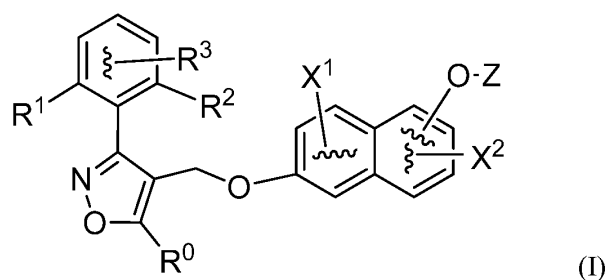


CLAIMS

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).

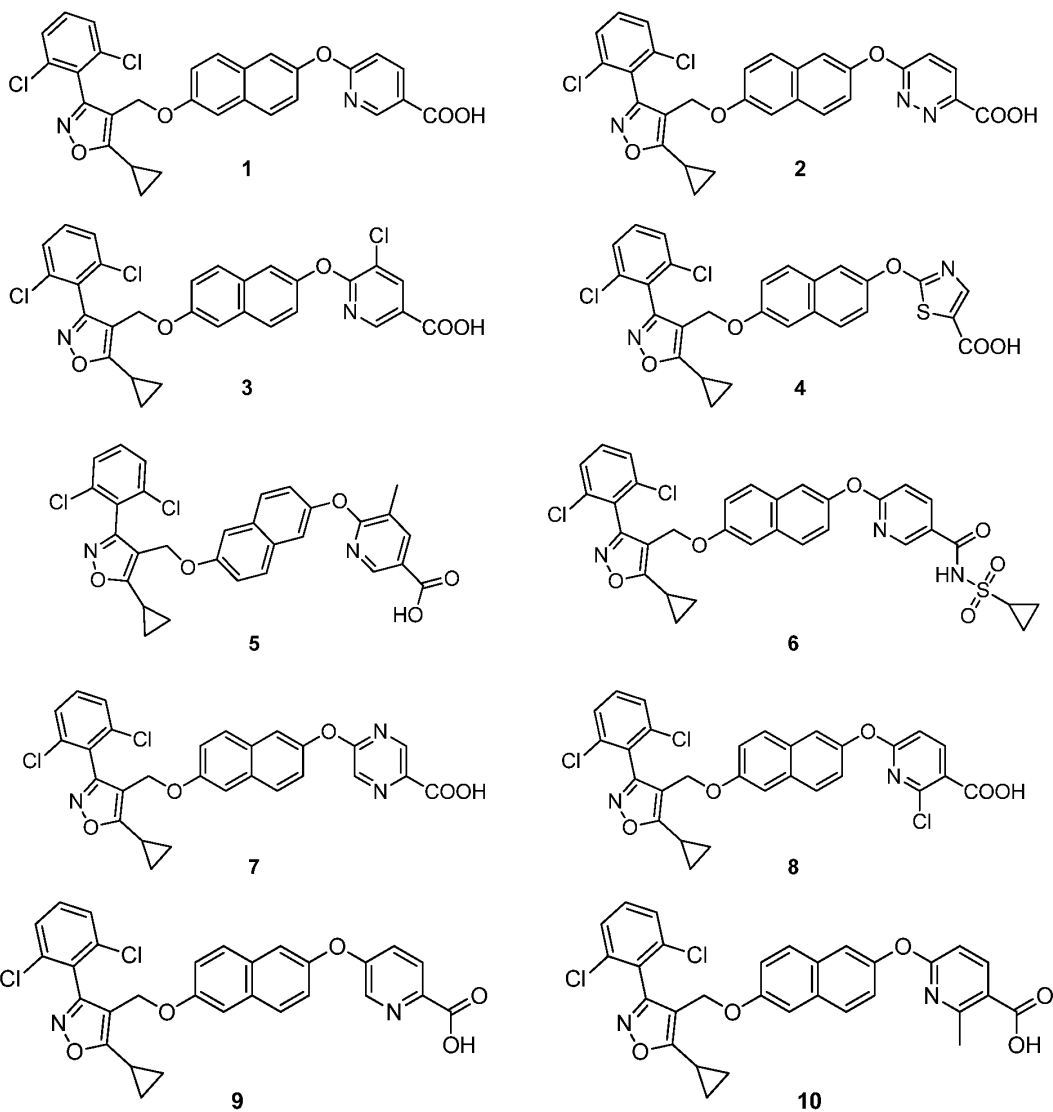
2. The method according to claim 1, wherein R^1 , R^2 and R^3 are independently selected from H, halogen and C_{1-3} perfluoroalkoxy, and R^0 is selected from isopropyl or cyclopropyl;
- wherein Z is a phenyl which is substituted by R^4 and is optionally substituted by R^5 ; or Z is a 5-10 membered heteroaryl 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.

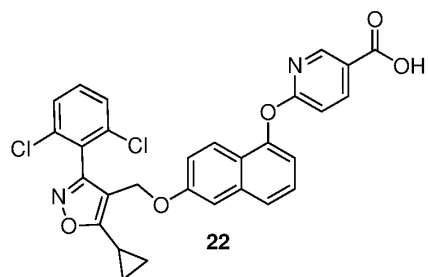
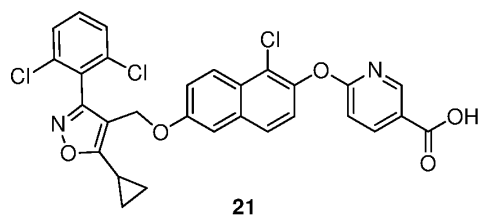
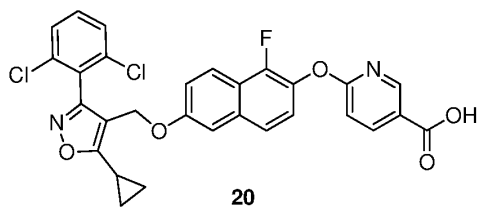
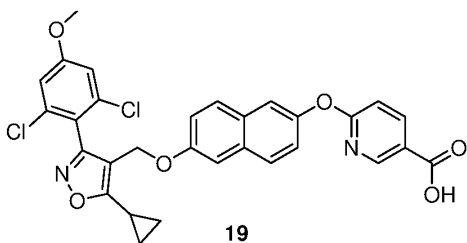
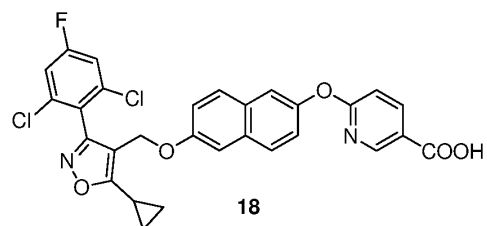
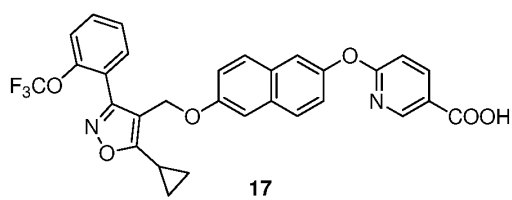
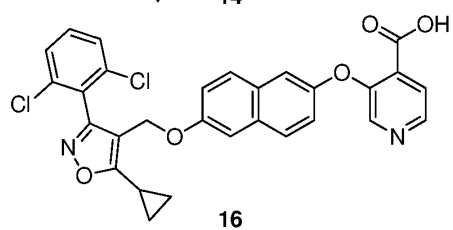
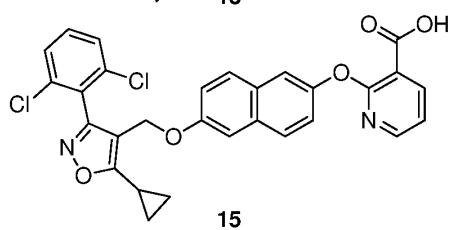
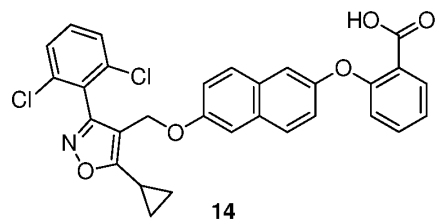
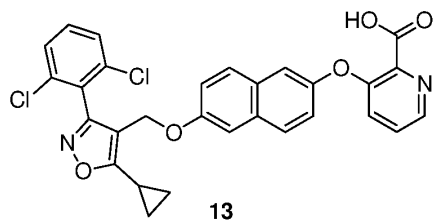
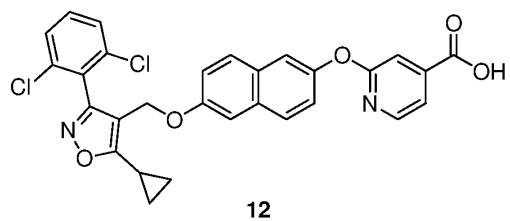
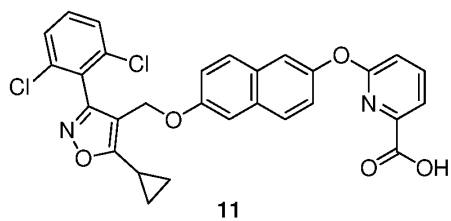
3. The method according to claim 2, wherein R^1 , R^2 and R^3 are independently selected from H, Cl, F and $-O-CF_3$; and

