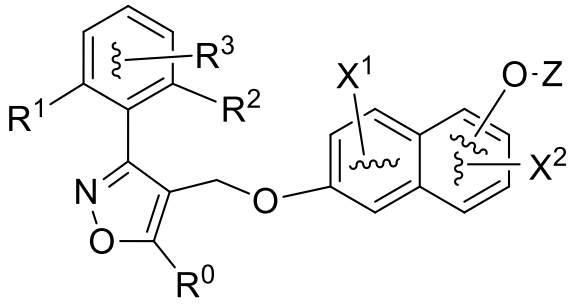
CLAIMS

1. A phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal:



(I)

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 cyclopropyl;

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 phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal 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 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

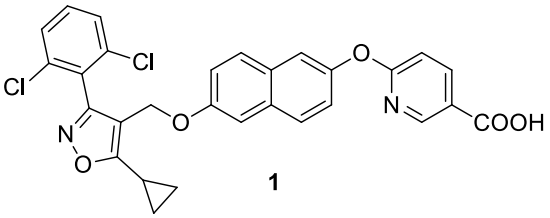
wherein the halogen is fluoro or chloro;

3. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 2, wherein R^1, R^2 and R^3 are independently selected from H, Cl, F and –O–CF_3; and

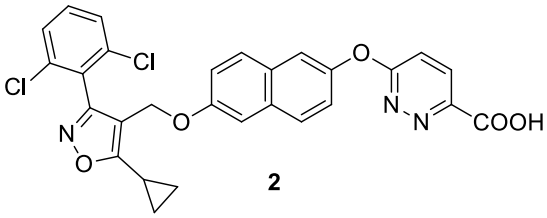
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5, wherein R^4 is selected from –COOH, –CH_2COOH, –CONHSO_2–C_{1-6} alkyl and –CONHSO_2–C_{3-6} cycloalkyl, R^5 is selected from H, C_{1-3} alkyl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

preferably, wherein Z is pyridyl; R^4 is –COOH; and R^5 is H or halogen.

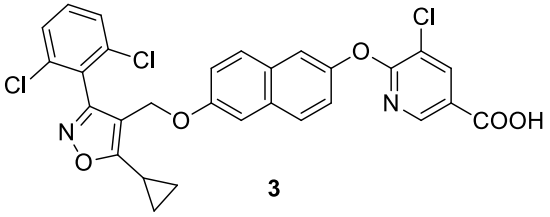
4. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



