

R¹¹ and R¹² together with carbon atom to which they are attached form a 3- to 7-saturated membered ring, optionally containing a heteroatom, the heteroatom being an oxygen or a nitrogen, the nitrogen being substituted with H, -C₁₋₆alkyl, -C₁₋₆alkoxy-C₁₋₆alkyl and -C₁₋₆alkylcarbonyl;

5 Q is selected from the group consisting of aryl, heteroaryl, and a 3- to 7- membered saturated ring, optionally containing a heteroatom, the heteroatom being an oxygen or a nitrogen, the nitrogen being substituted with H, -C₁₋₆alkyl, -C₁₋₆alkoxy-C₁₋₆alkyl and -C₁₋₆alkylcarbonyl;

R¹⁰ is selected from -COOH, -C(=O)NHS(=O)₂-C₁₋₆alkyl, tetrazolyl and carboxylic acid
10 bioisosteres.

Provided herein is a pharmaceutical composition comprising at least one compound of Formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

15 Provided herein is a pharmaceutical composition comprising at least one disclosed compound, together with a pharmaceutically acceptable carrier. In another aspect, provided herein is a pharmaceutical composition, which comprises the compound as defined herein and which further comprises at least one pharmaceutically acceptable carrier.

20 Provided herein is a method of treating an HBV infection or of an HBV-induced disease in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

25 Provided herein is a method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In an example, any of the methods provided herein can further comprise administering to the individual at least one additional therapeutic agent selected from the group consisting of HBV inhibitors as herein further defined.

30 In another aspect, provided herein is a compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, for use as a medicament.

In another aspect, provided herein is the compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, for use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in

need thereof.

In another aspect, provided herein is the compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, for use in the prevention or treatment of chronic Hepatitis B.

5 In another aspect, provided herein is a product comprising a first compound and a second compound as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof, wherein said first compound is different from said second compound, wherein said first compound is the compound or pharmaceutically acceptable salt as defined herein or
10 the pharmaceutical composition as defined herein, and wherein said second compound is another HBV inhibitor which is selected from the group consisting of HBV combination drugs, HBV DNA polymerase inhibitors, immunomodulators, toll-like (TLR) receptor modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HbsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors, cyclophilin inhibitors,
15 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, farnesoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 stimulators, NOD2
20 stimulators, phosphatidylinositol 3-kinase (P13K) inhibitors, indoleamine 2,3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and anti-HBV drugs.

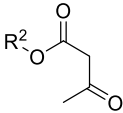
In another aspect, provided herein is use of a compound or pharmaceutically acceptable
25 salt as defined herein or the pharmaceutical composition as defined herein, in the manufacture of a medicament for prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof.

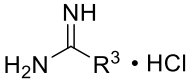
In another aspect, provided herein is use of a compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, in the manufacture
30 of a medicament for prevention or treatment of chronic Hepatitis B.

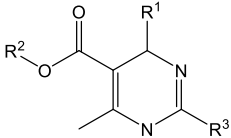
In another aspect, provided herein is use of a product comprising a first compound and a second compound in the manufacture of a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof, wherein said first compound is different from said

second compound, wherein said first compound is the compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, and wherein said second compound is another HBV inhibitor which is selected from the group consisting of HBV combination drugs, HBV DNA polymerase inhibitors, immunomodulators, toll-like (TLR) receptor modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HbsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ipi4) 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, farnoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, phosphatidylinositol 3-kinase (P13K) inhibitors, indoleamine 2,3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and anti-HBV drugs.

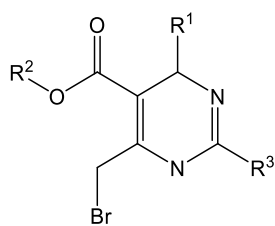
In another aspect, provided herein is a process for the preparation of a compound as defined herein, comprising the steps of:

a. The condensation of aldehyde of Formula (II), wherein Formula (II) is  (II),
 20 acetoacetate of Formula (III), wherein Formula (III) is  (III), and amidine of Formula

(IV), wherein Formula (IV) is  (IV), in the presence of a base, the base being

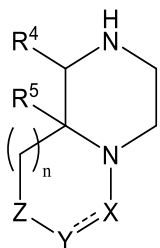
preferably NaOAc, to form a compound according to Formula (I-1):  (I-1);

b. The bromination of compound of Formula (I-1), the brominating agent being preferably N-Bromosuccinimide, to form a compound according to Formula (I-2), wherein