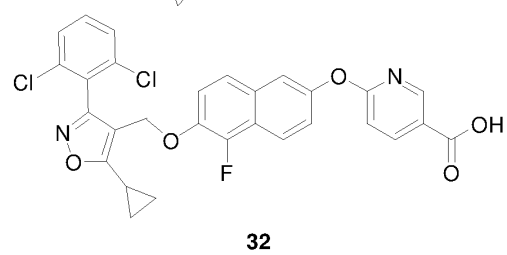
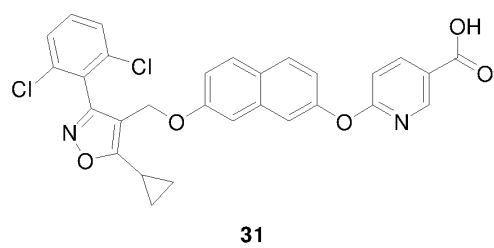
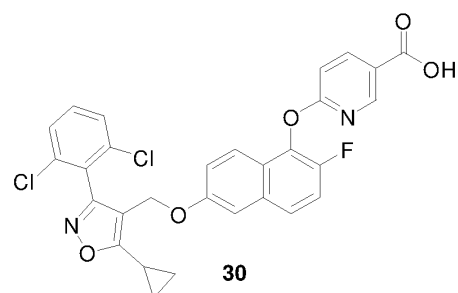
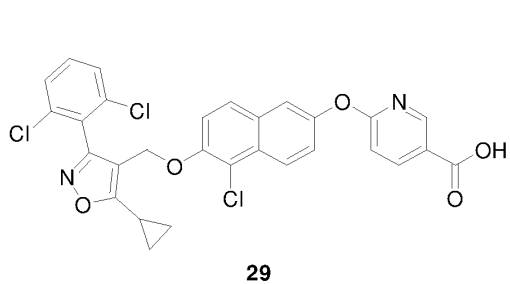
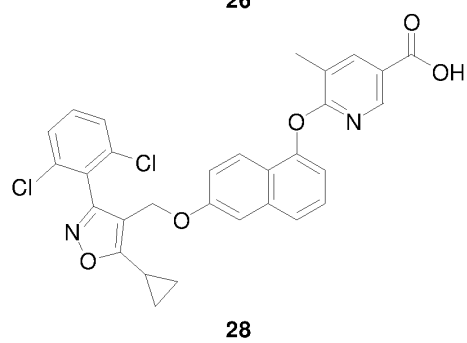
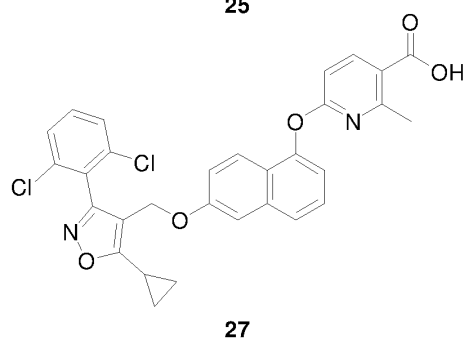
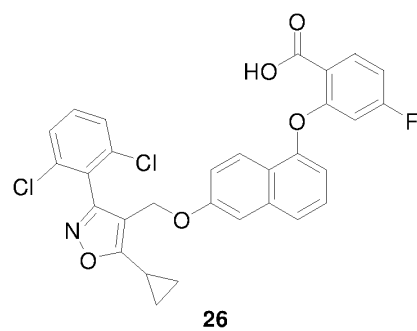
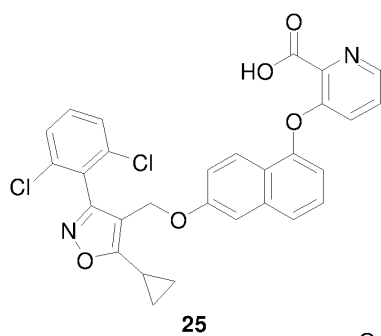
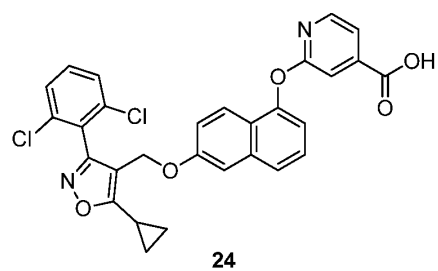
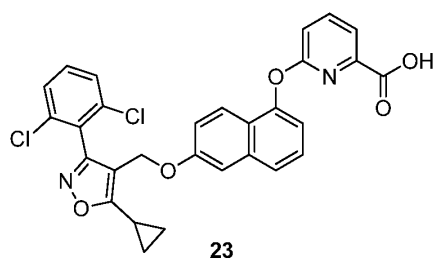
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5 , wherein R^4 is selected from $-COOH$, $-CH_2COOH$, $-CONHSO_2-C_{1-6}$ alkyl and $-CONHSO_2-C_{3-6}$ cycloalkyl, R^5 is selected from H,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