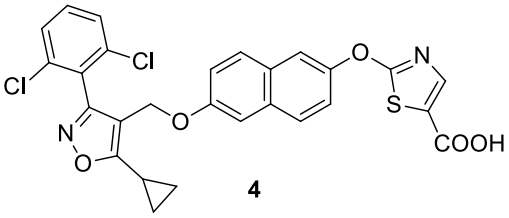
1



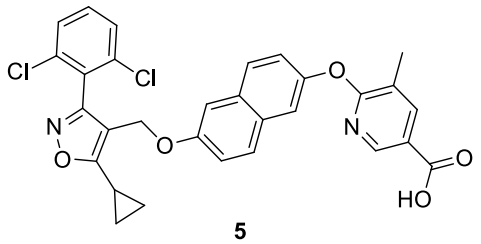
2



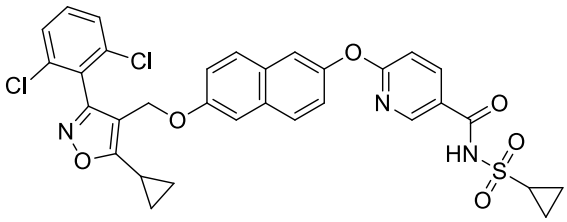
3



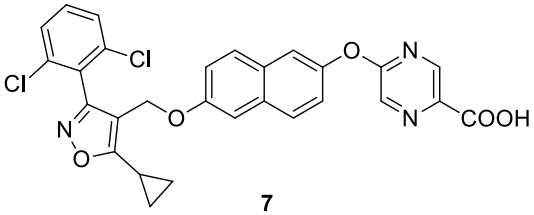
4



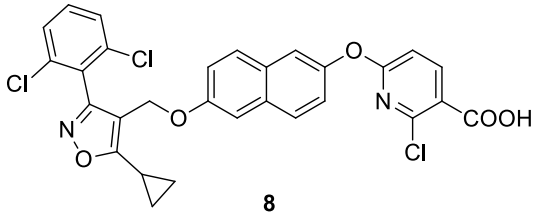
5



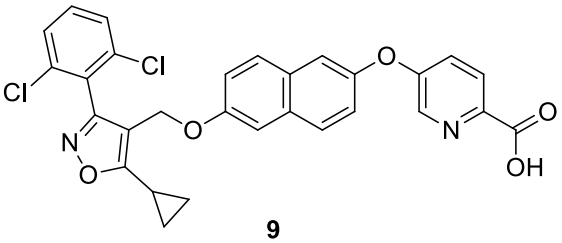
6



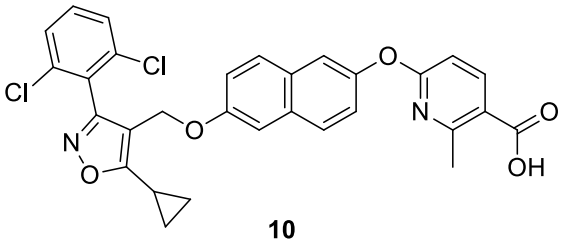
7



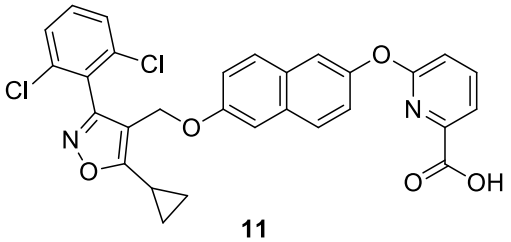
8



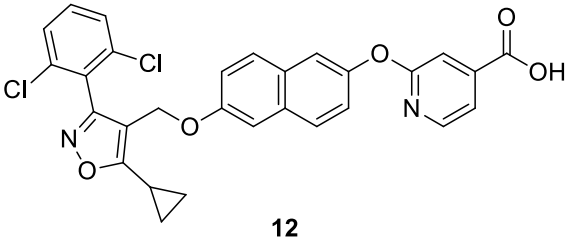
9



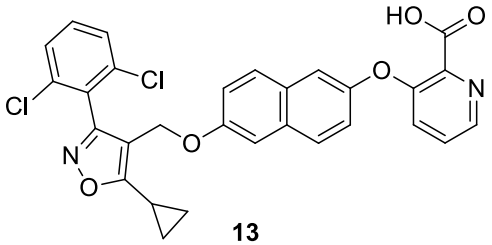
10



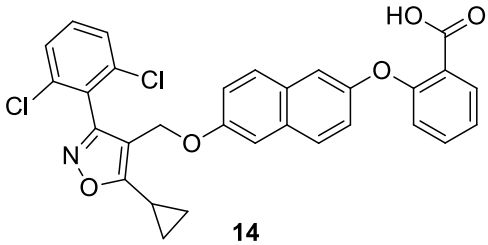
11



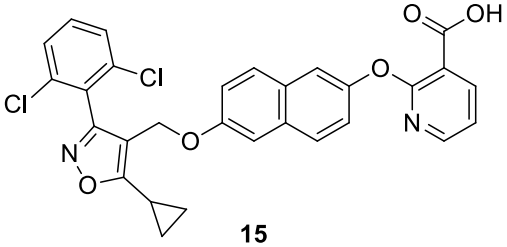
12



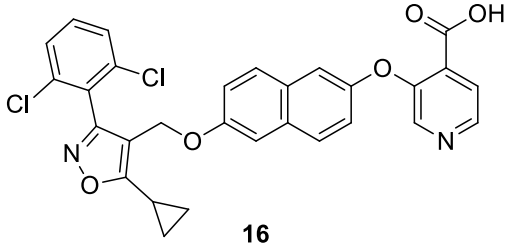
13



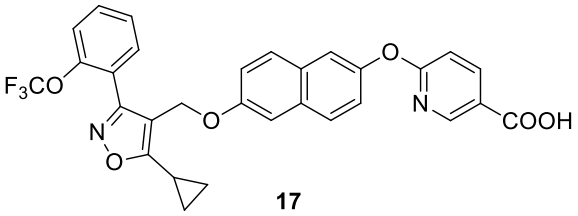
14



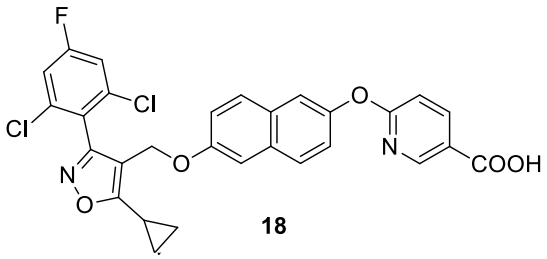
15



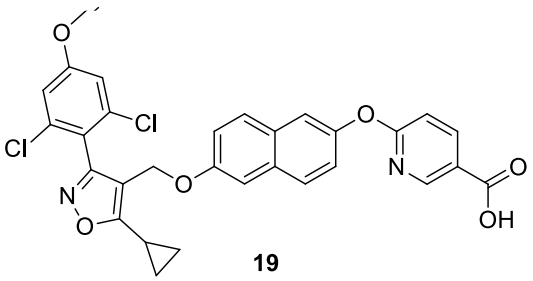
16



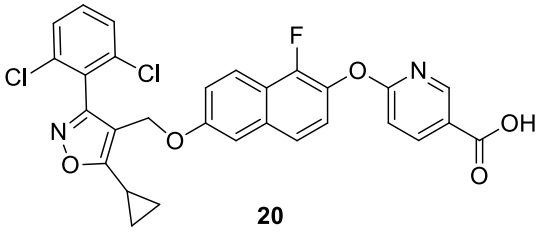
17



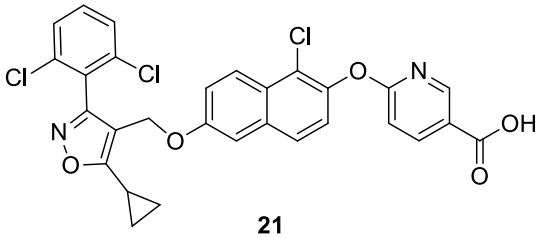
18



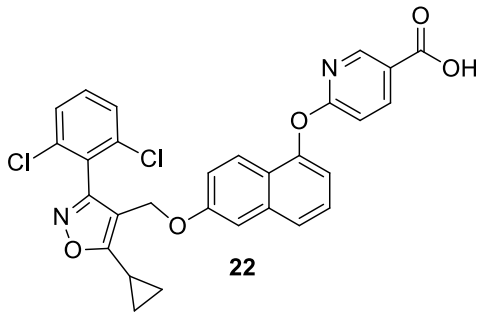
19



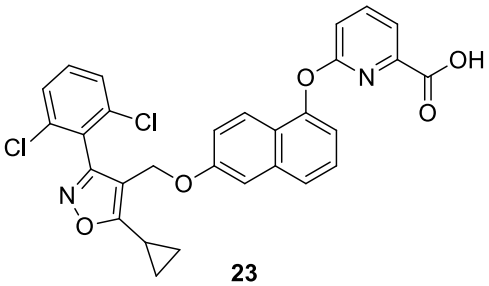
20



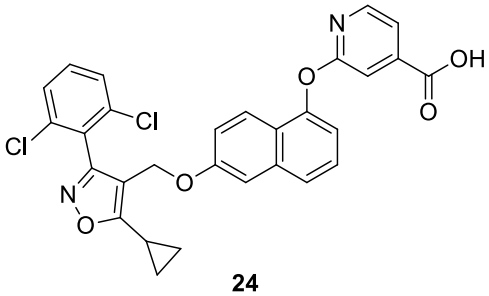
21



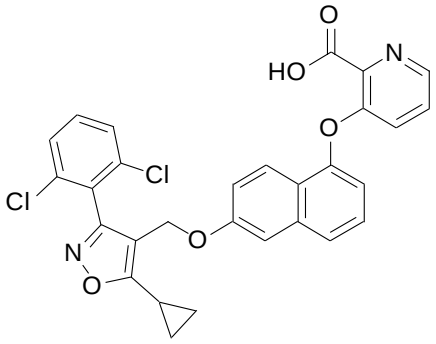
22



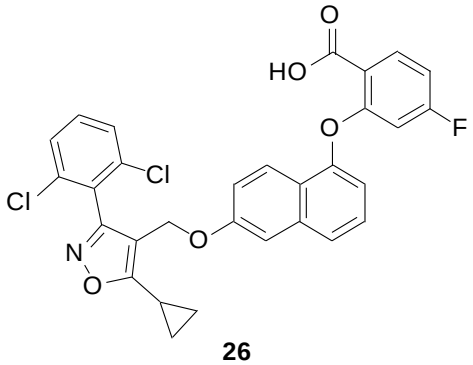
23



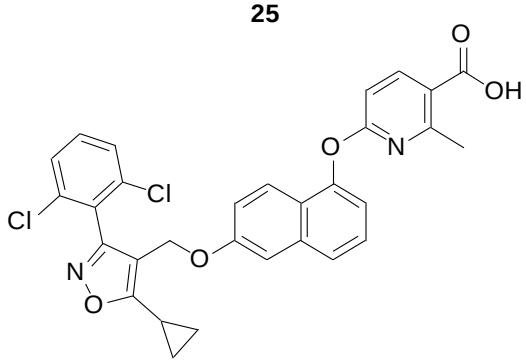
24



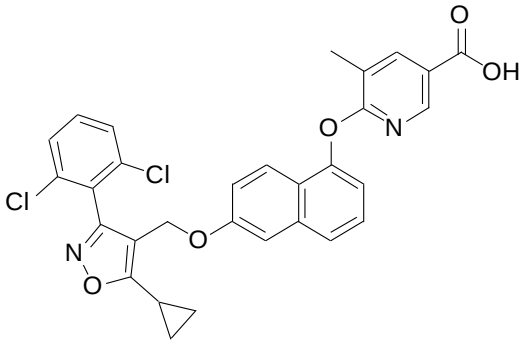
25



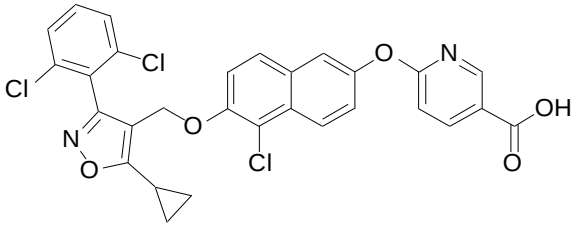
26



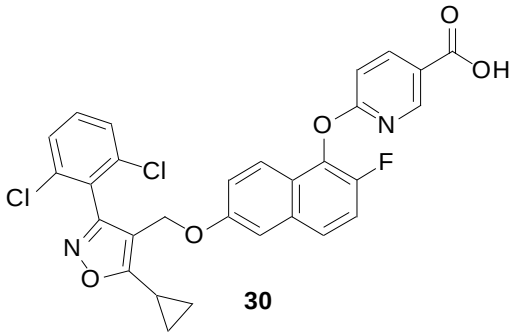
27



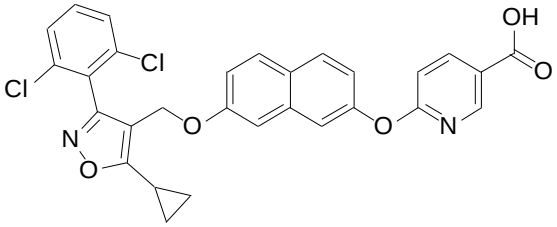
28



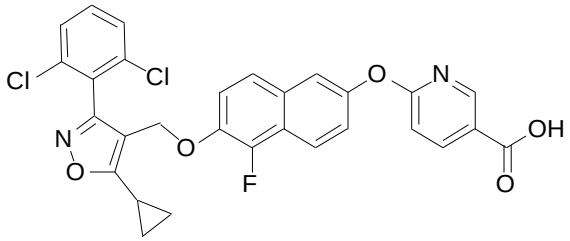
29



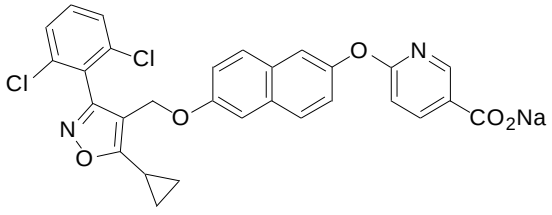
30



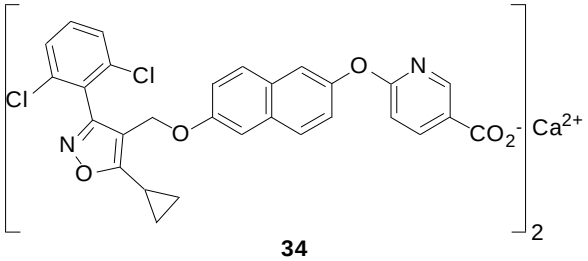
31



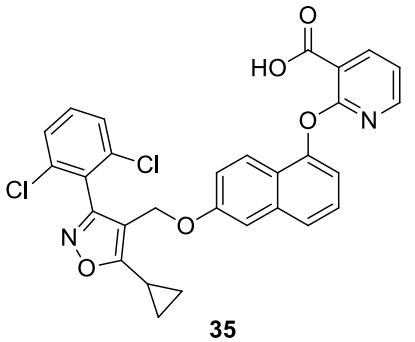
32



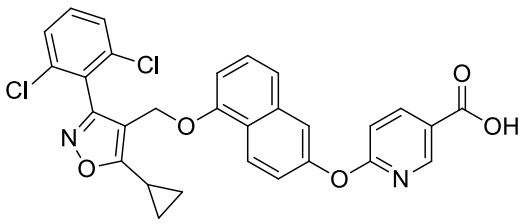
33



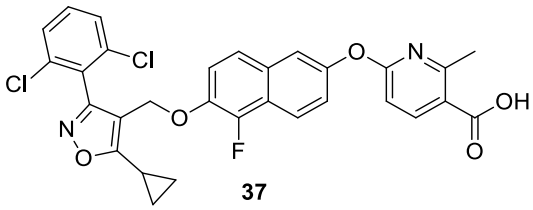
34



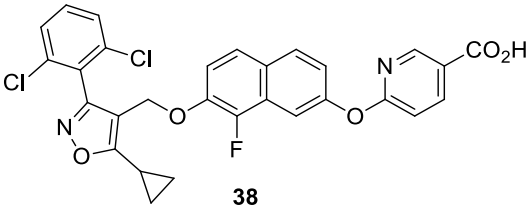
35



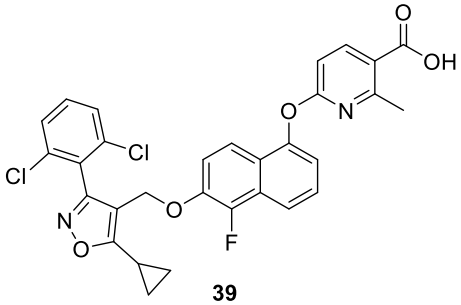
36



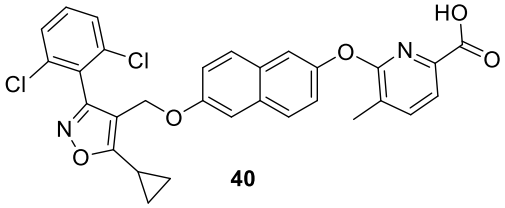
37



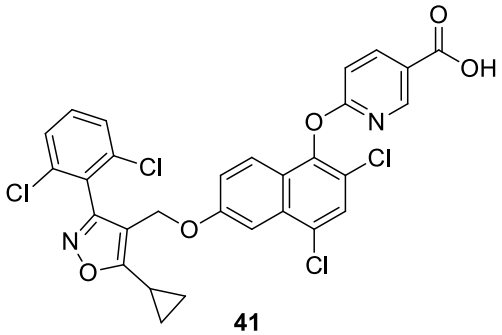
38



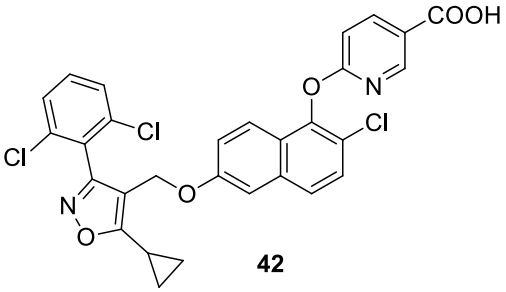
39



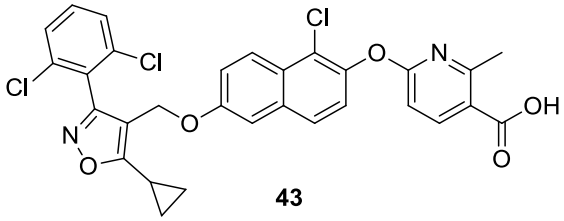
40



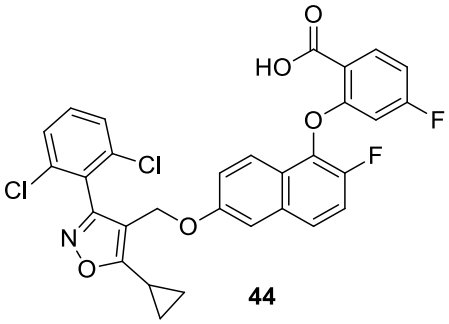
41



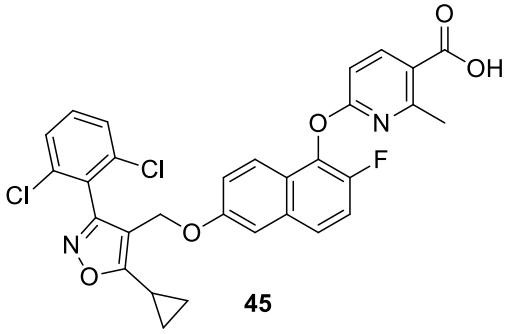
42



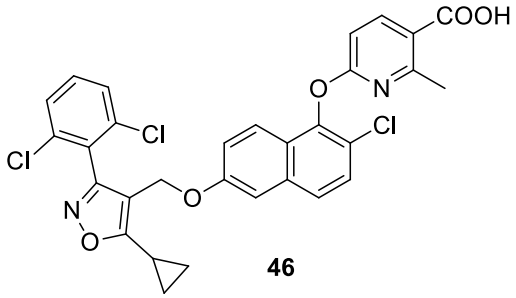
43



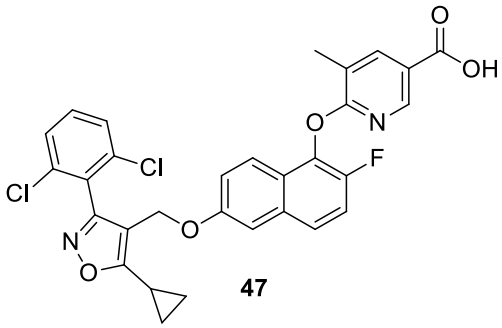
44



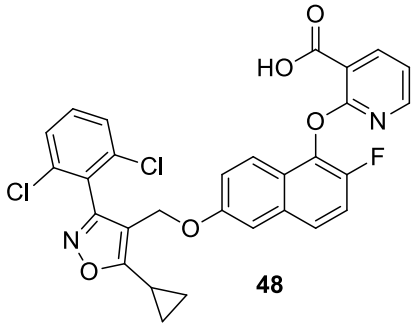
45



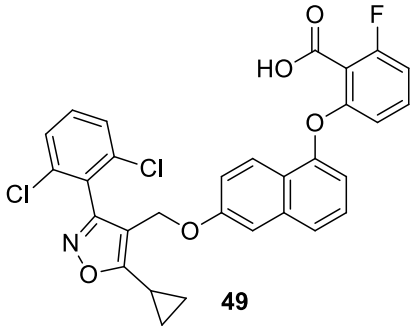
46



47



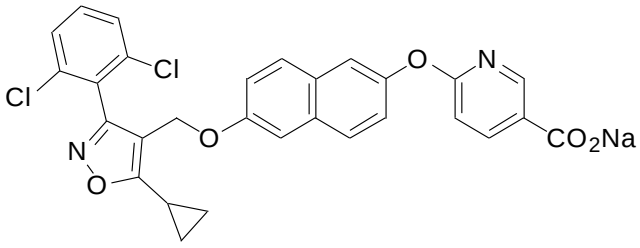
48



49

.

5. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 1, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



33

.

6. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim

1, wherein the phenylisoxazolylmethylene-naphthalene-ether derivative having the structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof is in combination with one or more other anti-HBV agents.

7. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 6, 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 endonuclease modulators, ribonucelotide 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, capsid inhibitors, and HBV replication inhibitors.

8. The phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 7, 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, WBP-3055), Balstilimab (AGEN2034) and dostarlimab (TSR-042);

the PD-L1 inhibitor 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

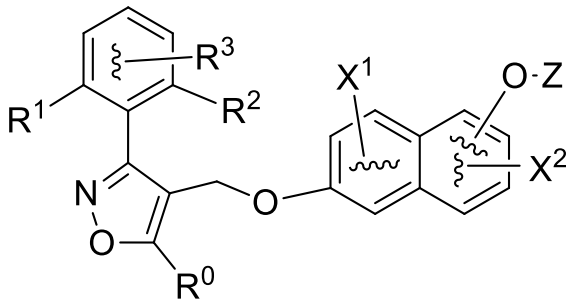
the short interfering RNA is JNJ-3989, or Vir-2218, or DCR-HBVS

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.

9. A pharmaceutical composition, which comprises a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal:



(I)

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 cyclopropyl;

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).

10. The pharmaceutical composition, which comprises a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 9, wherein R^1, R^2 and R^3 are independently selected from H, halogen and C_{1-3} perfluoroalkoxy, and R^0 is 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.

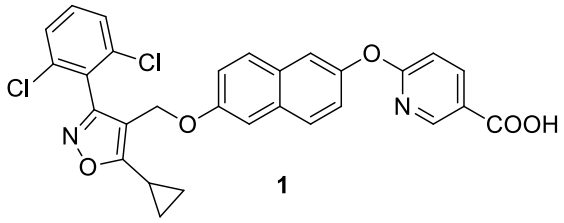
11. The pharmaceutical composition, which comprises a phenylisoxazolyl methylene-

naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 10, wherein R^1, R^2 and R^3 are independently selected from H, Cl, F and –O–CF_3; and

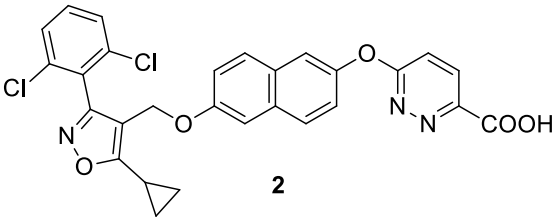
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5, wherein R^4 is selected from –COOH, –CH_2COOH, –CONHSO_2–C_{1-6} alkyl and –CONHSO_2–C_{3-6} cycloalkyl, R^5 is selected from H, C_{1-3} alkyl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

preferably, wherein Z is pyridyl; R^4 is –COOH; and R^5 is H or halogen.