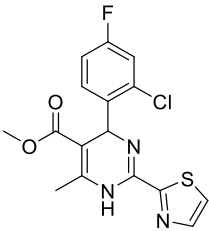
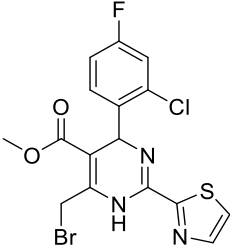
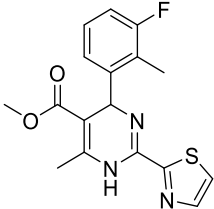
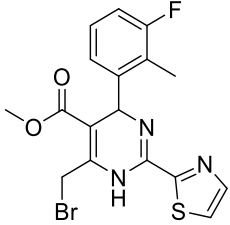
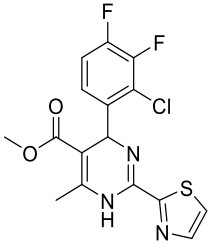
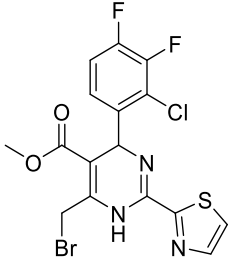
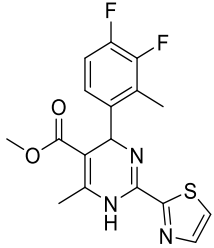
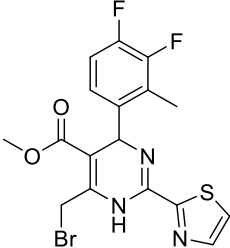
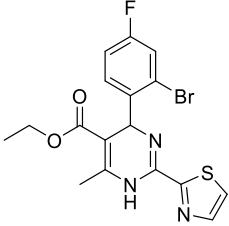
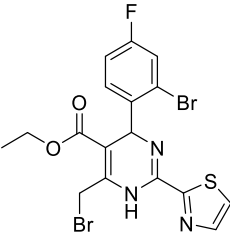
Formula (I-2) is (I-2) ;

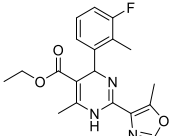
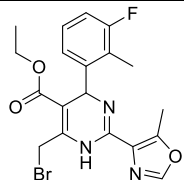
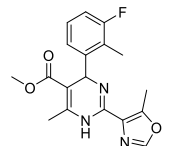
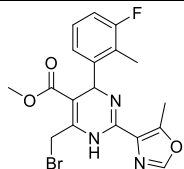
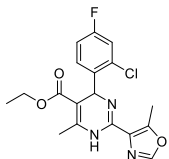
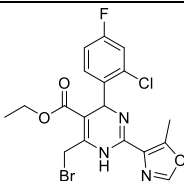
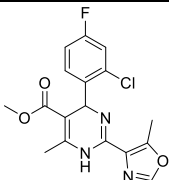
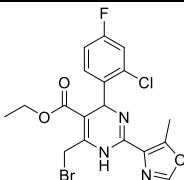
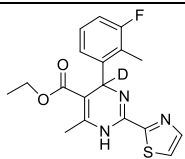
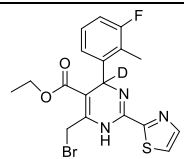
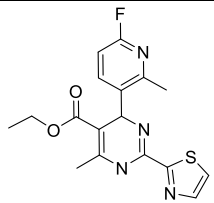
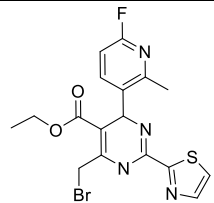
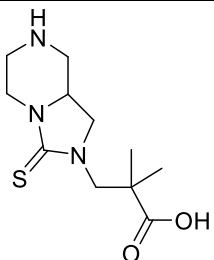
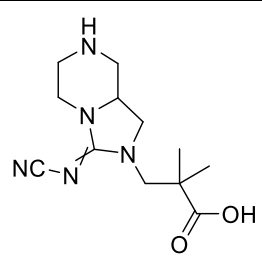
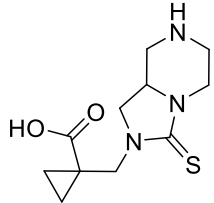
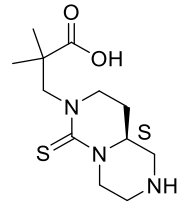
c. The coupling of compound of Formula (I-2) with a compound of Formula (V), wherein

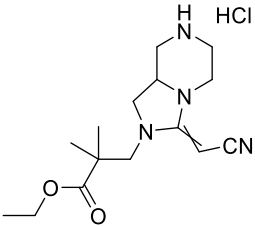
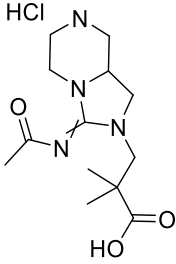
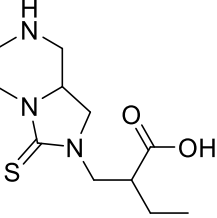
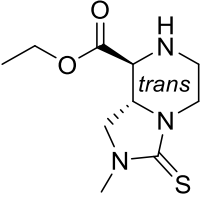
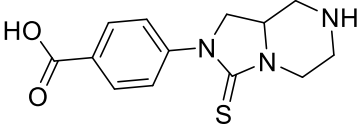
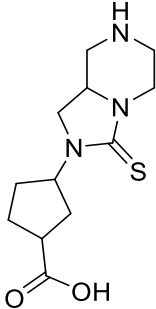
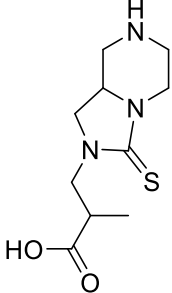


Formula (V) is (V) , in the presence of a base, the base being preferably triethylamine, to form a compound according to Formula (I).

5 In another aspect, provided herein is a compound, selected from the group consisting of the compounds having the following formulae, including any salts thereof:

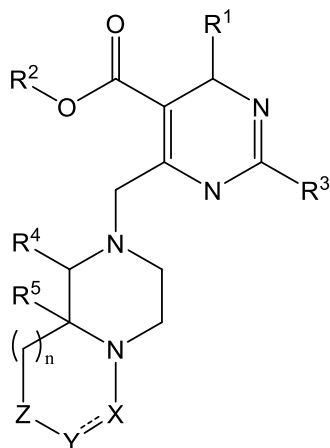
DETAILED DESCRIPTION

5 Provided herein are compounds, e.g., the compounds of I, or pharmaceutically acceptable salts thereof, that are useful in the treatment and prevention of HBV infection in subject.