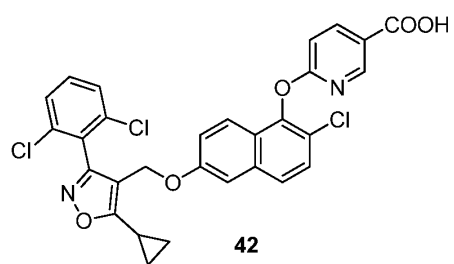
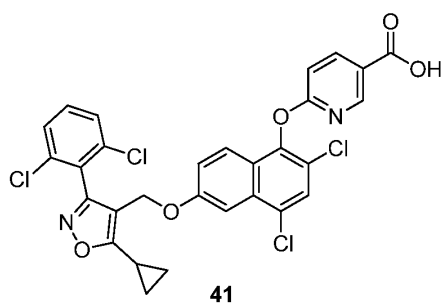
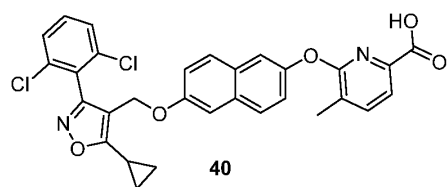
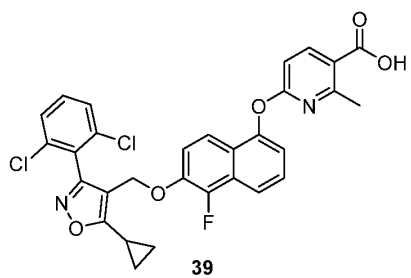
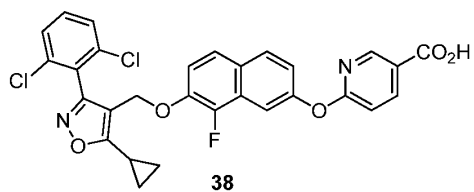
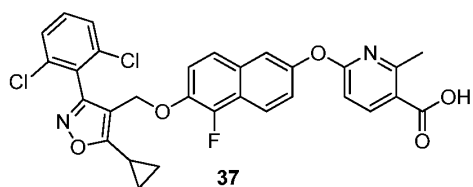
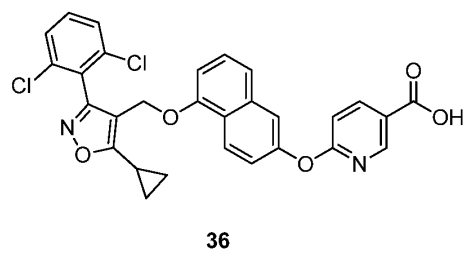
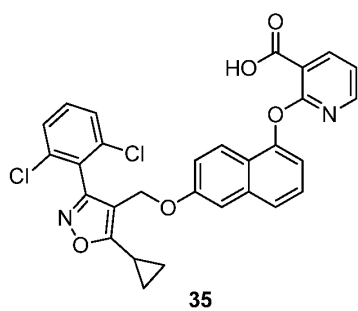
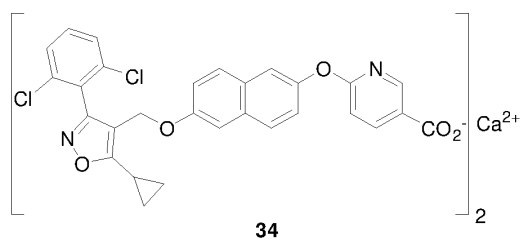
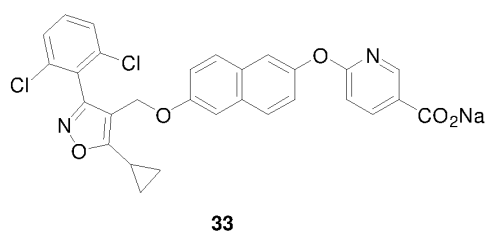
4. The method according to claim 3, wherein Z is pyridyl; R^4 is $-COOH$; and R^5 is H or halogen.

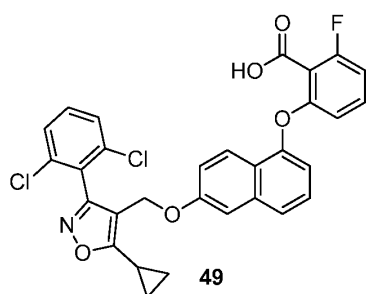
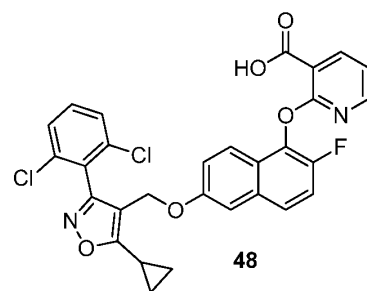
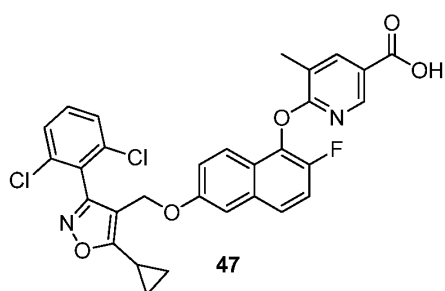
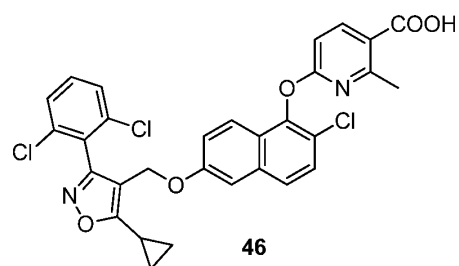
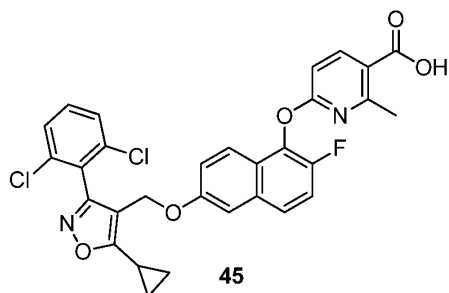
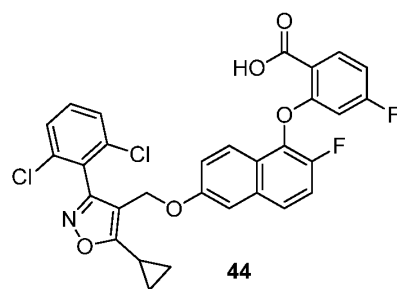
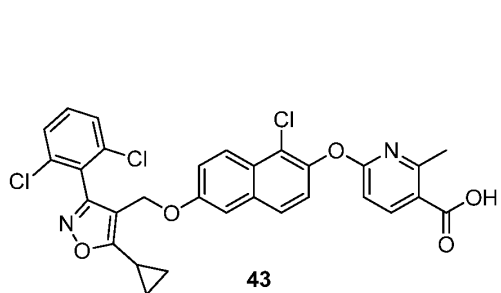
5. The method according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



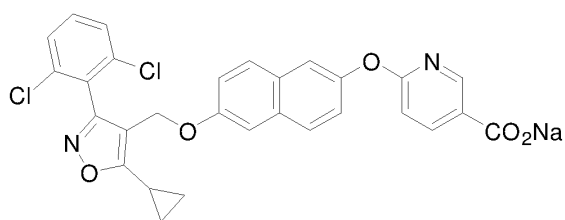








5 6. The method according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



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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

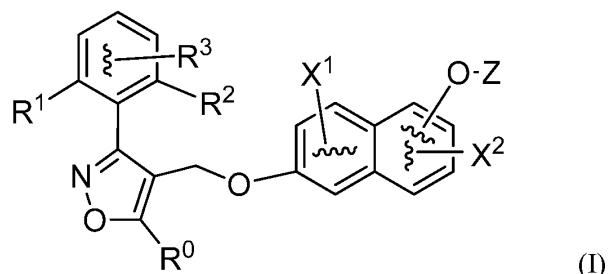
the fatty acid synthase inhibitor is TVB-2640 and/or TVB-3567;

