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(54) **Title**: COMBINATION THERAPY OF AN HBSAG INHIBITOR AND AN HBV CAPSID ASSEMBLY INHIBITOR

(57) **Abstract**: The present invention is directed to compositions and methods for treating hepatitis B virus infection. In particular, the present invention is directed to a combination therapy comprising administration of an HBs Ag inhibitor and an HBV capsid assembly inhibitor for use in the treatment or prophylaxis of chronic hepatitis B infected patients.

Combination therapy of an HBsAg inhibitor and an HBV capsid assembly inhibitor

The present invention is directed to compositions and methods for treating hepatitis B virus infection. In particular, the present invention is directed to a combination therapy comprising administration of an HBsAg inhibitor and an HBV capsid assembly inhibitor for use in the treatment or prophylaxis of chronic hepatitis B patient.

FIELD OF THE INVENTION

Chronic infection of Hepatitis B virus (HBV) is a serious public health problem worldwide, with more than 240 million people chronically infected worldwide. HBV belongs to the Hepadnaviridae family of viruses. Following entry into hepatocyte, its viral genome is delivered into nucleus where a covalently closed circular DNA (cccDNA) is formed through DNA repair of partially double-stranded viral genomecccDNA serves as the template for transcription of viral RNAs. Viral pre-genomic RNA interacts with other two viral components, capsid protein and polymerase to form capsid particles where viral DNA replication occurs. HBV has an icosahedral core comprising of 240 copies of the capsid (or core) protein. The predominant biological function of capsid protein is to act as a structural protein to encapsidate pre-genomic RNA and form immature capsid particles in the cytoplasm. This step is prerequisite for viral DNA replication. When a near full-length relaxed circular DNA is formed through reverse-transcription of viral pregenomic RNA, an immature capsid becomes a mature capsid. Most copies of the encapsidated genome efficiently associate with cellular lipids and viral envelope proteins (S, M, and L) for virion assembly and secretion. However, non-infectious particles are also produced that greatly outnumber the infectious virions. These empty, enveloped particles are referred to as subviral particles (SVPs). The S, M, and L envelope proteins are expressed from a single ORF (open reading frame) that contains three different start codons. All three proteins share a 226aa sequence, the S-domain, at their C-termini. S-domain contains the HBsAg epitope (Lambert, C. & R. Prange. *Virol J*, 2007, 4, 45).

Viral proteins expressed from the HBV genome include HBsAg, HBV polymerase, HBV X protein and core protein, and are involved in the multiple steps of the viral life cycle. Many observations showed that several HBV viral proteins could counteract the initial host cellular

response by interfering with the viral recognition signaling system. Among these, the excessive secretion of HBV empty subviral particles may participate to the maintenance of the immunological tolerant state observed in chronically infected patients (CHB). HBsAg, as well as other HBV antigens, may also play a role in suppressing host innate immune responses. The persistent exposure to HBsAg and other viral antigens can lead to HBV-specific T-cell deletion or to progressive functional impairment (Kondo *et al. Journal of Immunology* 1993, 150, 4659–4671; Kondo *et al. Journal of Medical Virology* 2004, 74, 425–433; Fisicaro *et al. Gastroenterology*, 2010, 138, 682-93;). Moreover HBsAg has been reported to suppress the function of immune cells such as monocytes, dendritic cells (DCs) and natural killer (NK) cells by direct interaction (Op den Brouw *et al. Immunology*, 2009b, 126, 280-9; Woltman *et al. PLoS One*, 2011, 6, e15324; Shi *et al. J Viral Hepat.* 2012, 19, e26-33; Kondo *et al. ISRN Gasteroenterology*, 2013, Article ID 935295). Therefore, targeting HBsAg together with HBV DNA levels in CHB patients may significantly improve CHB patient immune reactivation and remission (Wieland, S. F. & F. V. Chisari. *J Virol*, (2005), 79, 9369-80; Kumar et al. *J Virol*, (2011), 85, 987-95; Woltman et al. *PLoS One*, (2011), 6, e15324; Op den Brouw et al. *Immunology*, (2009b), 126, 280-9).