Without being bound to any particular mechanism of action, these compounds are believed to modulate or disrupt HBV assembly and other HBV core protein functions necessary for HBV replication or the generation of infectious particles and/or may disrupt

CLAIMS

1. A compound of Formula (I)



(I)

- 5 including the deuterated isomers, stereoisomers or tautomeric forms thereof, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of phenyl, thiophenyl, pyridyl, and pyridonyl, optionally substituted with one or more substituents selected from the group consisting of C₁₋₄alkyl, halogen and CN;

- 10 R² is C₁₋₄alkyl;

R³ is selected from the group consisting of thiazolyl, pyridyl, and oxazolyl, optionally substituted with one or more substituents selected from fluorine and C₁₋₆alkyl;

n is an integer of 0 or 1;

R⁴ and R⁵ are independently selected from H and -COOH;

- 15 ----- is a single bond or a double bond;

when X and Y are linked by a single bond, X is selected from the group consisting of C(=S), C(=NR⁶), C(=CHR⁷) and CHR⁸, and Y is NR⁹;

when X and Y are linked by a double bond, X is C-SR⁹ or C-OR⁹, and Y is N atom;

Z is selected from the group consisting of CH₂, and C(=O);

- 20 R⁶ is selected from the group consisting of CN, C(=O)CH₃ and SO₂CH₃;

R⁷ is CN;

R⁸ is CF₃;

R⁹ is selected from the group consisting of H, -C₁₋₆alkyl, -C₁₋₆alkyl-R¹⁰, -C₁₋₆alkoxy-C₁₋₆alkyl-R¹⁰, -(CH₂)_p-C(R¹¹R¹²)-R¹⁰ and -(CH₂)_p-Q-R¹⁰;

p is an integer of 0, 1, 2, or 3;

5 R¹¹ and R¹² together with carbon atom to which they are attached form a 3- to 7-saturated membered ring, optionally containing a heteroatom, the heteroatom being an oxygen or a nitrogen, the nitrogen being substituted with H, -C₁₋₆alkyl, -C₁₋₆alkoxy-C₁₋₆alkyl and -C₁₋₆alkylcarbonyl;

10 Q is selected from the group consisting of aryl, heteroaryl, and a 3- to 7- saturated membered ring, optionally containing a heteroatom, the heteroatom being an oxygen or a nitrogen, the nitrogen being substituted with H, -C₁₋₆alkyl, -C₁₋₆alkoxy-C₁₋₆alkyl and -C₁₋₆alkylcarbonyl;

R¹⁰ is selected from -COOH, -C(=O)NHS(=O)₂-C₁₋₆alkyl, tetrazolyl, and carboxylic acid bioisosteres.

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2. The compound of claim 1, wherein the carboxylic acid bioisosters are -S(=O)₂(OH), -P(=O)(OH)₂, -C(=O)NHOH, -C(=O)NHCN, 1,2,4-oxadiazol-5(4*H*)-one, and 3-hydroxy-4-methylcyclobut-3-ene-1,2-dione.

20 3. The compound of claim 1 or 2, wherein R¹ is phenyl substituted with one or more substituents selected from halogens and C₁₋₆alkyl.

4. The compound of any one of the preceding claims, wherein R² is methyl or ethyl.

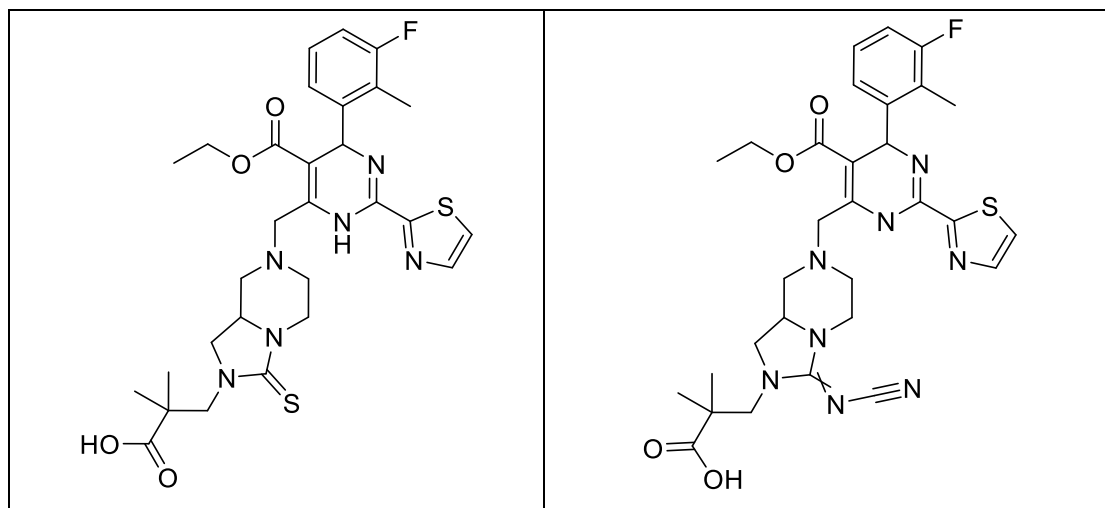
25 5. The compound of any one of the preceding claims, wherein R³ is thiazolyl.