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

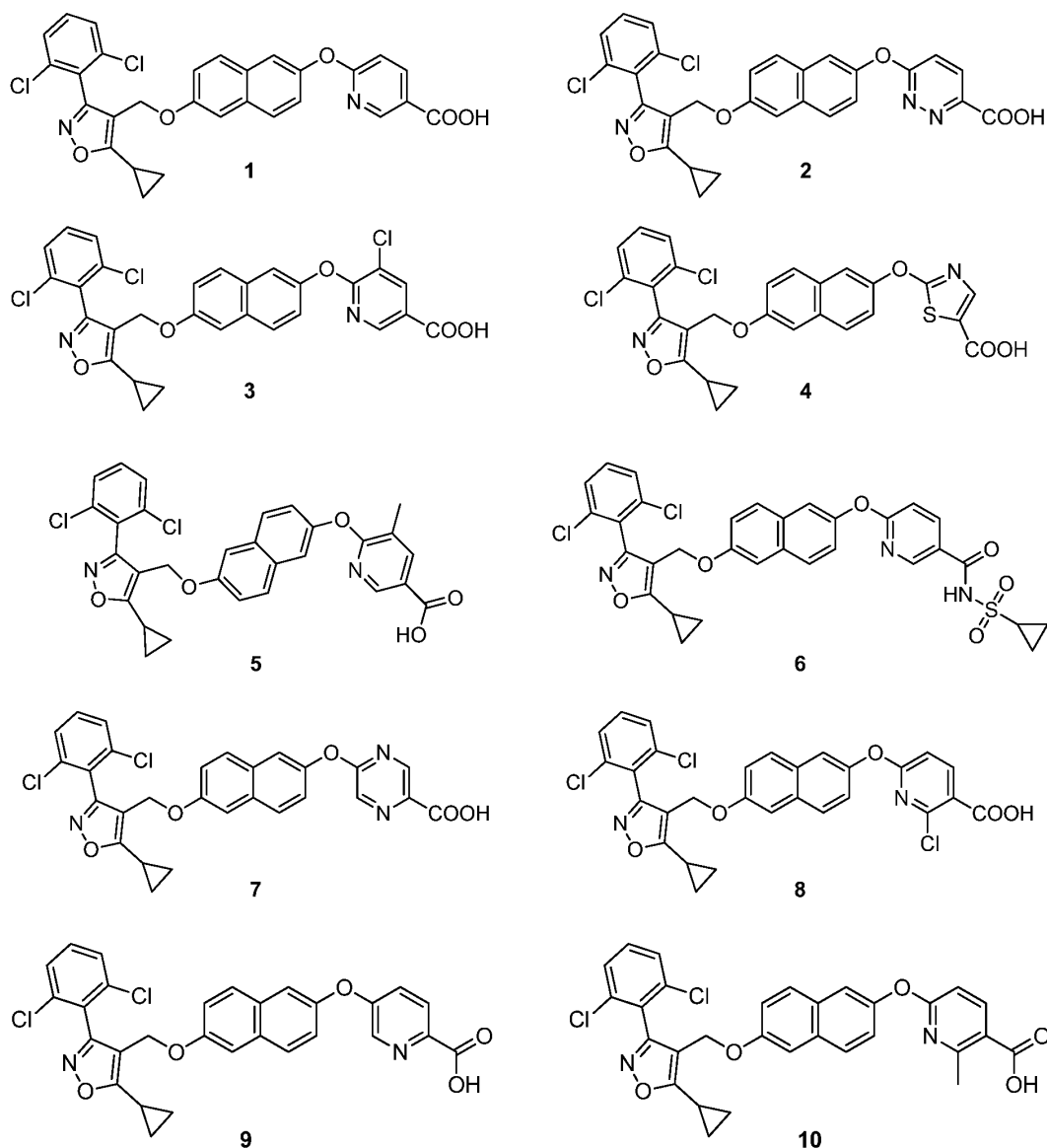
wherein the halogen is fluoro or chloro.

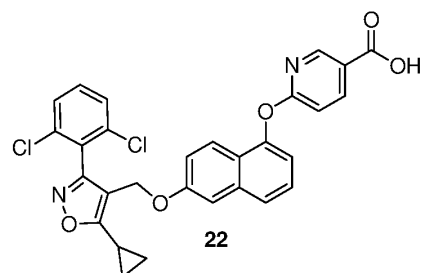
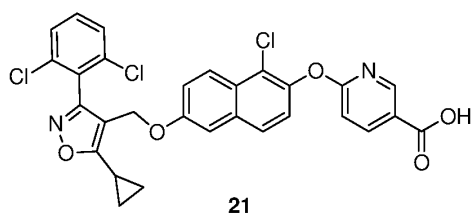
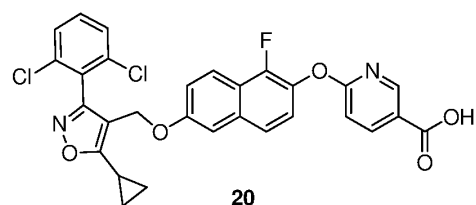
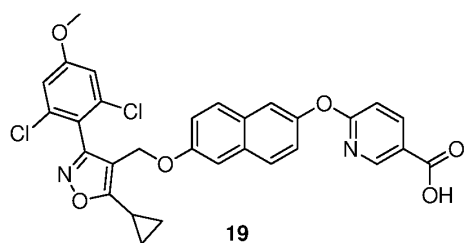
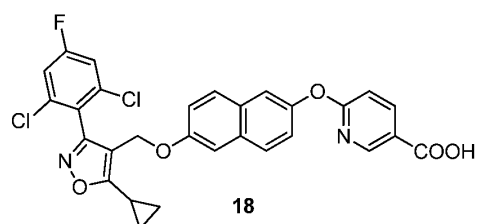
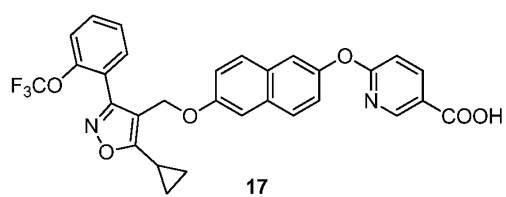
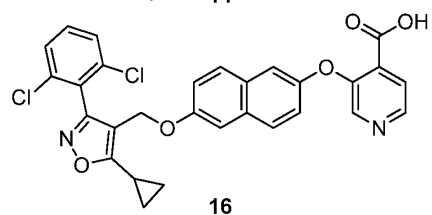
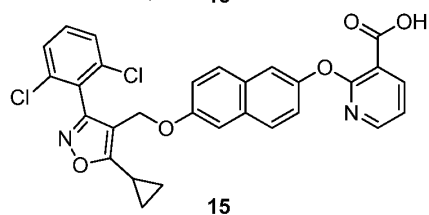
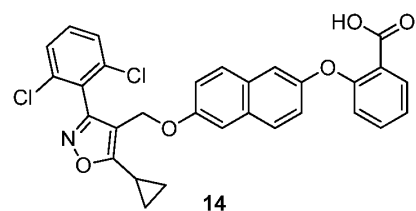
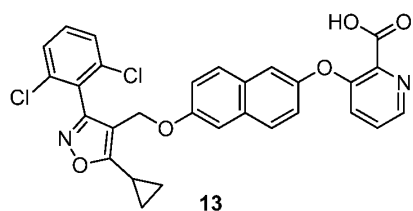
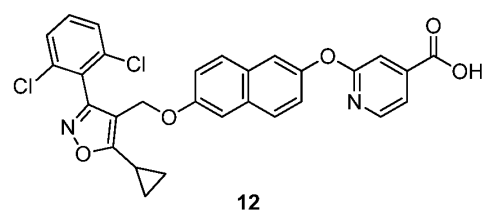
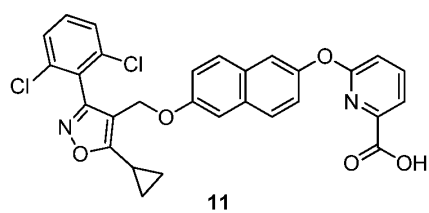
12. The use according to claim 11, wherein R^1 , R^2 and R^3 are independently selected from H, Cl, F and $-O-CF_3$; and