It has been well studied that HBV capsid protein plays essential roles in HBV replication. Heteroaryldihydropyrimidines or HAP, including compounds named Bay 41-4109, Bay 38-7690 and Bay 39-5493, were discovered in a tissue culture-based screening (Deres K. *et al. Science* **2003**, 893). These HAP analogs act as synthetic allosteric activators and are able to induce aberrant capsid formation that leads to degradation of the core protein. HAP analogs also reorganized core protein from preassembled capsids into noncapsid polymers, presumably by interaction of HAP with dimers freed during capsid 'breathing', the transitory breaking of individual intersubunit bonds. Bay 41-4109 was administered to HBV infected transgenic mouse or humanized mouse models and demonstrated *in vivo* efficacy with HBV DNA reduction (Deres K. *et al. Science* **2003**, 893; Brezillon N. *et al. PLoS ONE* **2011**, e25096). It was also shown that bis-ANS, a small molecule that acts as a molecular 'wedge' and interferes with normal capsid-protein geometry and capsid formation (Zlotnick A. *et al. J. Virol.* **2002**, 4848-4854).

HBsAg is a biomarker for prognosis and treatment response in CHB. Now, the standard of clinic cure of HBV infection is the loss and/or seroconversion of HBsAg. Even though PEG-IFN-α are available to HBV patients, the majority (around or more than 90%) of treated patients fail to achieve this goal. The Hepatitis B virus (HBV) infection remains a major health problem

worldwide which concerns an estimated 240 million chronic carriers who have a higher risk of liver cirrhosis and hepatocellular carcinoma. Hence, there is certainly an unmet medical need for treatments with improved success rate of inducing HBsAg loss, and/or HBeAg loss, and/or HBV DNA reduction, and/or HBV clearance and/or seroconversion, and/or normalization of ALT, and/or promoting the production of anti-HBs to address the Hepatitis B virus (HBV) infections.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier.

In one embodiment, the "HBsAg inhibitor" is a compound of formula (I) or (II), or any one of the compounds disclosed in patent application WO 2015113990, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof. Particularly the "HBsAg inhibitor" herein is (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In one embodiment, the "HBV capsid assembly inhibitor" herein is a compound of formula (III), (IV) or (V), or any one of the compounds disclosed in patent WO2014/037480, WO 2014/184328 and WO2015/132276; particularly the "HBV capsid assembly inhibitor" herein is (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid, (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester, (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid, 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid, 3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid, 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid, 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid, (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid, (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid, 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid, 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Isobologram of FIC for the pair-wise checkerboard combination of **Compound 1A** and **Compound 7** (at the 50% effect level). The diagonal lane connecting points (0 , 1) and (1 , 0) represents additivity (CI =1). Data points below this lane show synergism, data points above show antagonism. Shown are mean values from 3 independent experiments.

Figure 2: Isobologram of FIC for the pair-wise checkerboard combination of **Compound 1A** and **Compound 10** (at the 50% effect level). The diagonal lane connecting points (0 , 1) and (1 , 0) represents additivity (CI =1). Data points below this lane show synergism, data points above show antagonism. Shown are mean values from 3 independent experiments.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

As used herein, the term "C_{1-6}alkyl" refers to a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. In particular embodiments, C_{1-6}alkyl has 1 to 6 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of C_{1-6}alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl or tert-butyl.

As used herein, the term "halo" or "halogen" are used interchangeably herein and refer to fluoro, chloro, bromo, or iodo. Halogen is particularly fluorine, chlorine or bromine.

The term "haloC_{1-6}alkyl" refers to a C_{1-6}alkyl group wherein at least one of the hydrogen atoms of the C_{1-6}alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC_{1-6}alkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, trifluoroethyl, fluoromethyl, difluoromethyl, difluoroethyl or trifluoromethyl.

As used herein, the term "C_{1-6}alkoxy" refers to a group of C_{1-6}alkyl-O-, wherein the "C_{1-6}alkyl" is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy and the like. Particular "C_{1-6}alkoxy" groups are methoxy and ethoxy and more particularly methoxy.

As used herein, the term "C_{3-7}cycloalkyl" refers to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular "C_{3-7}cycloalkyl" groups are cyclopropyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_{2-6}alkenyl" refers to an unsaturated, linear or branched chain alkenyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example vinyl, propenyl, allyl, butenyl and the like. Particular "C_{2-6}alkenyl" group is allyl.