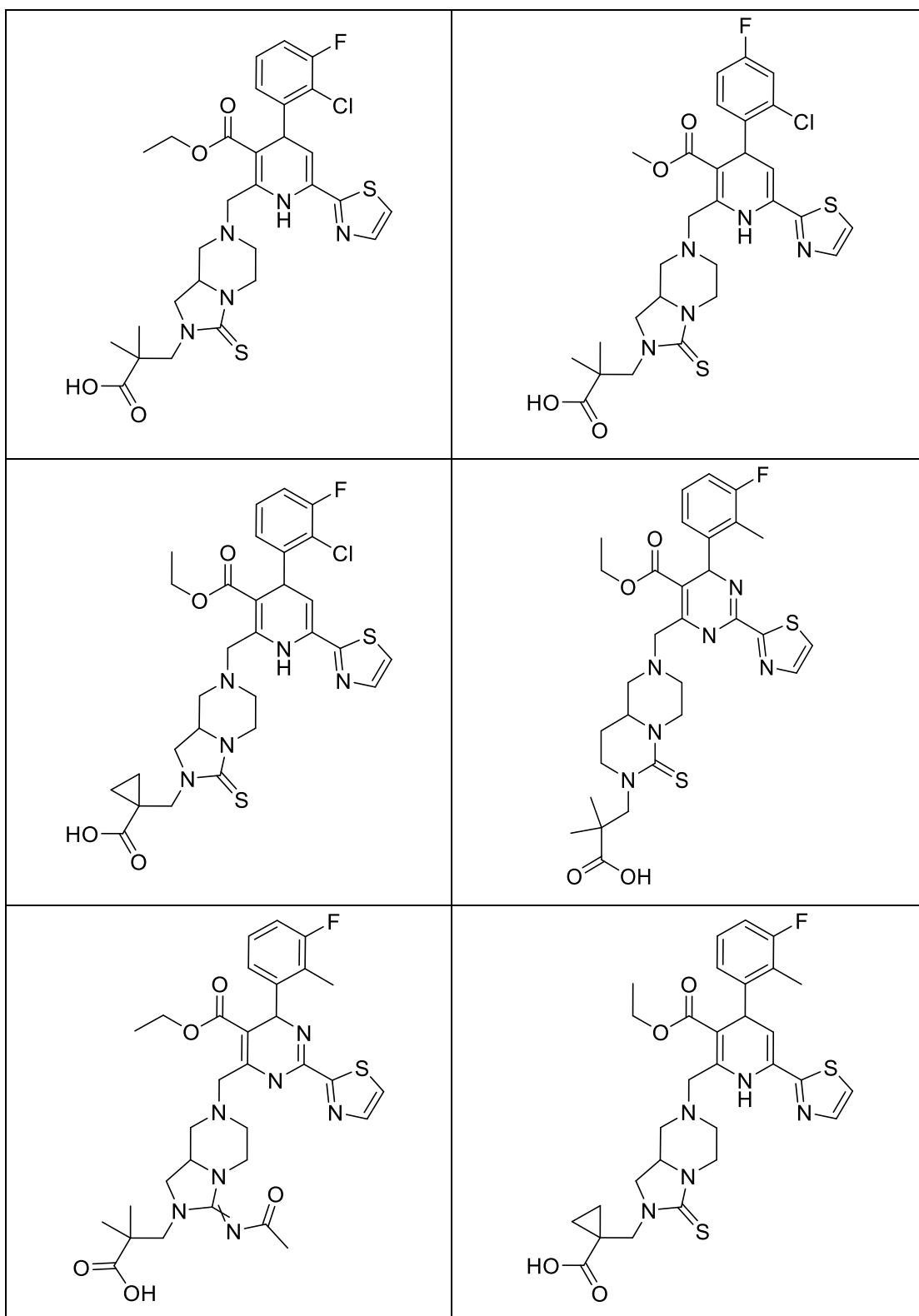
6. The compound of any one of the preceding claims, wherein R⁴ and R⁵ are H.