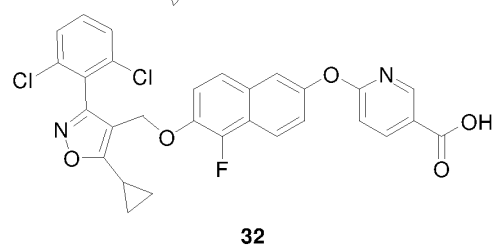
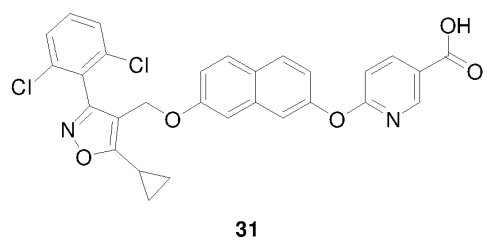
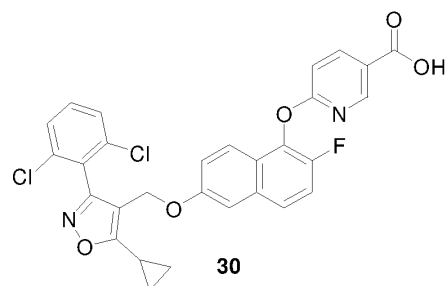
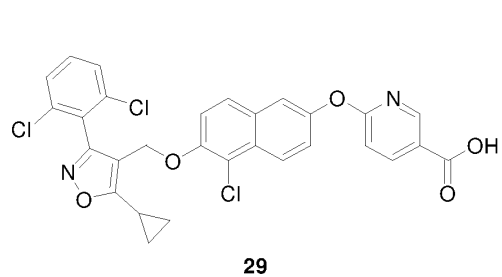
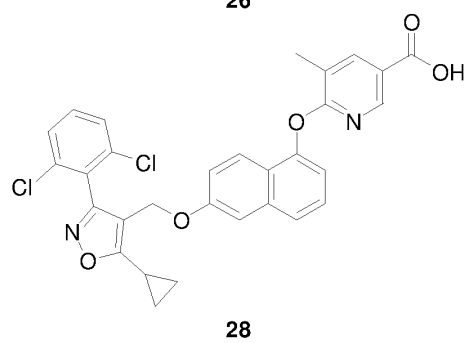
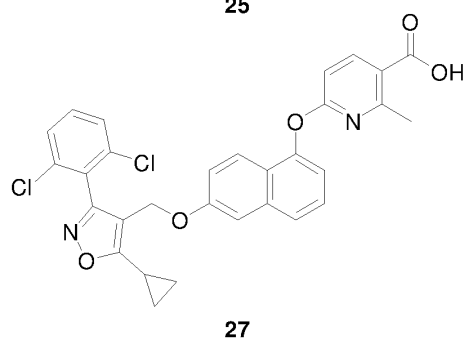
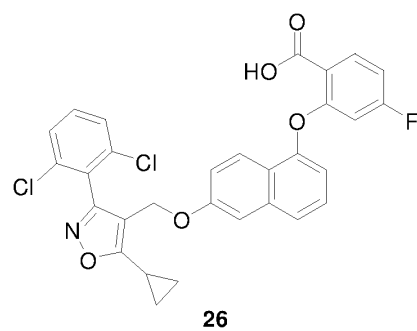
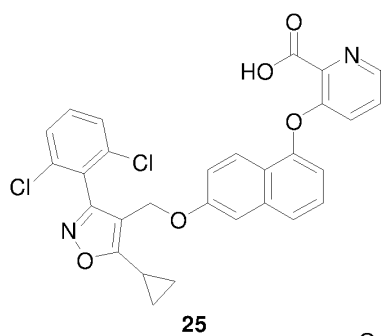
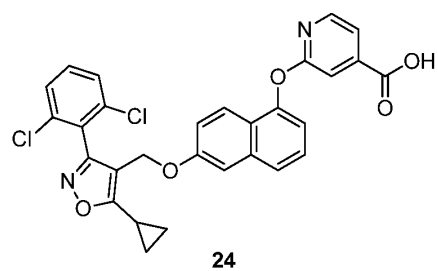
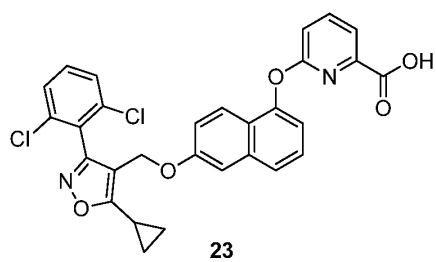
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵, wherein R⁴ is selected from -COOH, -CH₂COOH, -CONHSO₂-C₁₋₆ alkyl and -CONHSO₂-C₃₋₆ cycloalkyl, R⁵ is selected from H, C₁₋₃ alkyl and halogen.

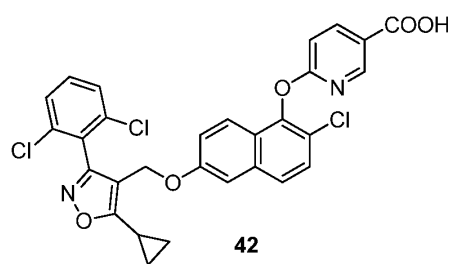
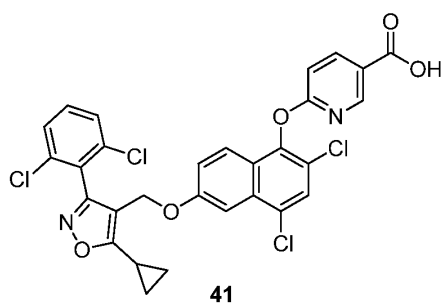
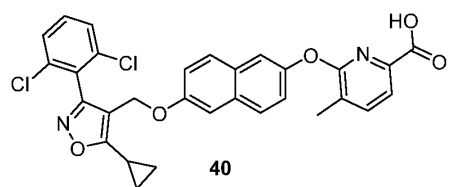
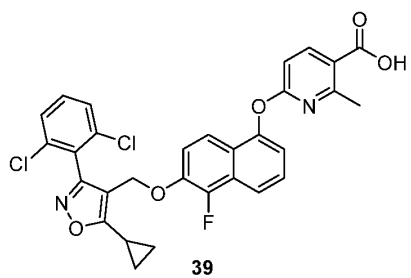
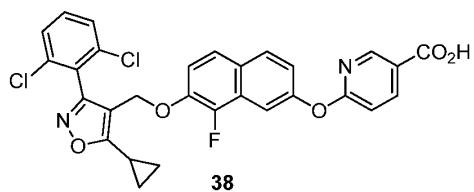
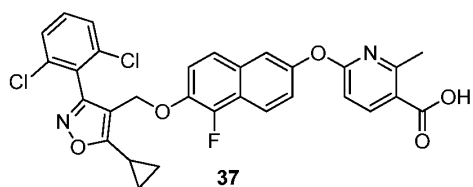
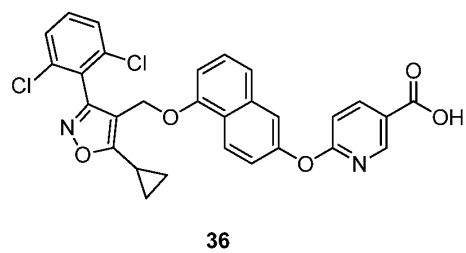
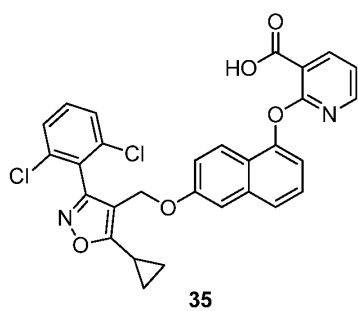
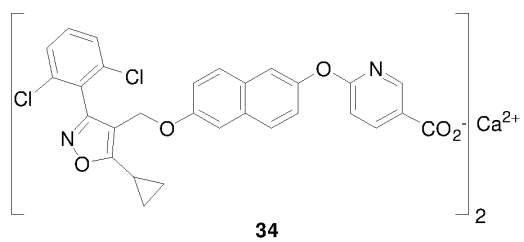
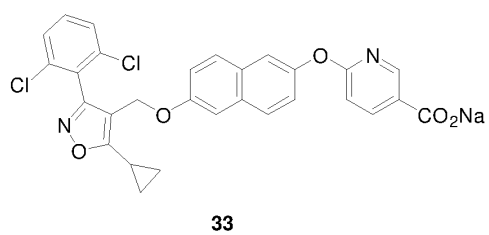
5 13. The use according to claim 12, wherein Z is pyridyl; R⁴ is -COOH; and R⁵ is H or halogen.

