl, $-CONHSO_2-5-10$ membered aryl and $-CONHSO_2-5-10$ membered aryl substituted by C_{1-6} alkyl at the aryl, and wherein R^5 is selected from H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, $-O-(C_{1-6}$ alkyl) and $-NH-(C_{1-6}$ alkyl).

17. The pharmaceutical composition according to claim 16, wherein R^1 , R^2 and R^3 are

independently selected from H, halogen and C₁₋₃ perfluoroalkoxy, and R⁰ is selected from isopropyl or cyclopropyl;

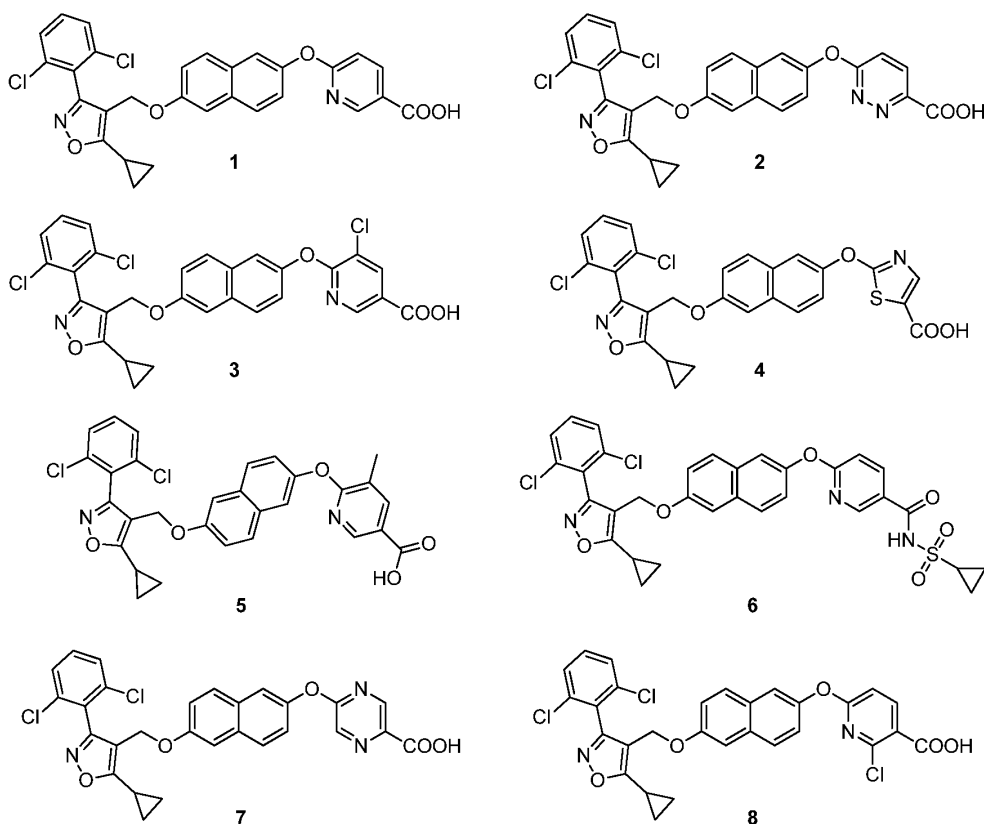
wherein Z is a phenyl which is substituted by R⁴ and is optionally substituted by R⁵; or Z is a 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵; and
 5 wherein the halogen is fluoro or chloro.