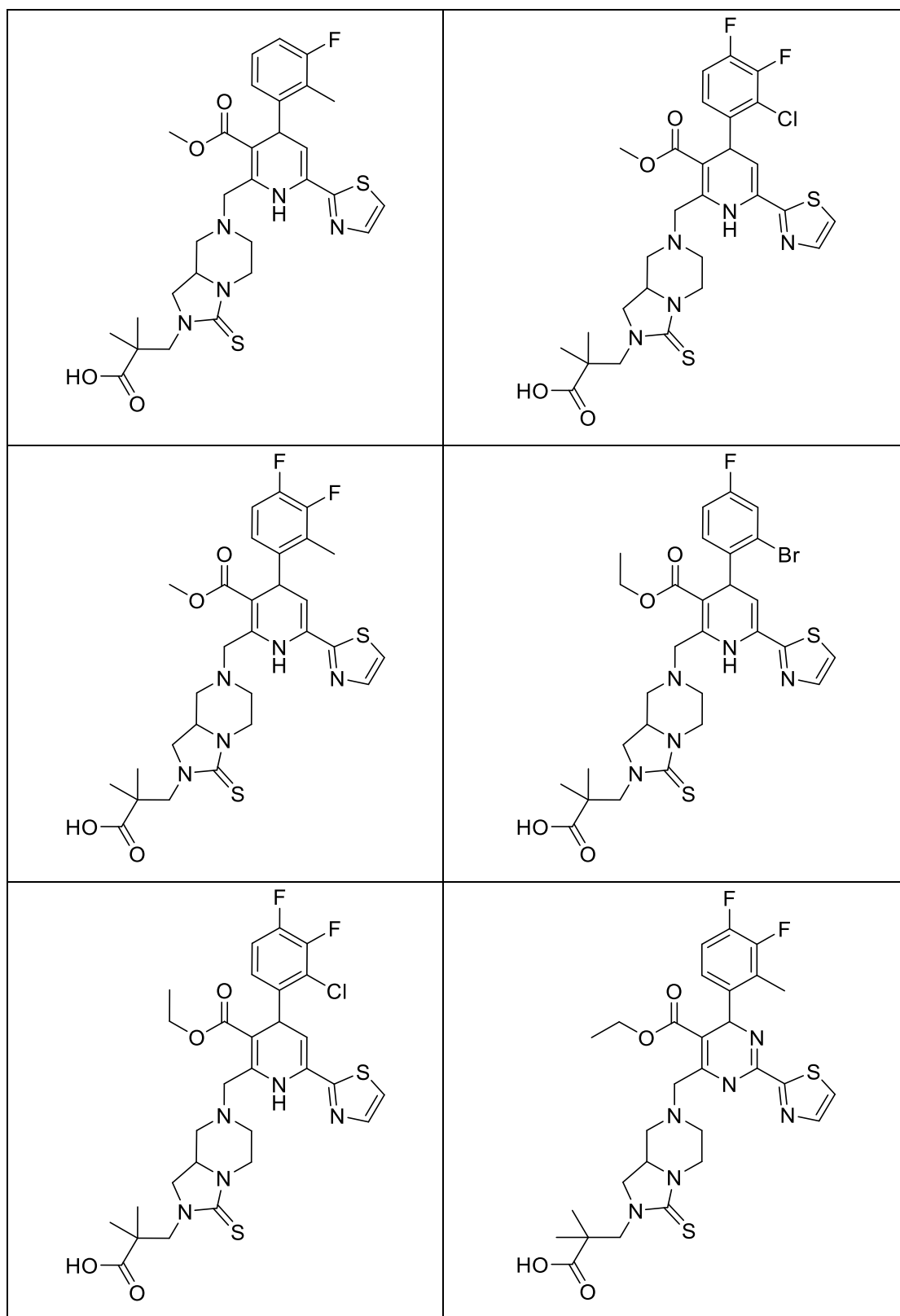
7. The compound of any one of the preceding claims, wherein X is C(=S).