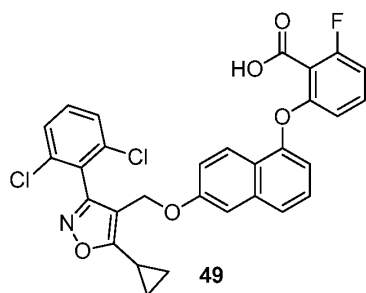
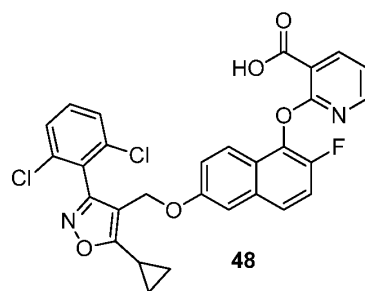
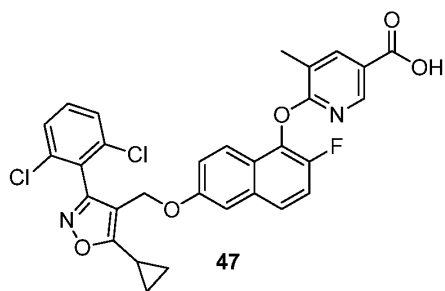
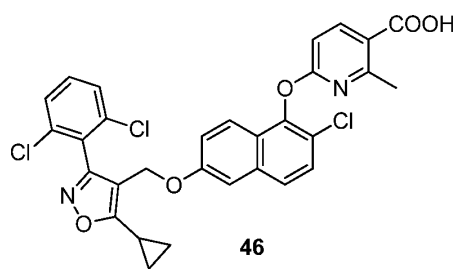
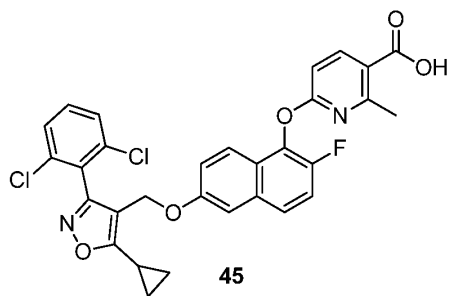
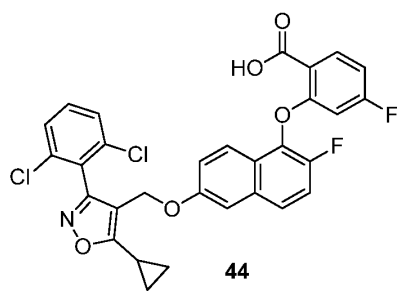
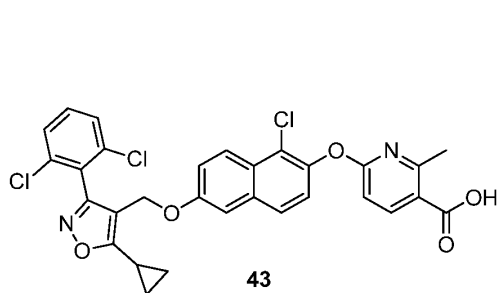
14. The use according to claim 10, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



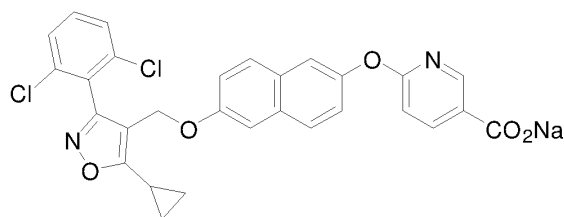






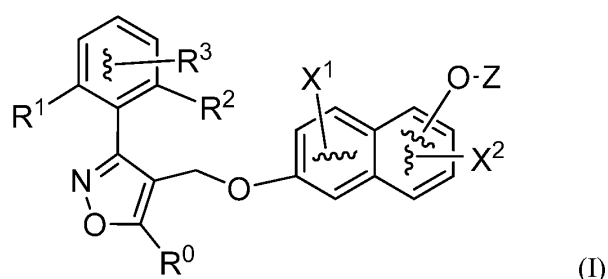


5 15. The use according to claim 10, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



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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;

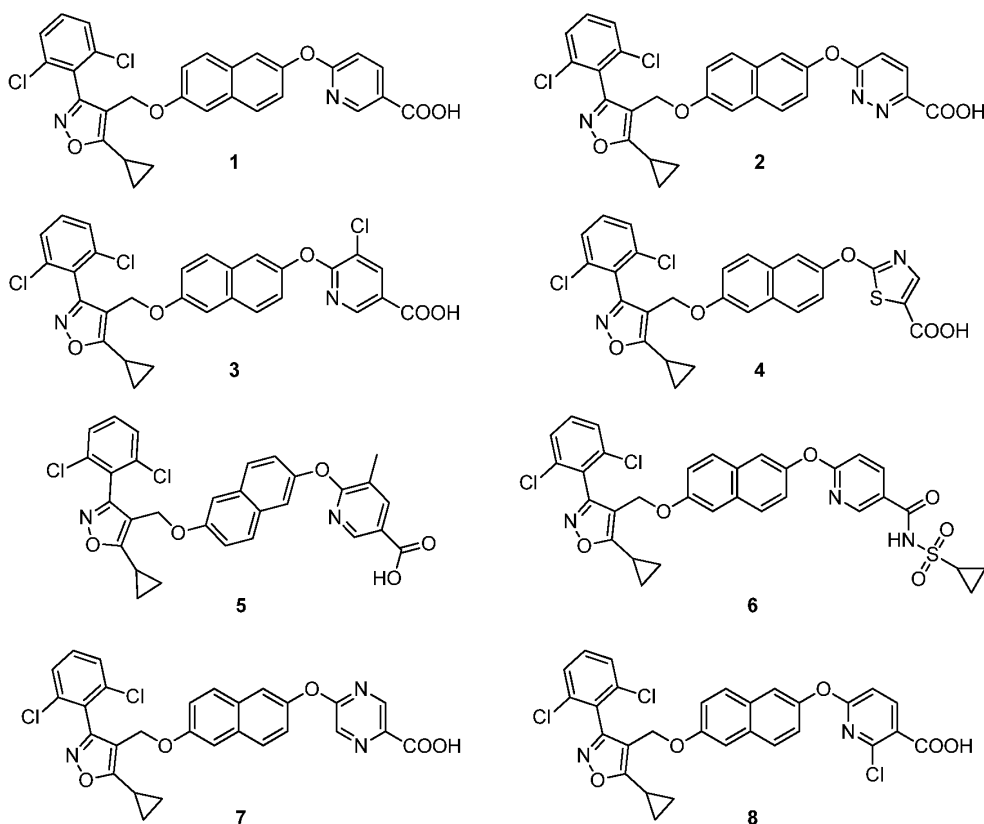
wherein Z is a phenyl which is substituted by R⁴ and is optionally substituted by R⁵; or Z is a 5-10 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵; and
 5 wherein the halogen is fluoro or chloro.