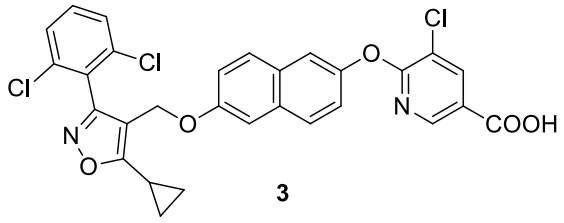
12. The pharmaceutical composition, which comprises a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 9, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



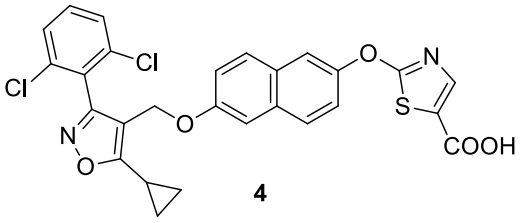
1



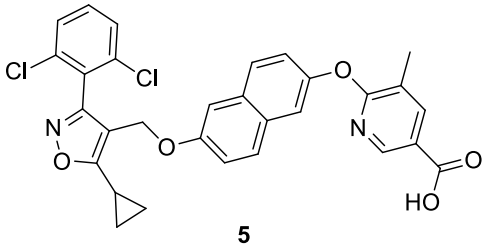
2



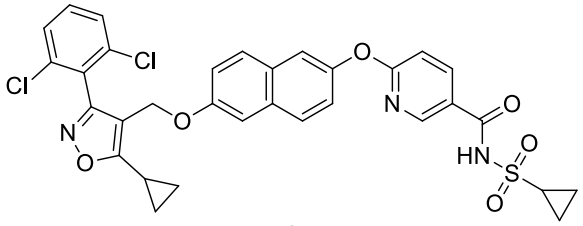
3



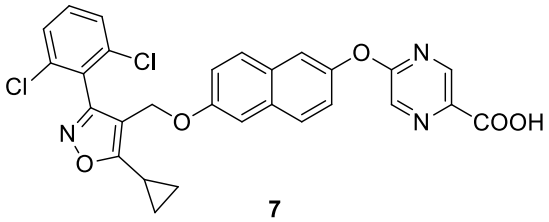
4



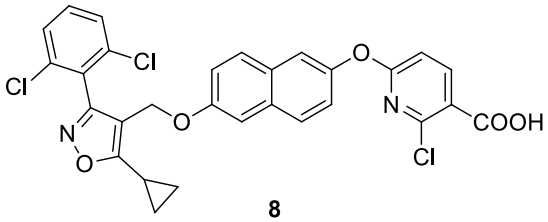
5



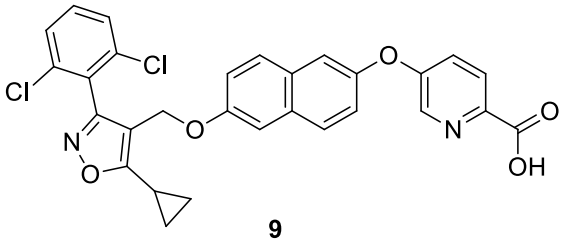
6



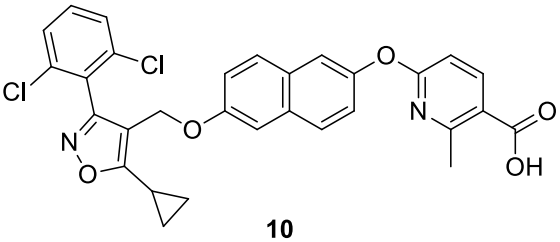
7



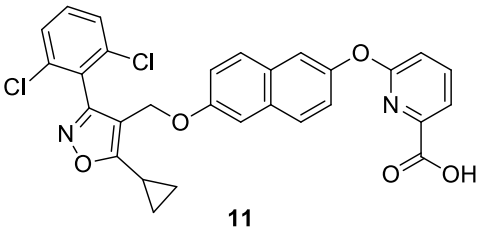
8



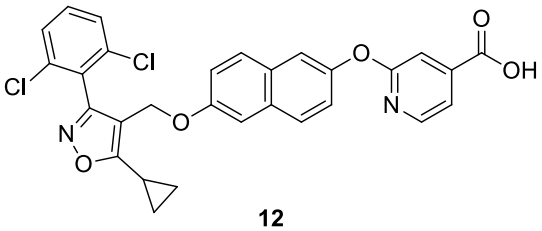
9



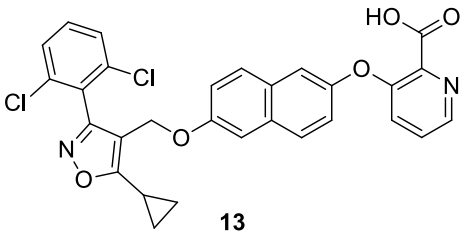
10



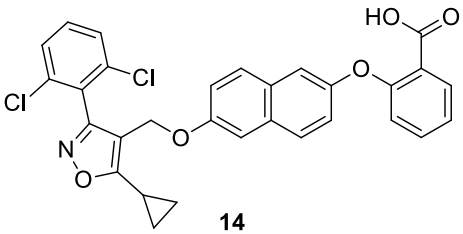
11



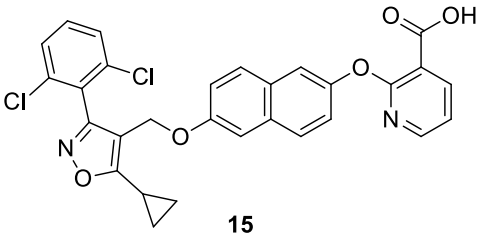
12



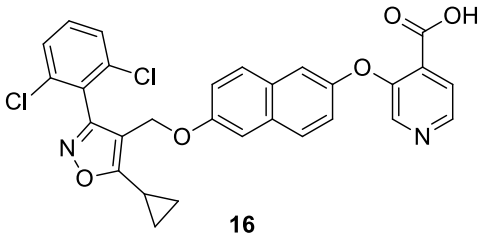
13



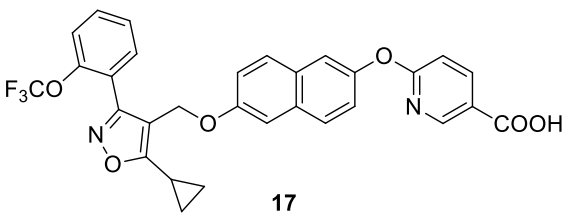
14



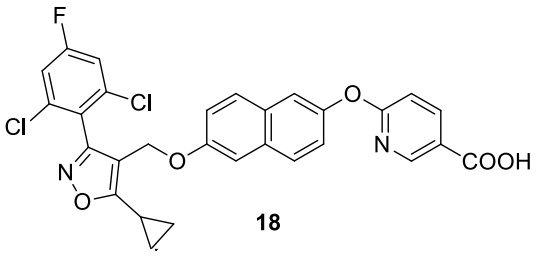
15



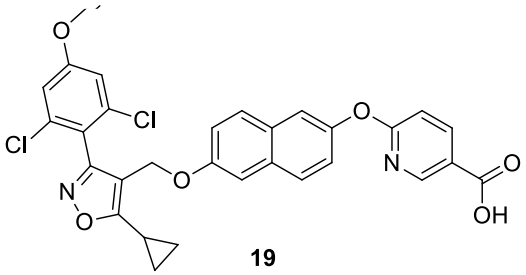
16



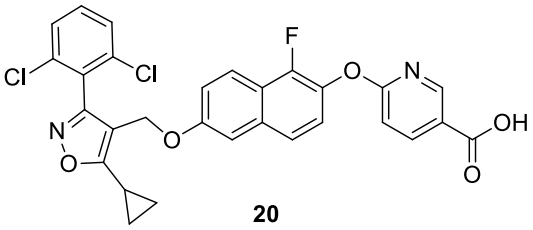
17



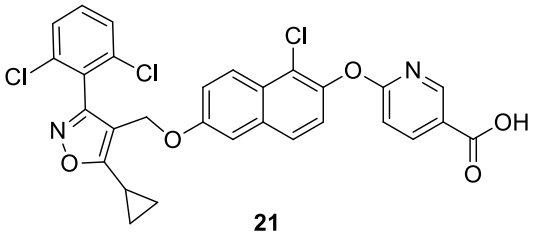
18



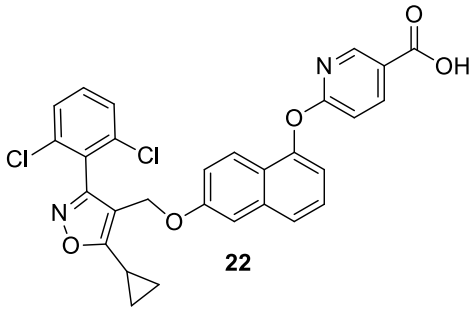
19



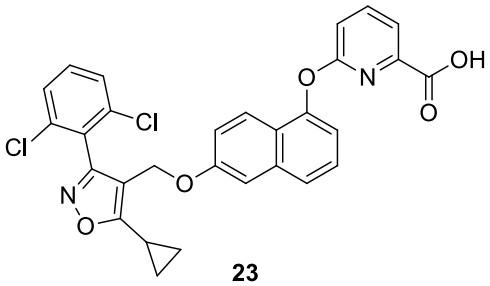
20



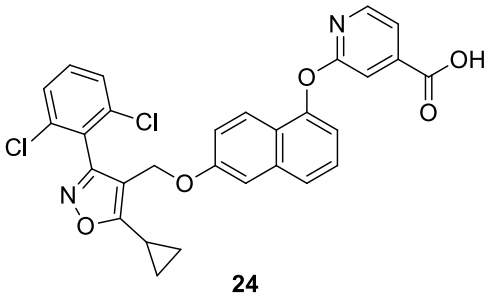
21



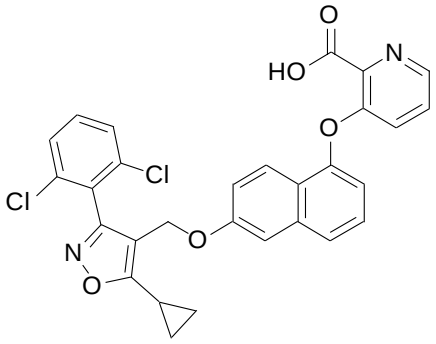
22



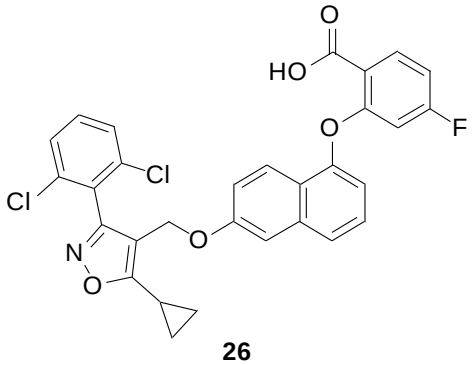
23



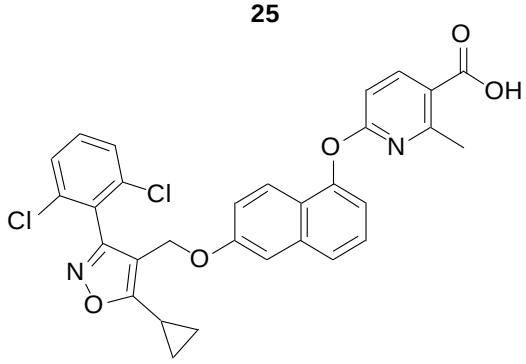
24



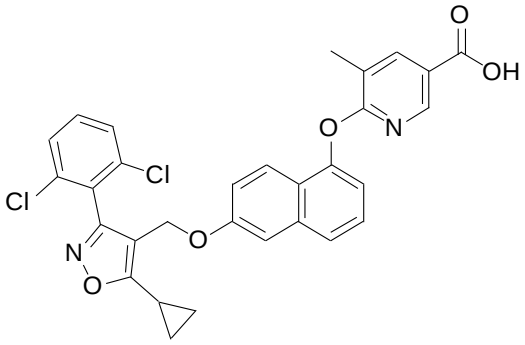
25



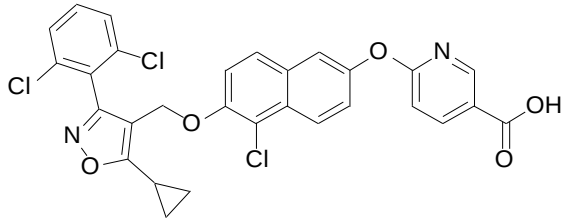