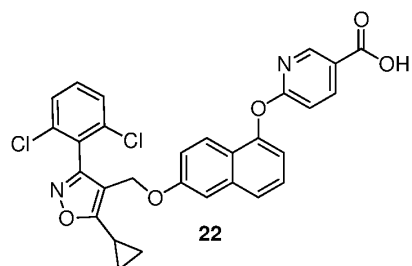
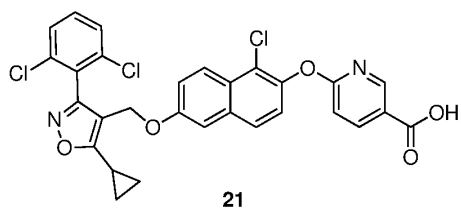
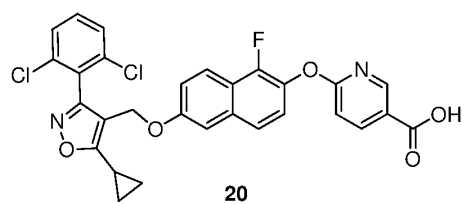
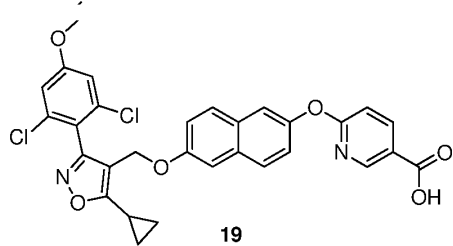
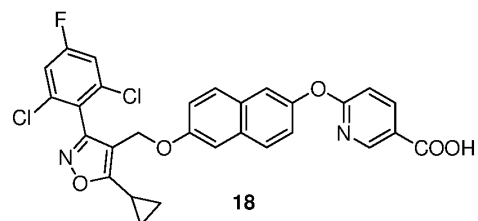
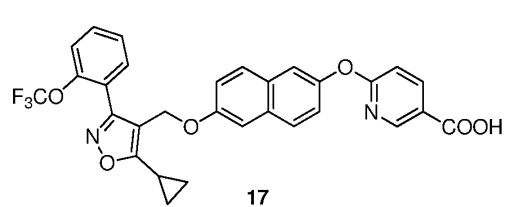
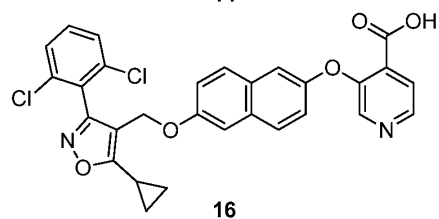
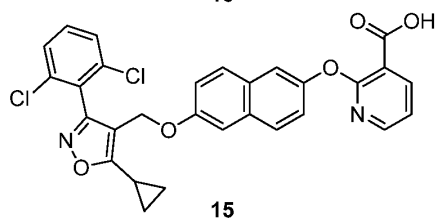
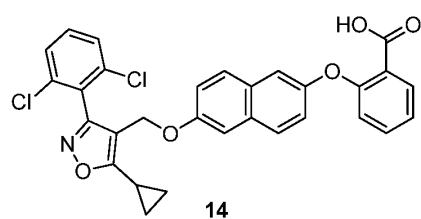
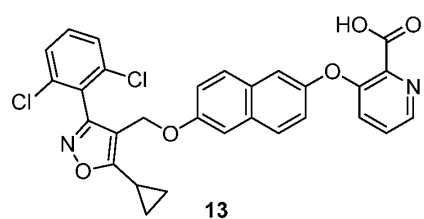
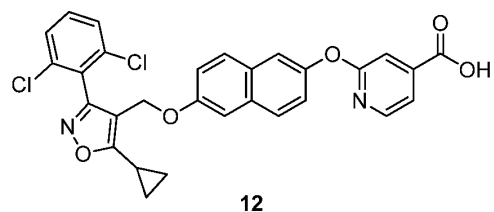
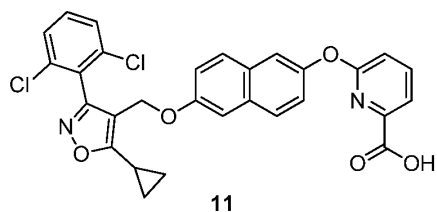
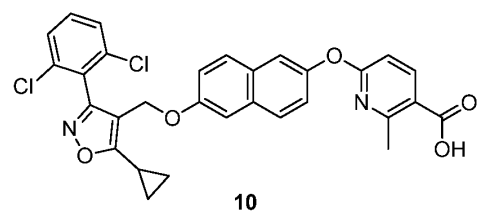
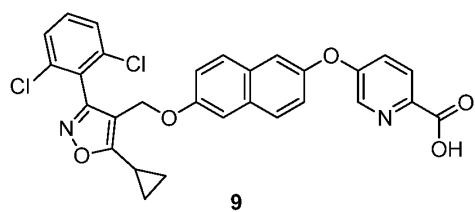
18. The pharmaceutical composition according to claim 17, wherein R¹, R² and R³ are independently selected from H, Cl, F and -O-CF₃; and