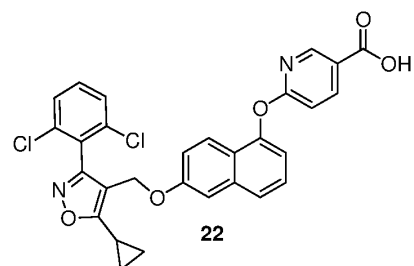
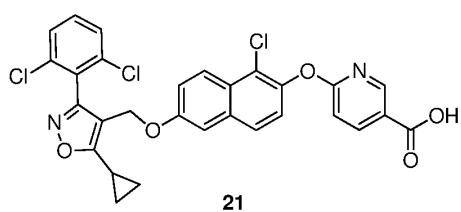
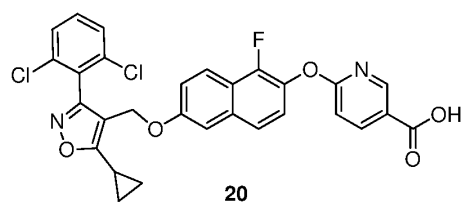
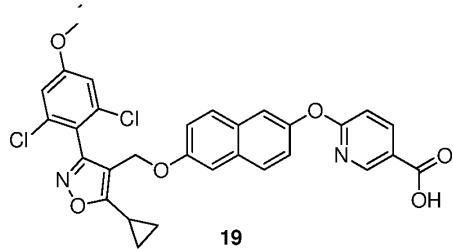
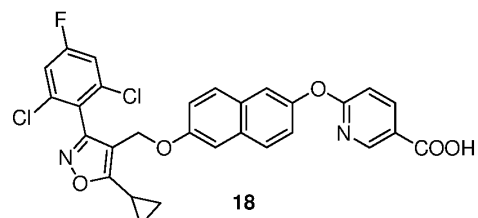
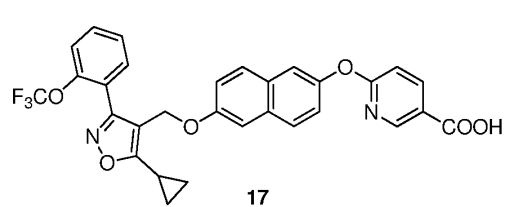
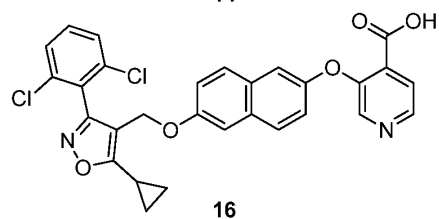
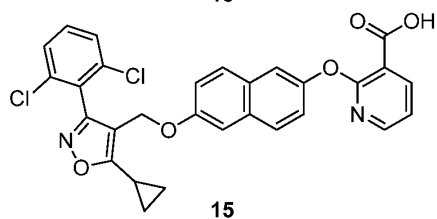
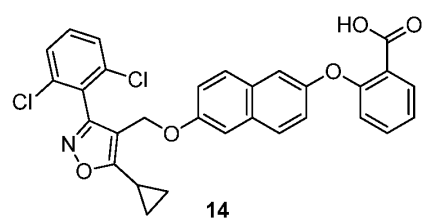
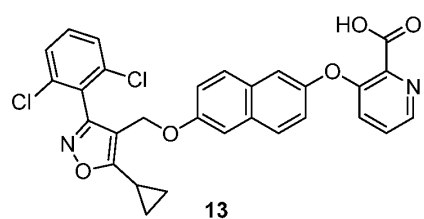
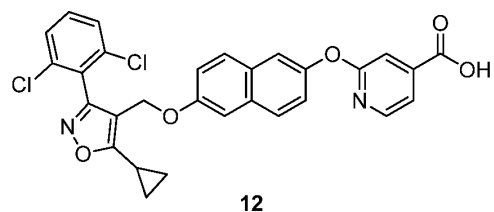
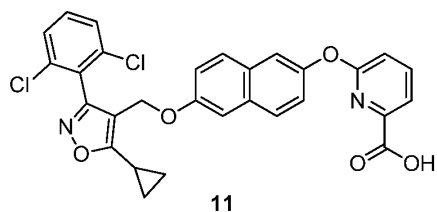
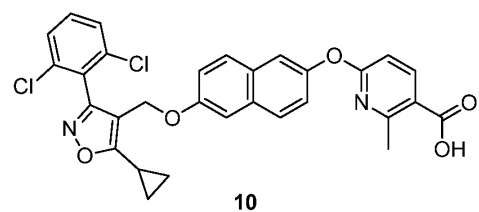
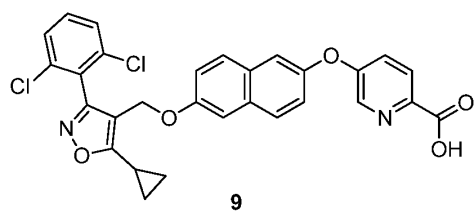
18. The pharmaceutical composition according to claim 17, wherein R¹, R² and R³ are independently selected from H, Cl, F and -O-CF₃; and

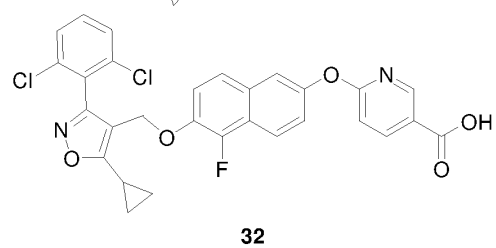
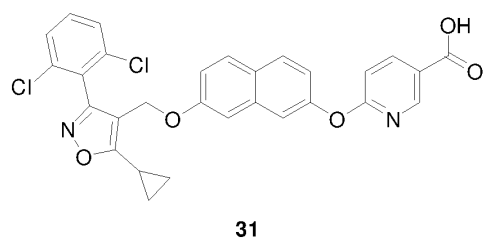
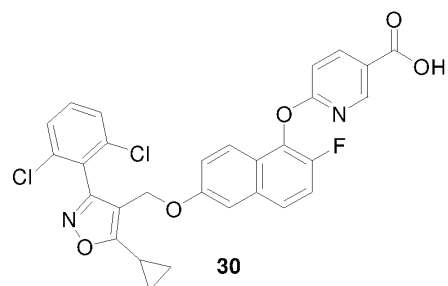
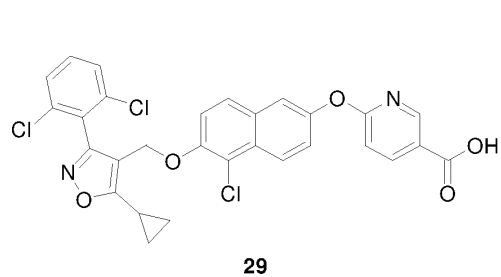
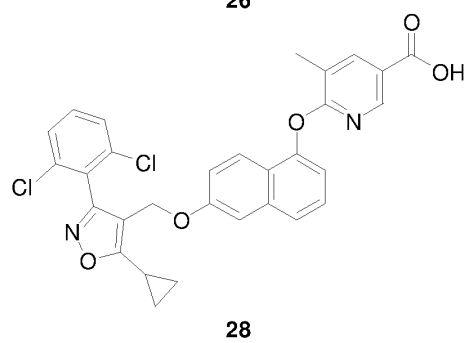
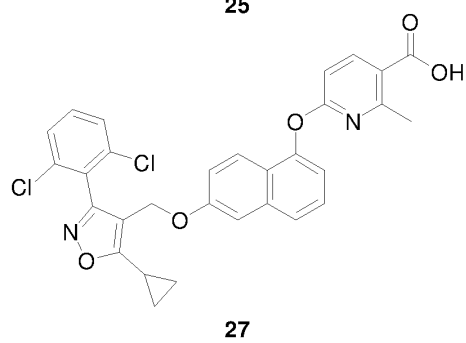
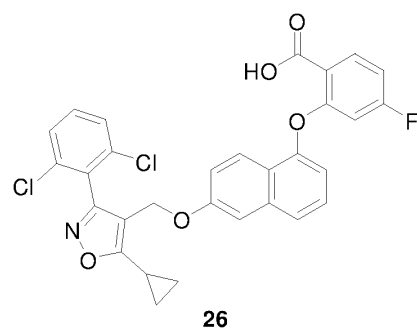
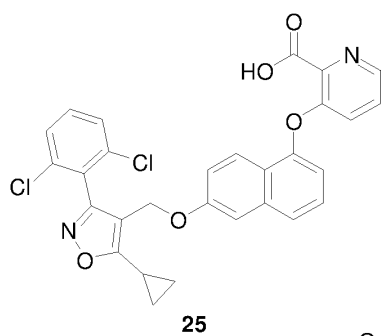
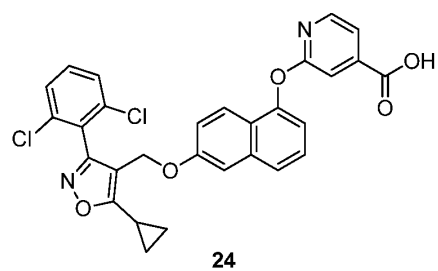
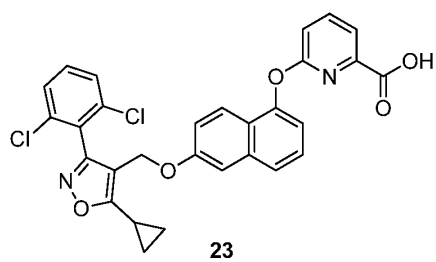
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R⁴ and is optionally substituted by R⁵, wherein R⁴ is selected from -COOH, -CH₂COOH, -CONHSO₂-C₁₋₆ alkyl and -CONHSO₂-C₃₋₆ cycloalkyl, R⁵ is selected from H, C₁₋₃ alkyl and halogen.