26



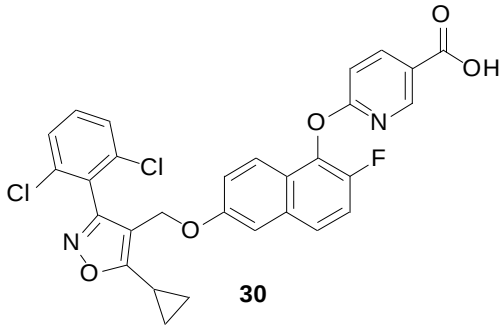
27



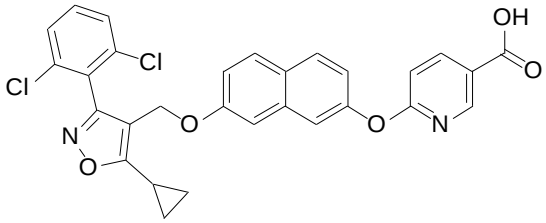
28



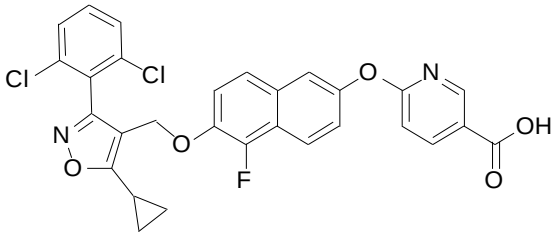
29



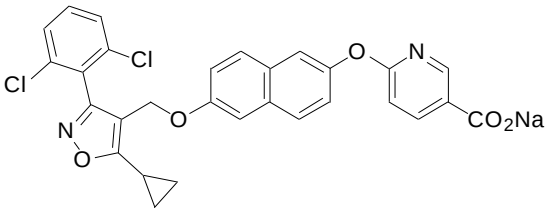
30



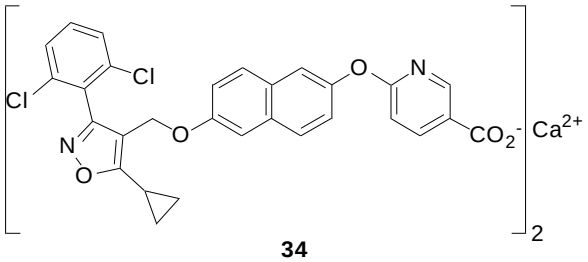
31



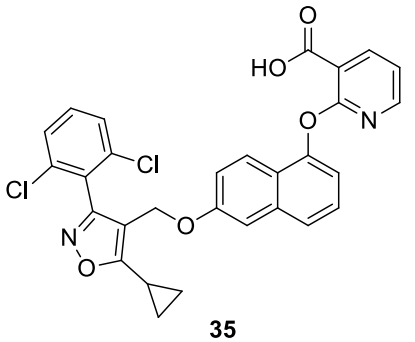
32



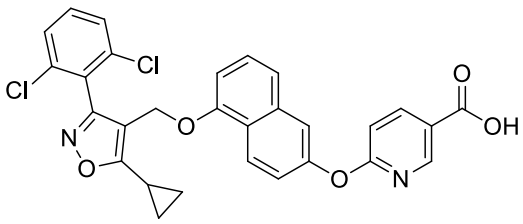
33



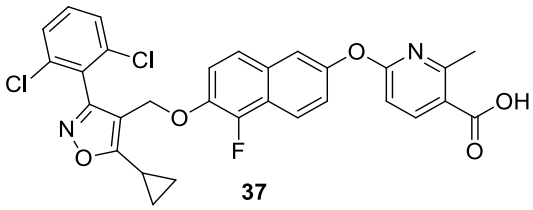
34



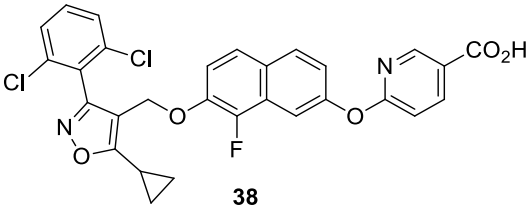
35



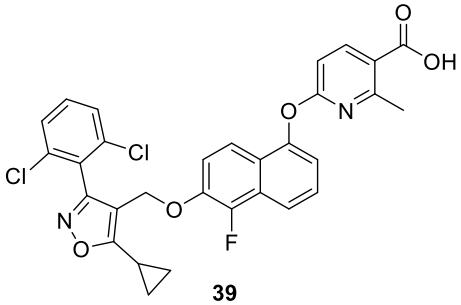
36



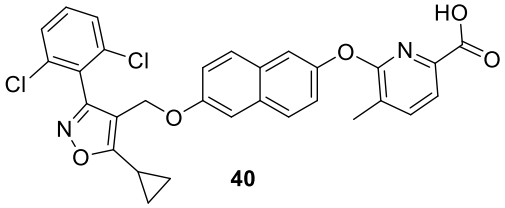
37



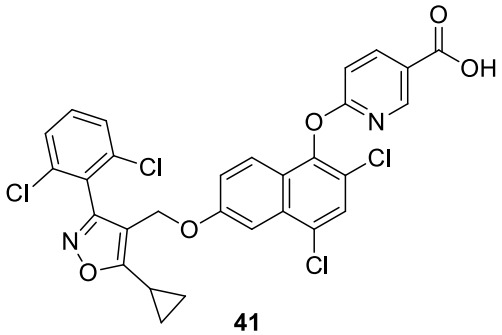
38



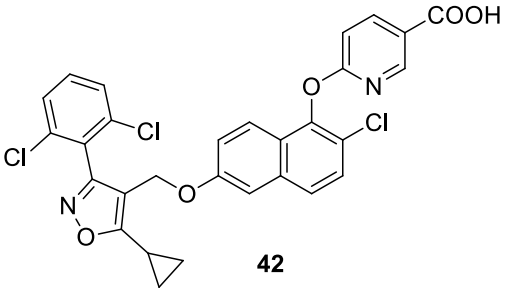
39



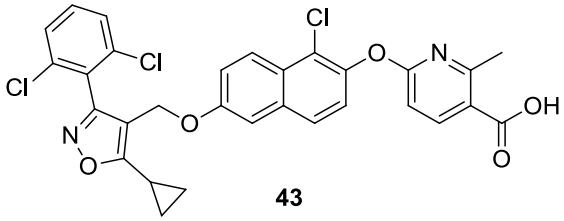
40



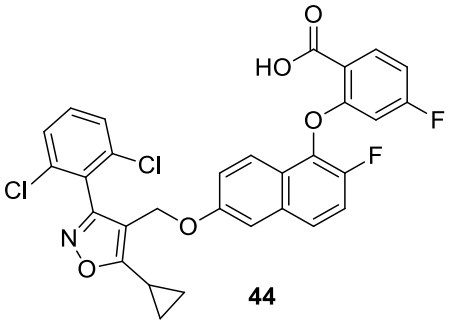
41



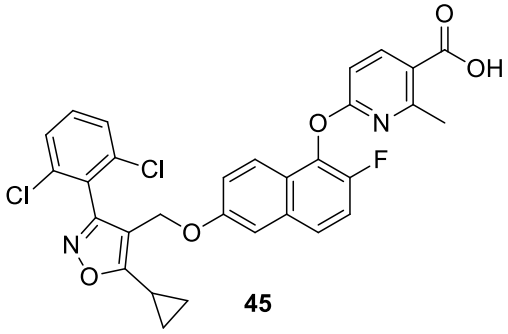
42



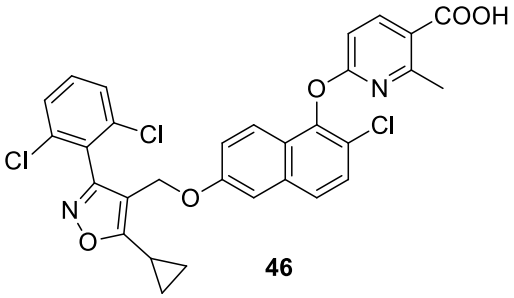
43



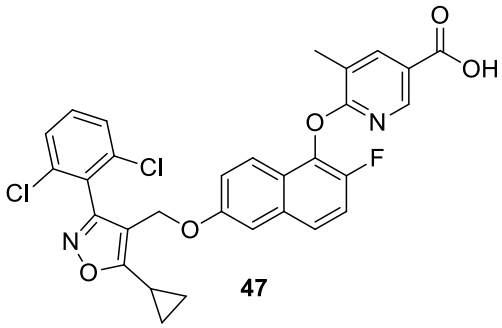
44



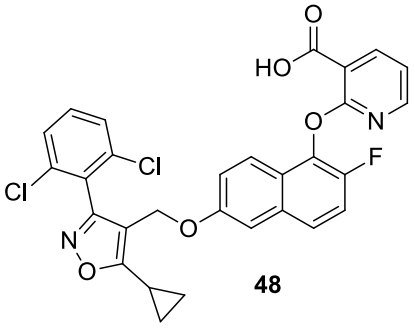
45



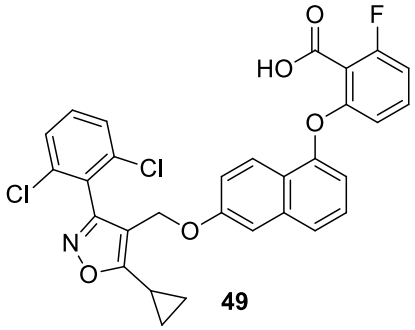
46



47



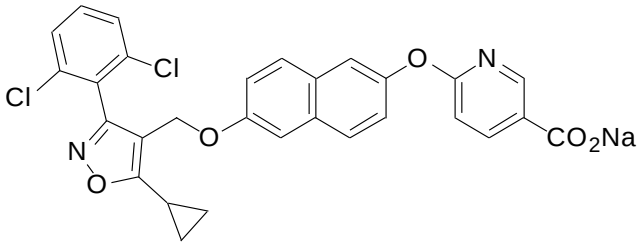
48



49

.

13. The pharmaceutical composition, which comprises a phenylisoxazolyl methylene-naphthalene-ether derivative having a structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof, for use in the treatment or preventing infection of hepatitis B virus in a human or animal according to claim 9, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:

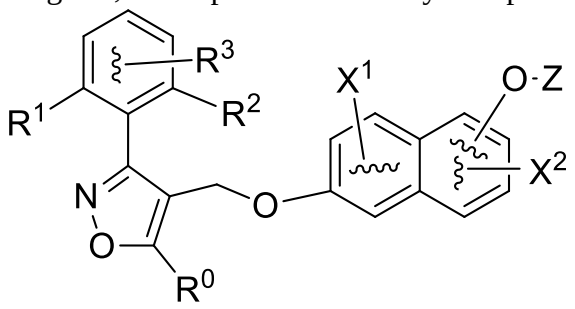