As used herein, the term "C_{2-6}alkynyl" refers to an unsaturated, linear or branched chain alkynyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example ethynyl, 1-propynyl, propargyl, butynyl and the like. Particular "C_{2-6}alkynyl" groups are ethynyl, 1-propynyl and propargyl.

As used herein, the term "C_xH_{2x}" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

As used herein, the term "monocyclic heteroaryl" denotes a monovalent aromatic heterocyclic mono- ring system of 5 to 8 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples of monocyclic heteroaryl moieties include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, isothiazolyl and the like.

As used herein, the term "*N*-containing monocyclic heteroaryl" refers to a monocyclic heteroaryl wherein at least one of the heteroatoms is N. Examples for *N*-containing monocyclic heteroaryl are pyrrolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, isothiazolyl and the like. Particular "*N*-containing monocyclic heteroaryl" groups are imidazolyl, pyrazolyl and triazolyl.

As used herein, the term "monocyclic heterocycloalkyl" is a monovalent saturated or partly unsaturated monocyclic ring system of 3 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic heterocycloalkyl are aziridinyl, oxiranyl, azetidinyl, oxetanyl, pyrrolidinyl, 2-oxo-pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Particular "monocyclic heterocycloalkyl" groups are morpholinyl, 2-oxo-pyrrolidinyl, pyrrolidinyl, tetrahydropyranyl.

As used herein, the term "heterocyclic" ring or "heterocyclyl" refers to a saturated or partly unsaturated monocyclic or bicyclic ring containing from 3 to 10 ring atoms which can comprise one, two or three atoms selected from nitrogen, oxygen and/or sulfur. Examples of monocyclic heterocyclyl rings containing in particular from 3 to 7 ring atoms include, but not limited to, aziridinyl, azetidinyl, oxetanyl, piperidinyl, piperazinyl, azepinyl, diazepanyl, pyrrolidinyl, morpholinyl, dihydrofuryl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl and thiomorpholinyl. Bicyclic heterocyclyl can be bicyclic fused ring or bicyclic bridged ring. Examples for bicyclic heterocyclyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, 3-thia-9-aza-bicyclo[3.3.1]nonyl, or difluoroazabicyclo[3.2.1]octyl. Monocyclic and bicyclic heterocyclyl can be further substituted by halogen, C_{1-6}alkyl, cyano, carboxy, carboxyC_{1-6}alkyl.

As used herein, the term "diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, activities and reactivities.

As used herein, the term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

As used herein, the term "pharmaceutically acceptable salts" refers to salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. As used herein, the term "prodrug" refers to a form or derivative of a compound which is metabolized in vivo, e.g., by biological fluids or enzymes by a subject after administration, into a pharmacologically active form of the compound in order to produce the desired pharmacological effect. Prodrugs are described e.g. in the Organic Chemistry of Drug Design and Drug Action by Richard B. Silverman, Academic Press, San Diego, 2004, Chapter 8 Prodrugs and Drug Delivery Systems, pp. 497-558.

The term "pharmaceutically acceptable acid addition salt" refers to those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric

acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" refers to those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, *N*-ethylpiperidine, and polyamine resins.

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

As used herein, "HBV DNA" refers to DNA material of HBV.

As used herein, "HBsAg" refers to hepatitis B surface antigen.

As used herein, "HBeAg" refers to hepatitis B e antigen.

As used herein, "HBsAg inhibitor" refers to a compound that inhibits expression of the hepatitis B virus surface antigen. Unless otherwise indicated, an HBsAg inhibitor can include the compound in any pharmaceutically acceptable form, including any isomer (e.g., diastereomer or enantiomer), salt, solvate, polymorph, and the like.