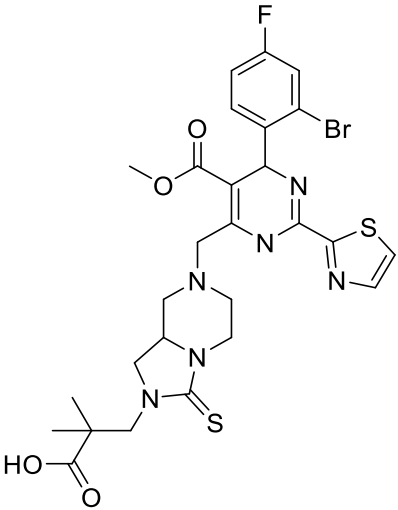
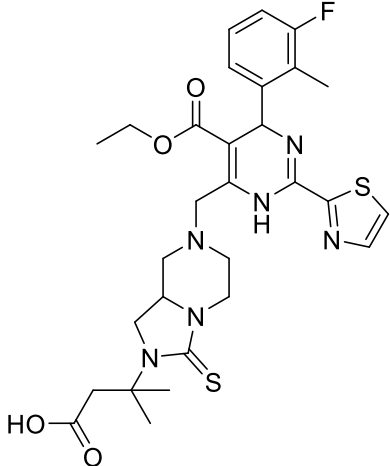
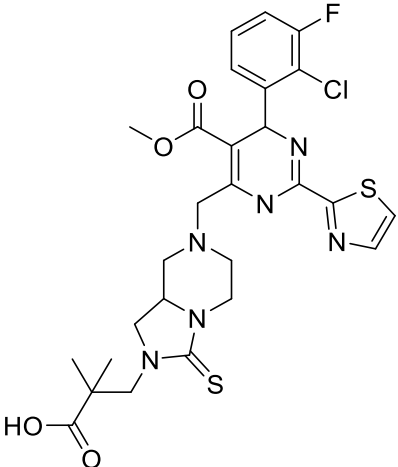
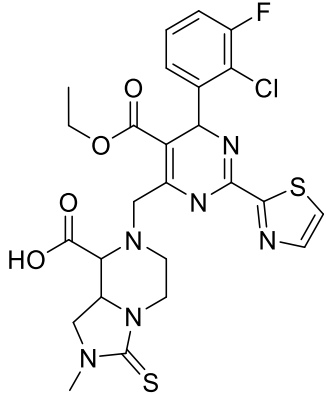
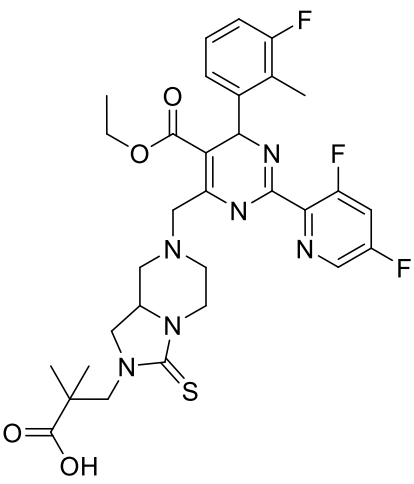
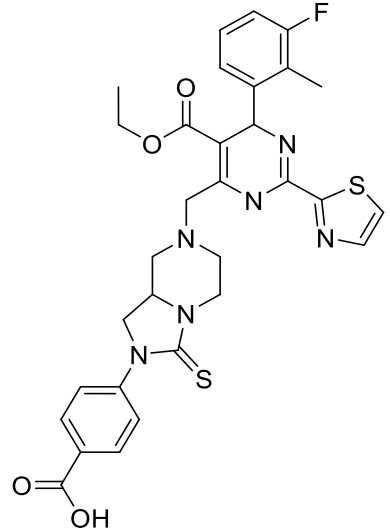
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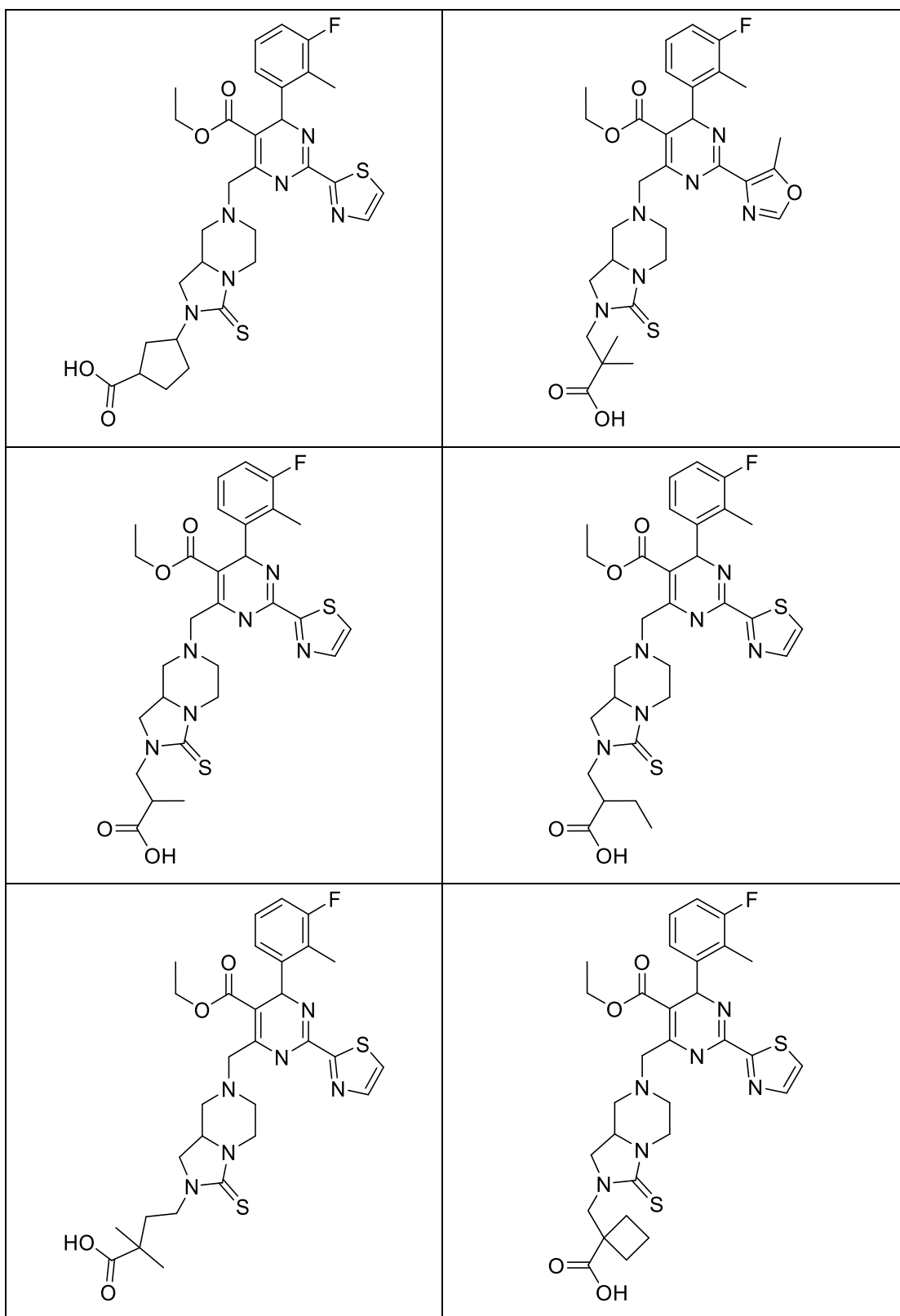
8. The compounds of any one of the preceding claims, wherein Z is CH₂.
9. The compound of any one of the preceding claims, wherein R⁹ is -C₁₋₆alkyl-CO₂H, -(CH₂)_p-C(R¹¹R¹²)-R¹⁰ or -(CH₂)_p-Q-R¹⁰.
10. The compound of any one preceding claims, wherein Q is phenyl.
11. The compound of any one of claims 1 to 9, wherein Q is a C₃₋₆cycloalkyl, or R¹¹ and R¹² together with carbon atom to which they are attached form a C₃₋₆cycloalkyl.
12. The compound of any one of claims 1 to 9, wherein Q is a 3- to 6-saturated membered ring containing an oxygen, or R¹¹ and R¹² together with carbon atom to which they are attached form a 3- to 6-saturated membered ring containing an oxygen.
13. The compound according to claim 1, selected from the group consisting of the compounds having the following formulae:

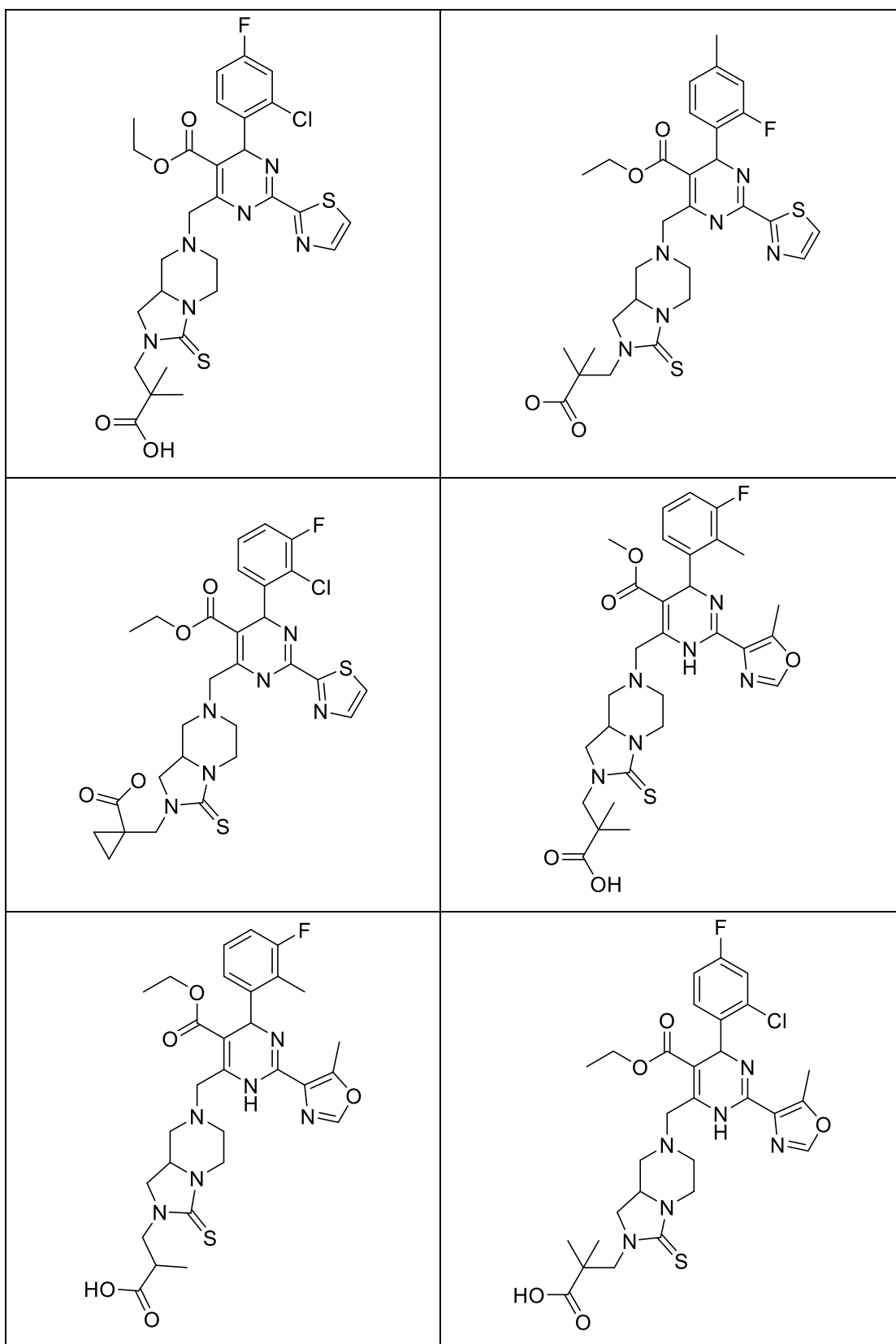


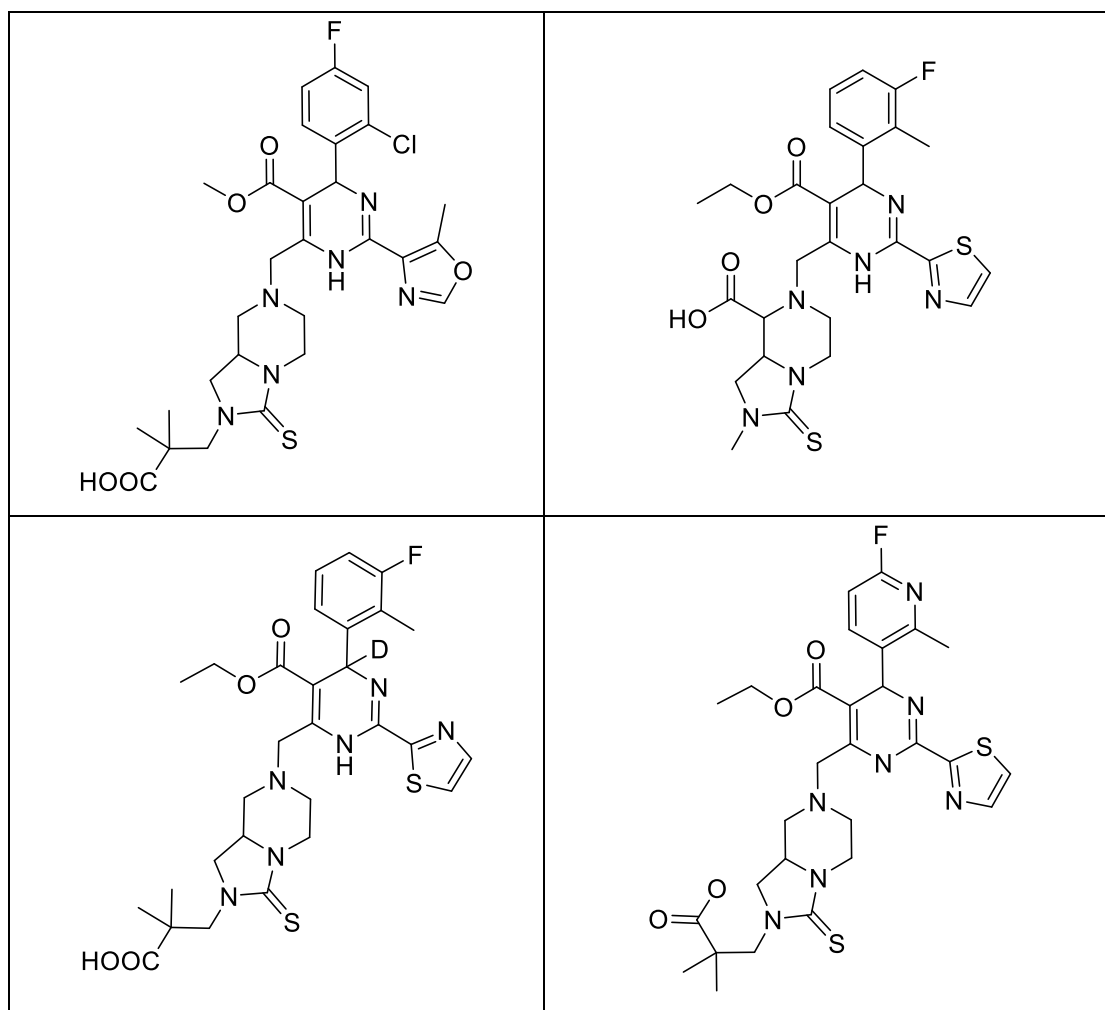










14. A pharmaceutical composition, which comprises the compound of any one of claims 1-13 and which further comprises at least one pharmaceutically acceptable carrier.

5 15. The compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 15, for use as a medicament.

10 16. The compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, for use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof.

17. The compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, for use in the prevention or treatment of chronic Hepatitis B.

18. A product comprising a first compound and a second compound as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof, wherein said first compound is different from said second compound, wherein said first compound is the compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, and wherein said second compound is another HBV inhibitor which is selected from the group consisting of HBV combination drugs, HBV DNA polymerase inhibitors, immunomodulators, toll-like (TLR) receptor modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HbsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ipi4) 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, farnesoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, phosphatidylinositol 3-kinase (P13K) inhibitors, indoleamine 2,3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and anti-HBV drugs.

19. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, in the manufacture of a medicament for prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof.

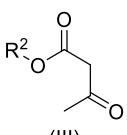
20. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, in the manufacture of a medicament for prevention or treatment of chronic Hepatitis B.

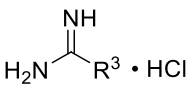
21. Use of a product comprising a first compound and a second compound in the manufacture of a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in