33

.

14. 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 and

one or more other anti-HBV agents, and a pharmaceutically acceptable auxiliary material,



(I)

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 cyclopropyl;

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).

15. The pharmaceutical composition according to claim 14, wherein R^1, R^2 and R^3 are independently selected from H, halogen and C_{1-3} perfluoroalkoxy, and R^0 is 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

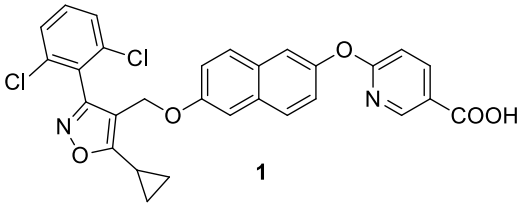
wherein the halogen is fluoro or chloro.

16. The pharmaceutical composition according to claim 15 wherein R^1, R^2 and R^3 are independently selected from H, Cl, F and $–O–CF_3$; and

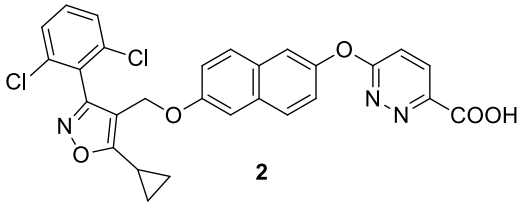
wherein Z is a 5-6 membered heteroaryl having one or more hetero atoms selected from N, O and S, which is substituted by R^4 and is optionally substituted by R^5, wherein R^4 is selected from –COOH, $–CH_2COOH$, $–CONHSO_2–C_{1-6}$ alkyl and $–CONHSO_2–C_{3-6}$ cycloalkyl, R^5 is selected from H, C_{1-3}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

preferably, wherein Z is pyridyl; R^4 is –COOH; and R^5 is H or halogen.

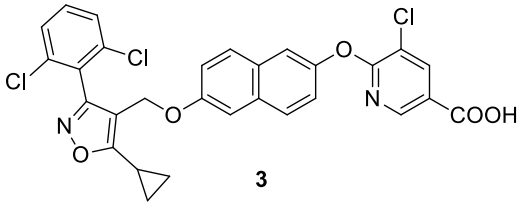
17. The pharmaceutical composition according to claim 14, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of one of the following structures:



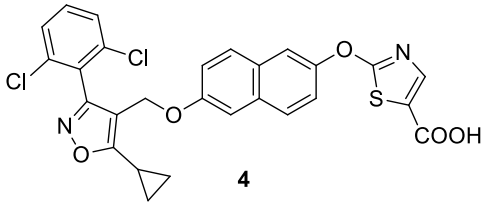
1



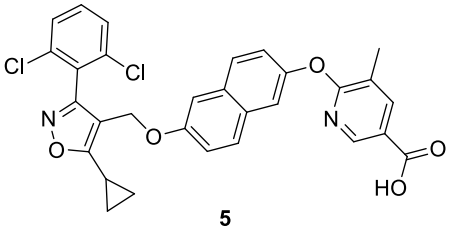
2



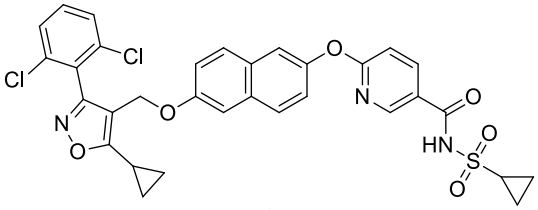
3



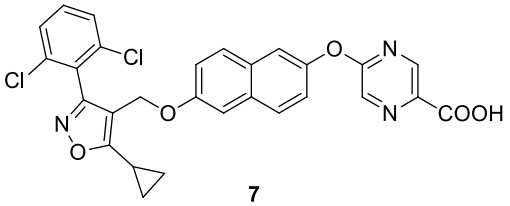
4



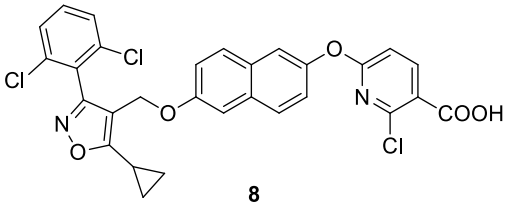
5



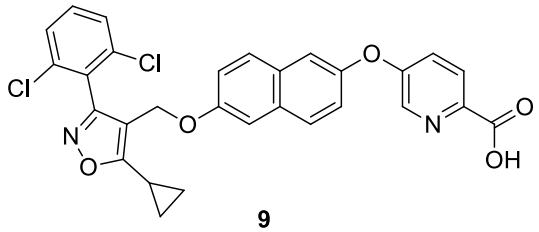
6



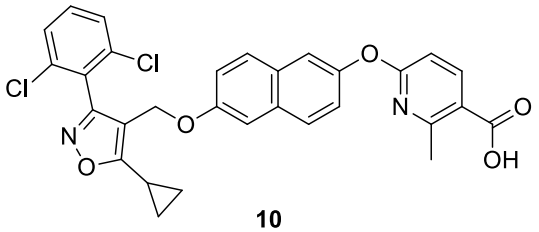
7



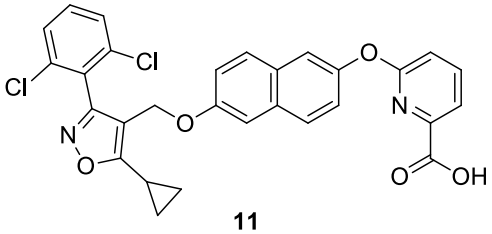
8



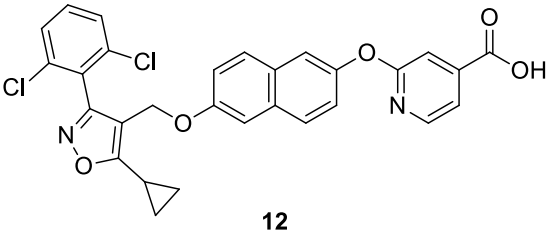
9



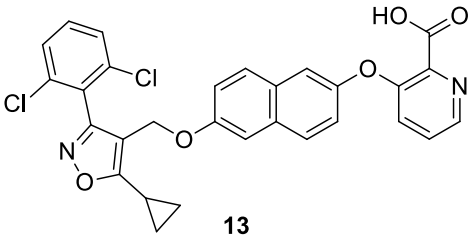
10



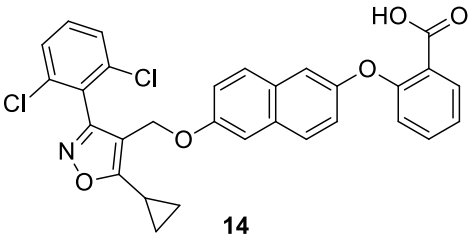
11



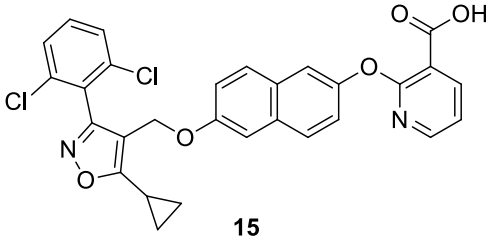
12



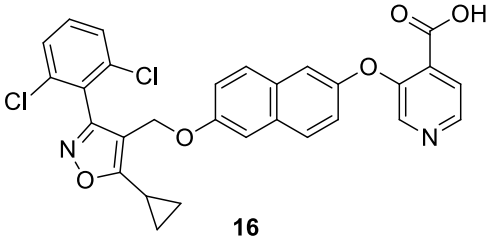
13



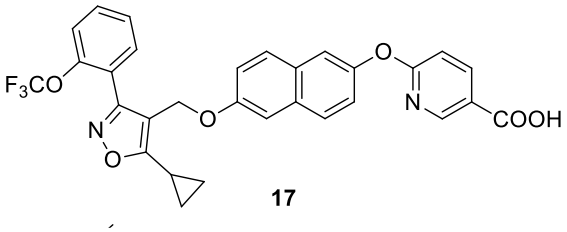
14



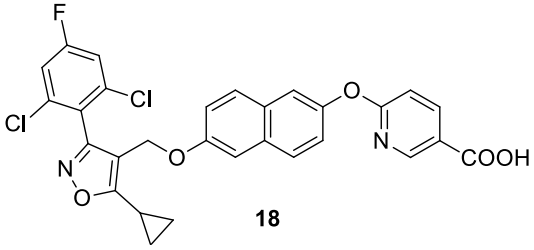
15



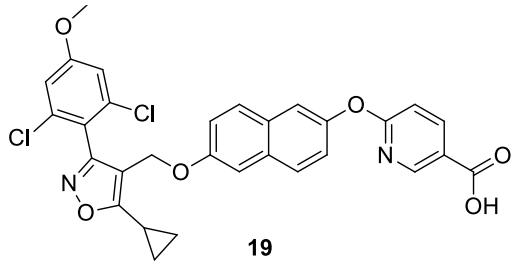
16



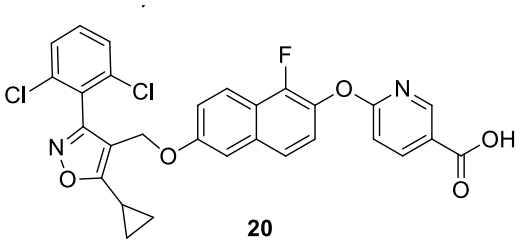
17



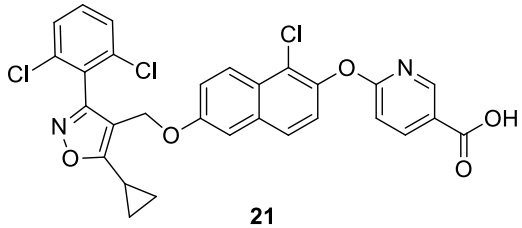
18



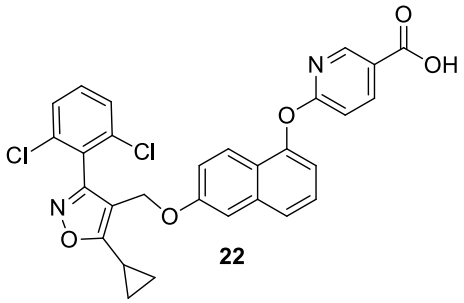
19



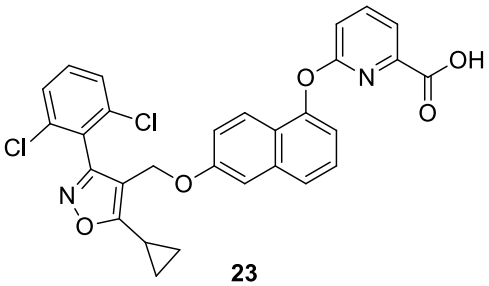
20



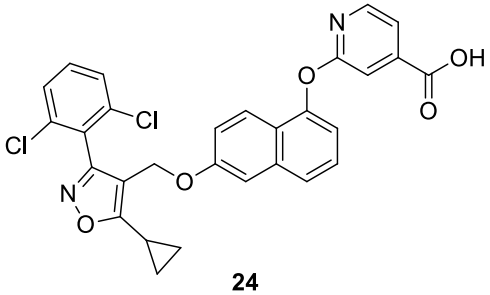
21



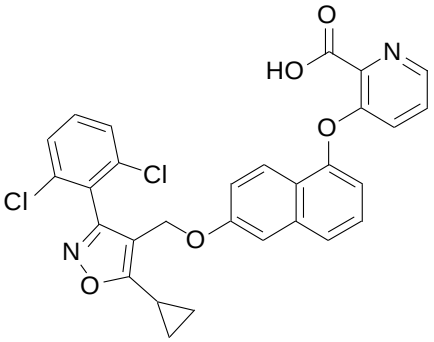
22



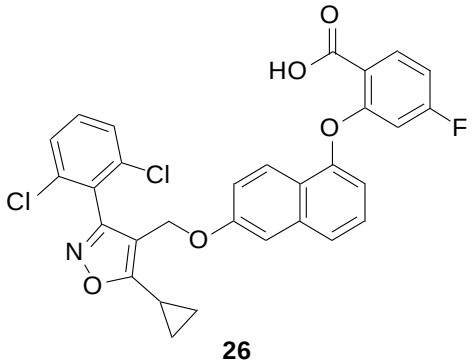
23



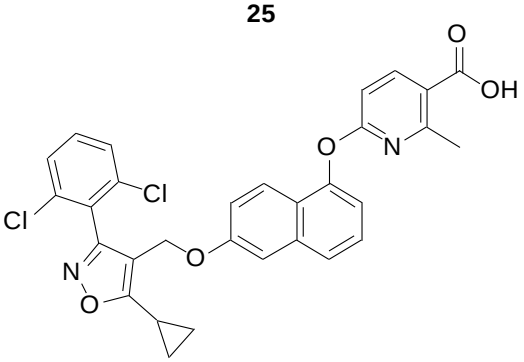
24



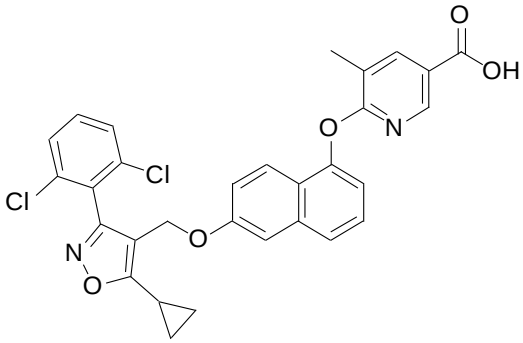
25



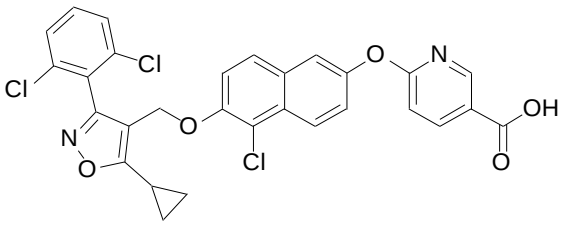
26



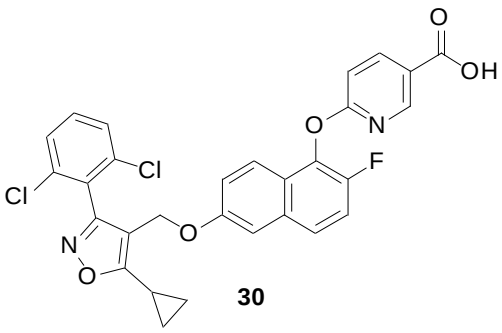
27



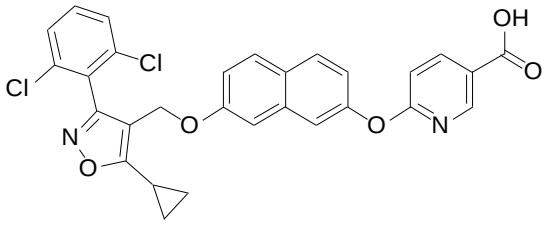
28



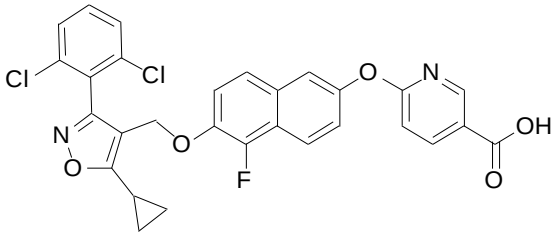
29



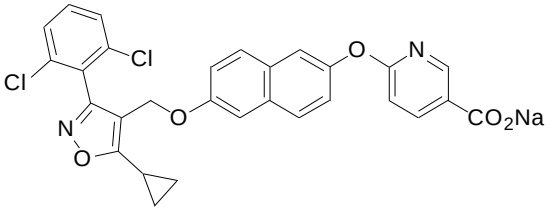
30



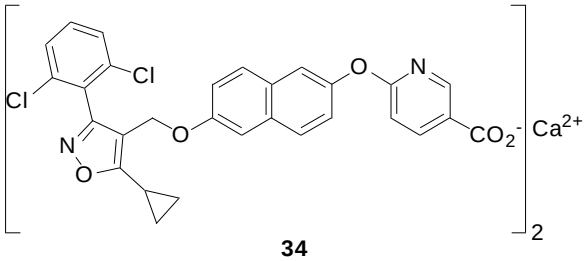
31



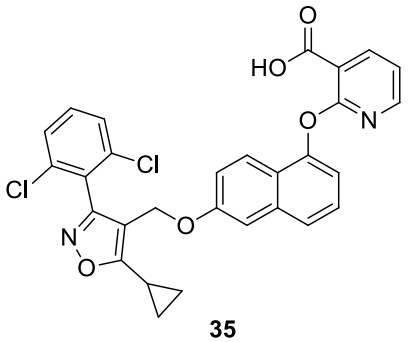
32



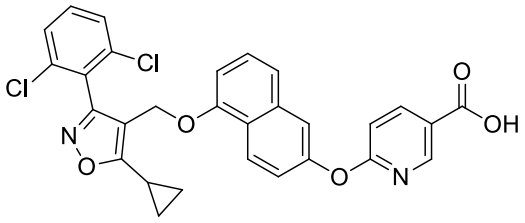
33



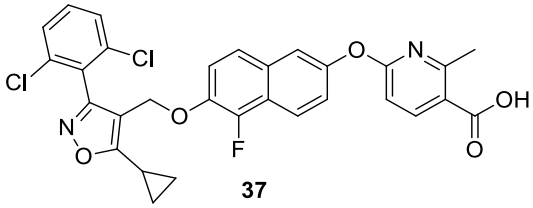
34