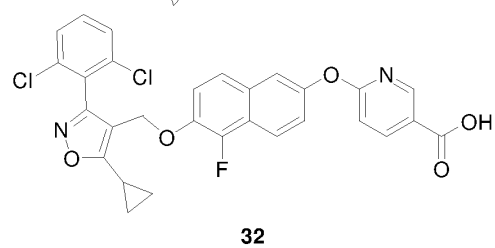
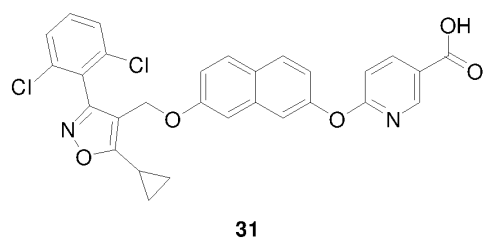
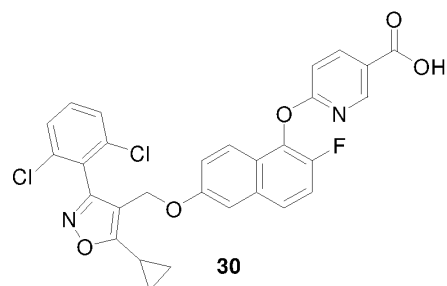
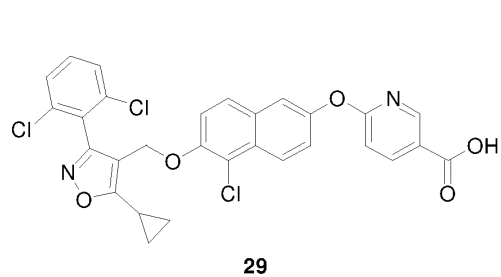
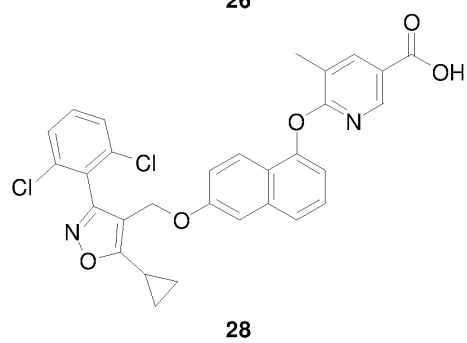
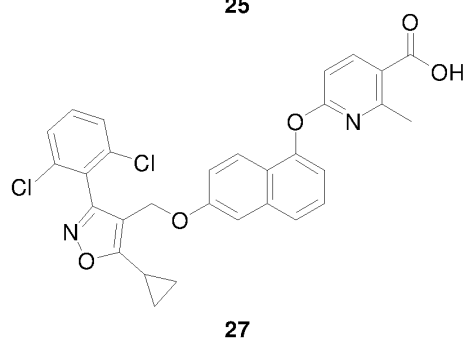
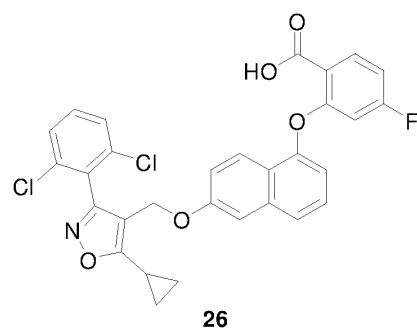
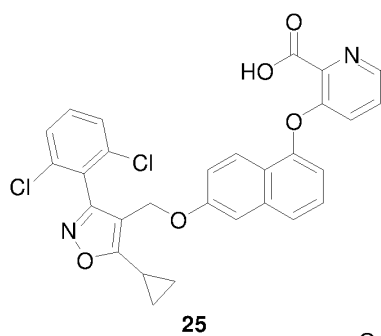
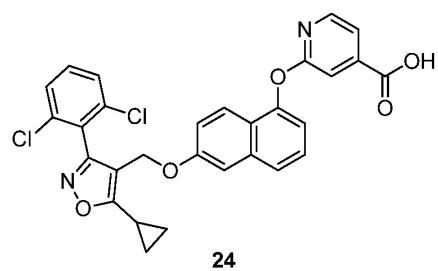
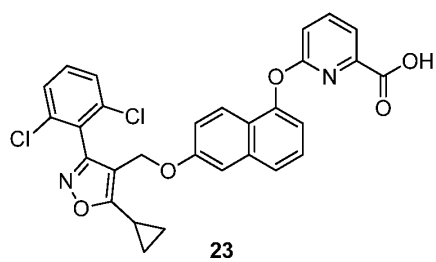
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵, wherein R⁴ is selected from -COOH, -CH₂COOH, -CONHSO₂-C₁₋₆ alkyl and -CONHSO₂-C₃₋₆ cycloalkyl, R⁵ is
 10 selected from H, C₁₋₃ alkyl and halogen.