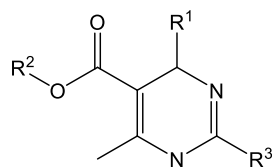
mammal in need thereof, wherein said first compound is different from said second compound, wherein said first compound is the compound or pharmaceutically acceptable salt of any one of claims 1-13 or the pharmaceutical composition of claim 14, and wherein said second compound is another HBV inhibitor which is selected from the group consisting of HBV combination drugs, HBV DNA polymerase inhibitors, immunomodulators, toll-like (TLR) receptor modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HbsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ip4) 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, farnsoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, phosphatidylinositol 3-kinase (P13K) inhibitors, indoleamine 2,3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and anti-HBV drugs.

22. A process for the preparation of a compound according to claims 1 to 12, comprising the steps of:

a. The condensation of aldehyde of Formula (II), wherein Formula (II) is  (II) ,

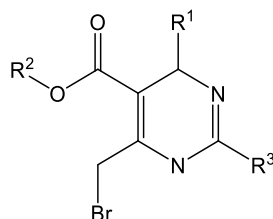
acetoacetate of Formula (III), wherein Formula (III) is  (III) , and amidine

of Formula (IV), wherein Formula (IV) is  • HCl (IV) , in the presence of a base, the base being preferably NaOAc, to form a compound according to



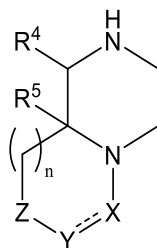
Formula (I-1): (I-1) ;

- b. The bromination of compound of Formula (I-1), the brominating agent being preferably N-Bromosuccinimide, to form a compound according to Formula



(I-2), wherein Formula (I-2) is (I-2) ;

- 5 c. The coupling of compound of Formula (I-2) with a compound of Formula (V),



wherein Formula (V) is (V) , in the presence of a base, the base being preferably triethylamine, to form a compound according to Formula (I).

23. A compound, selected from the group consisting of the compounds having the following formulae, including any salts thereof:

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