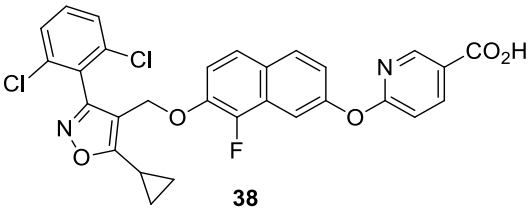
35



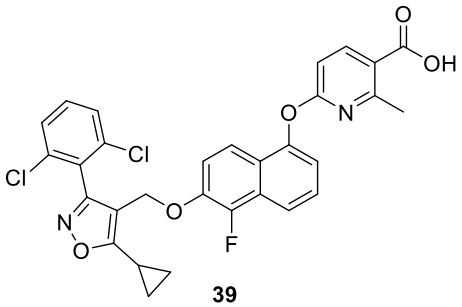
36



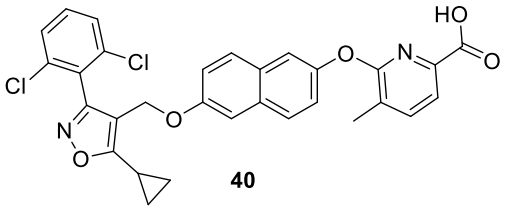
37



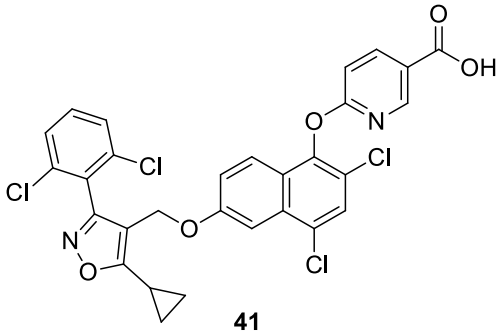
38



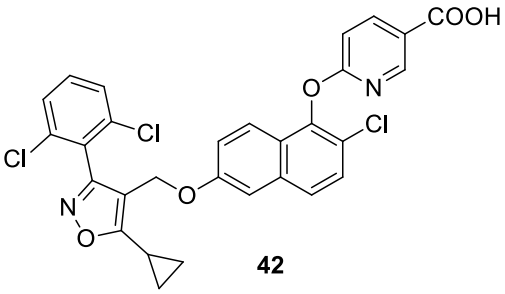
39



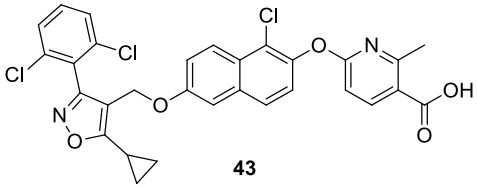
40



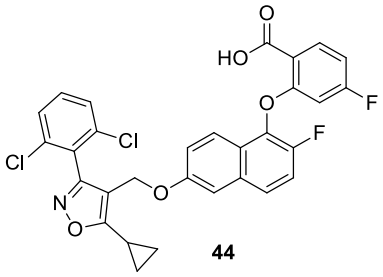
41



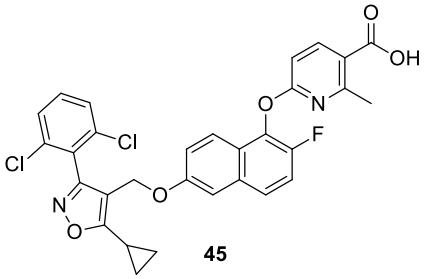
42



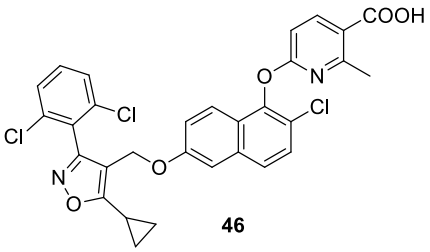
43



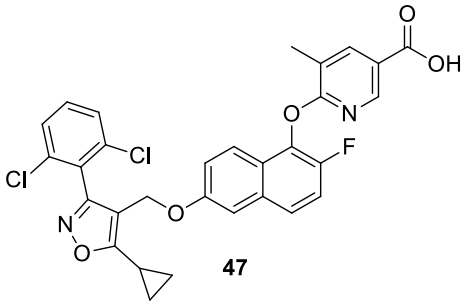
44



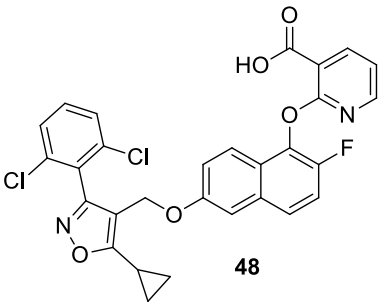
45



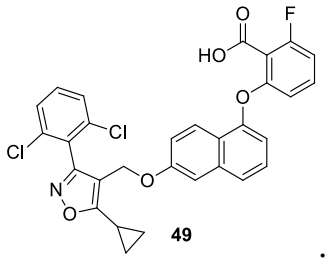
46



47



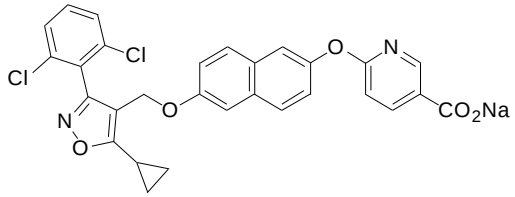
48



49

.

18. The pharmaceutical composition according to claim 14, wherein the phenylisoxazolyl methylene-naphthalene-ether derivative is of the following structure:



33

.

19. The pharmaceutical composition according to claim 14, wherein the pharmaceutical composition comprises one or more other anti-HBV agents and the phenylisoxazolyl methylene-naphthalene-ether derivative having the structure of formula (I), or a pharmaceutically acceptable salt, ester or stereoisomer thereof.

20. The pharmaceutical composition of claim 19, 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 endonuclease modulators, ribonucelotide 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, capsid inhibitors, and HBV replication inhibitors;

preferably, 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, WBP-3055), Balstilimab (AGEN2034) and dostarlimab (TSR-042);

the PD-L1 inhibitor 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;

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.