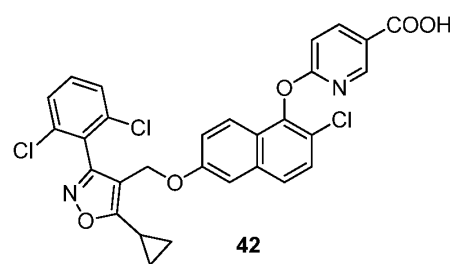
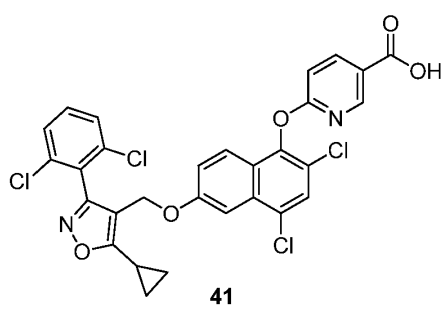
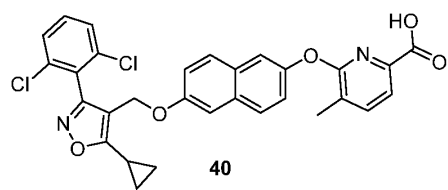
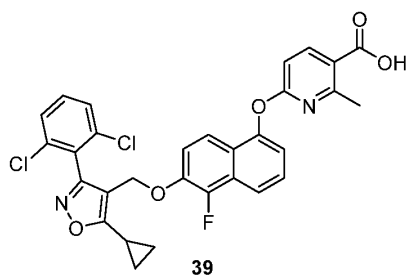
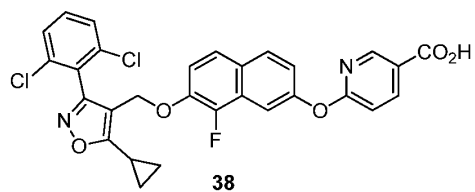
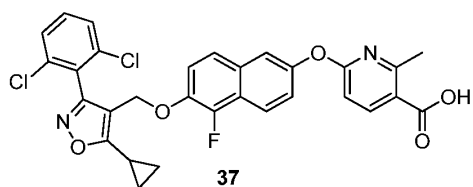
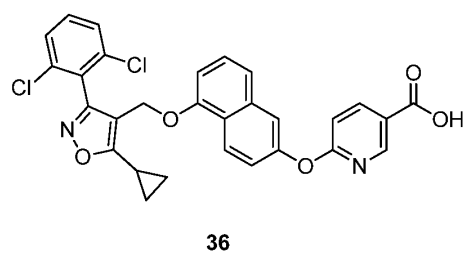
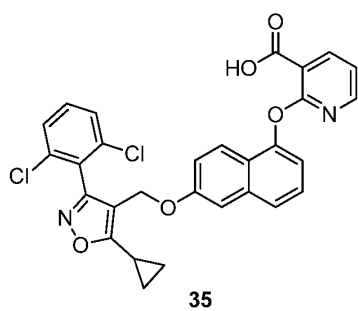
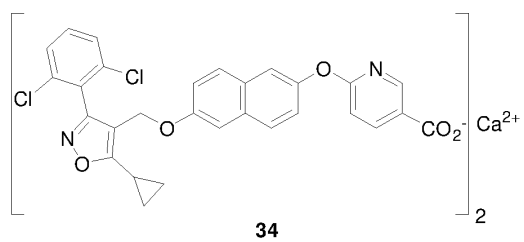
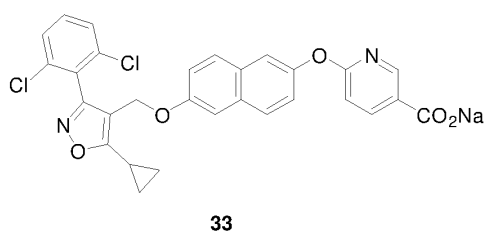
19. The pharmaceutical composition according to claim 18, wherein Z is pyridyl; R⁴ is -COOH; and R⁵ is H or halogen.