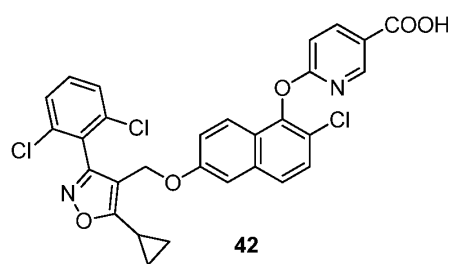
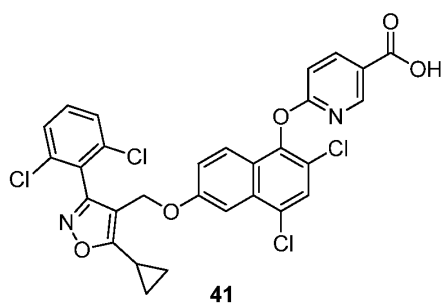
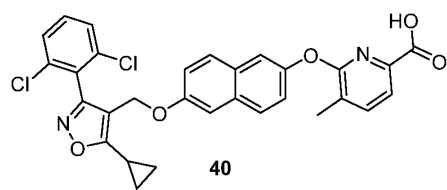
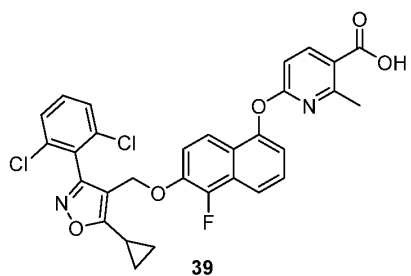
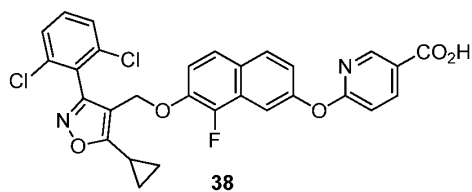
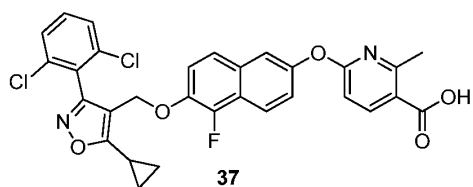
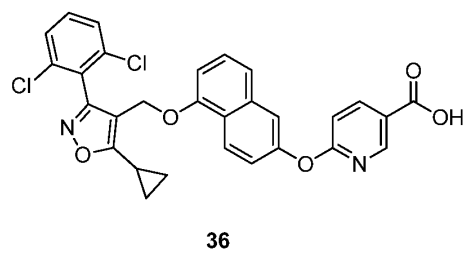
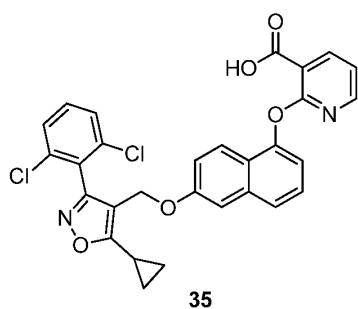
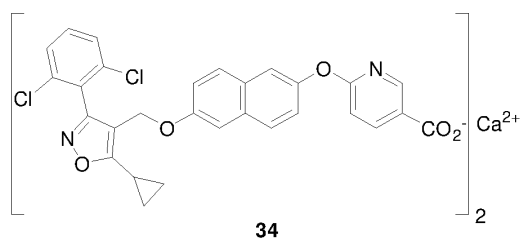
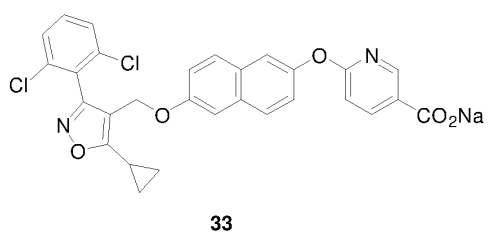
19. The pharmaceutical composition according to claim 18, wherein Z is pyridyl; R⁴ is -COOH; and R⁵ is H or halogen.

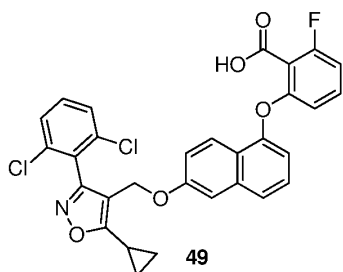
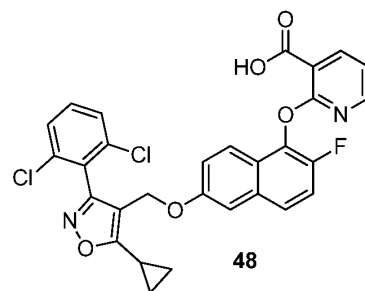
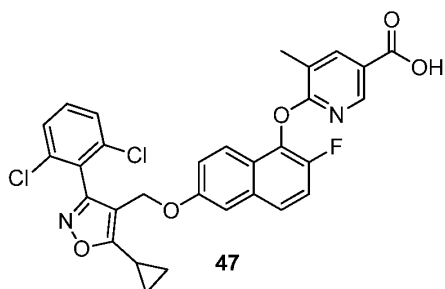
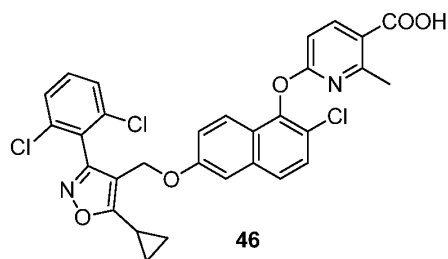
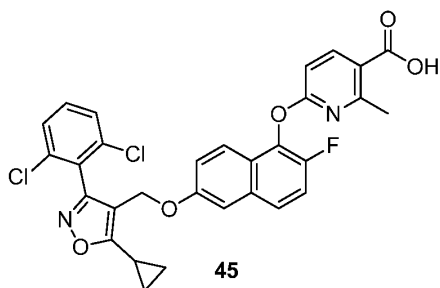
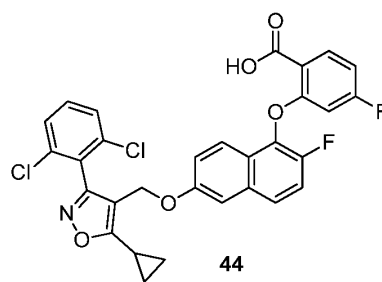
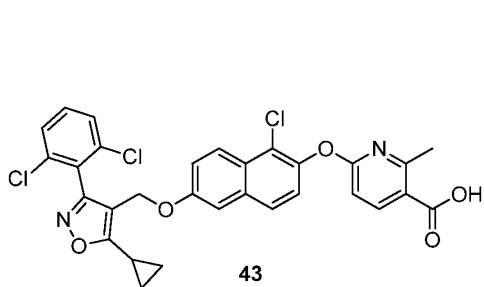
20. The pharmaceutical composition according to claim 16, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



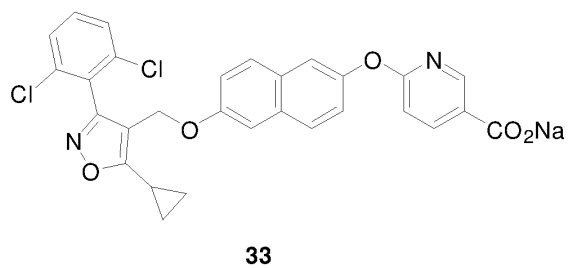








- 5 21. The pharmaceutical composition according to claim 16, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



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.