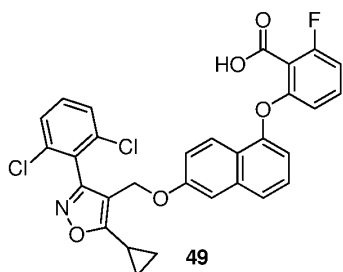
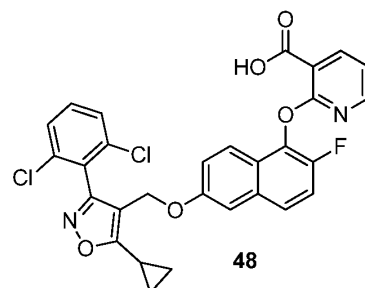
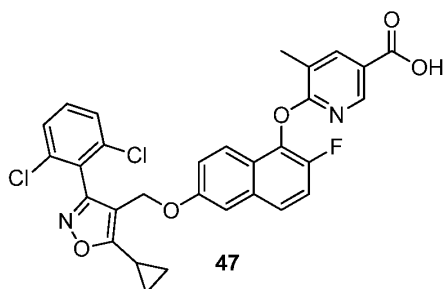
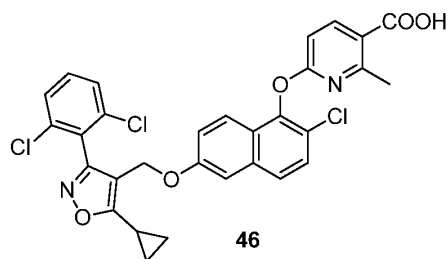
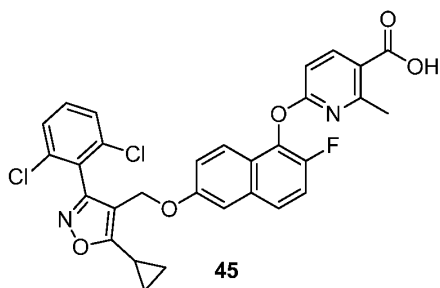
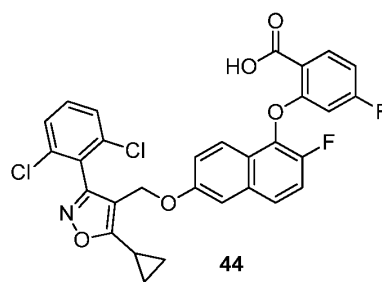
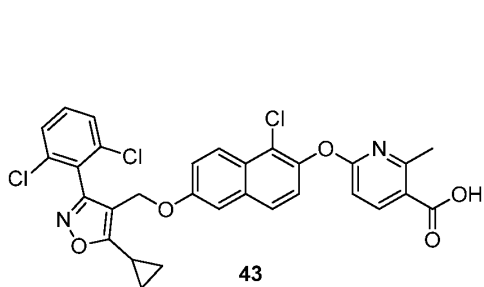
20. The pharmaceutical composition according to claim 16, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



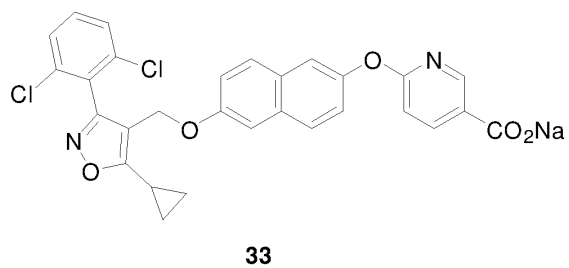








- 5 21. The pharmaceutical composition according to claim 16, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



22. The pharmaceutical composition according to claim 16, wherein the method comprises administering the phenylisoxazolylmethylene-naphthalene-ether derivative having the structure of formula (I), its pharmaceutically acceptable salt, and ester or stereoisomer in combination with one or more other anti-HBV agents.

5 23. The pharmaceutical composition of claim 22, wherein the other anti-HBV agents are selected from HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators, toll-like receptor (TLR) modulators, interferon alpha receptor ligands, hepatitis b surface antigen (HBsAg) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA) and ddRNAi
10 endonuclease modulators, ribonucleotide reductase inhibitors, HBV E antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, fatty acid synthesis inhibitors, HBV antibodies, CCR2 chemokine antagonists, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, PD-1 inhibitors, PD-L1 inhibitors, KDM inhibitors, and HBV replication inhibitors.

15 24. The pharmaceutical composition of claim 23, wherein the HBV DNA polymerase inhibitor is entecavir or tenofovir;

the PD-1 inhibitor is one or more selected from nivolumab, pembrolizumab, pidilizumab, BGB-108, SHR-1210, PDR-001, PF-06801591, IBI-308, cemiplimab, camrelizumab, sintilimab, tislelizumab (BGB-A317), BCD-100, JNJ-63723283, Zimberelimab (GLS-010,
20 WBP-3055), Balstilimab (AGEN2034) and dostarlimab (TSR-042);

the PD-L1 inhibitors is one or more selected from atezolizumab (RG-7446), avelumab, BGB-A333, BMS-936559 (MDX-1105), durvalumab, CX-072, GX-P2, KN035 (ASC022), GS-4224 and INCB086550;

the antisense oligonucleotide is Ionis-HBVRx or Ionis-HBV-LRx;

25 the short interfering RNA is JNJ-3989, Vir-2218, or DCR-HBVS;

the fatty acid synthase inhibitor is TVB-2640 and/or TVB-3567;

the interferon is Pegasys; and

the capsid inhibitor is one or more selected from ABI-H0731, ABI-H2158, ABI-H3733, CB-HBV-001, JNJ-6379, JNJ-0440, QL-007, RG-7907 and RO7049389.