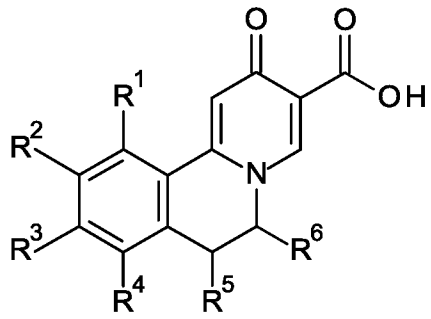
As used herein, "HBV capsid assembly inhibitor" refers to a compound that inhibits and/or disrupt and/or accelerates and/or hinders and/or delays and or reduces and/or modifies normal HBV capsid assembly (e.g., during maturation) and/or normal capsid disassembly (e.g., during infectivity) and/or perturbs capsid stability, thereby inducing aberrant capsid morphology and function.

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

Compounds of the general formula (I), (II), (III), (IV) and (V) which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

The present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier.

In one embodiment of the present invention, the "HBsAg inhibitor" is a compound of formula (I),



(I)

wherein

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkylamino or C_{1-6}alkoxy;

R^2 is hydrogen; halogen; C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C_{1-6}alkoxy, which is unsubstituted or once, twice or three times substituted by fluoro; cyano; C_{3-7}cycloalkyl; hydroxy or phenyl-C_xH_{2x}-O-;

R^3 is hydrogen;

halogen;

C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro;

cyano;

pyrrolidinyl;

amino;

phenyl-C_xH_{2x}-*N*(C_{1-6}alkyl)-;

C_{1-6}alkoxycarbonylpiperazinyl;

or R^7-O- , wherein R^7 is hydrogen; C_{1-6}alkyl, which is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy and C_{2-6}alkenyl; C_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkyl; aminoC_{1-8}alkyl; C_{1-6}alkylcarbonylaminoC_{1-8}alkyl; C_{1-6}alkylsulfonylaminoC_{1-8}alkyl; C_{1-6}alkylsulfanylC_{1-6}alkyl; C_{1-6}alkylsulfonylC_{1-6}alkyl; cyanoC_{1-6}alkyl; C_{3-7}cycloalkylC_{1-6}alkyl; cyanoC_{3-7}cycloalkylC_{1-6}alkyl; phenylC_{1-6}alkyl; pyrrolidinylcarbonylC_{1-6}alkyl; C_{2-6}alkynyl; hydroxyC_{1-6}alkylC_{2-6}alkynyl; aminoC_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkoxyC_{1-6}alkyl; diC_{1-6}alkylaminoC_{1-6}alkoxyC_{1-6}alkyl; carboxyC_{1-6}alkyl; or C_{1-6}alkoxycarbonylaminoC_{1-8}alkyl; heteroarylC_{1-6}alkyl, wherein heteroaryl is *N*-containing monocyclic heteroaryl; or heterocycloalkylC_{1-6}alkyl, wherein heterocycloalkyl is monocyclic heterocycloalkyl;

R^4 is hydrogen, halogen, C_{1-6}alkyl, cyano or C_{1-6}alkoxy;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is hydrogen; C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C_{3-7}cycloalkyl, which is unsubstituted or once, twice or three times substituted by fluoro or C_{1-6}alkyl; or phenyl-C_xH_{2x}-;

x is 1-6;

or pharmaceutically acceptable salts, or enantiomers thereof.

Compounds of formula (I) and Compounds 1A, 1B, 2A, 2B, 3A and 3B can be obtained according to the synthetic procedures disclosed in WO 2015/113990.

Particularly, the "HBsAg inhibitor" of the present invention relates to

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

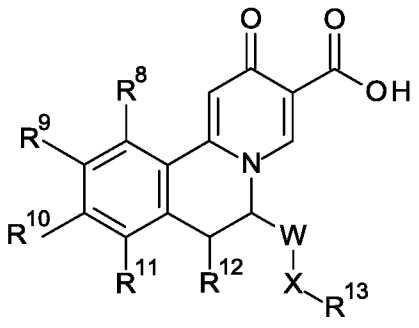
(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or any other compound disclosed in WO 2015/113990;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another embodiment of the present invention, the "HBsAg inhibitor" is a compound of formula (II):



(II)

wherein

R^8, R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, C_{1-6}alkyl, diC_{1-6}alkylamino, cyano, *N*-containing monocyclic heterocycloalkyl and OR^{14}, wherein R^{14} is hydrogen; C_{1-6}alkyl; or C_{1-6}alkyl which is substituted once or more times by fluoro, C_{3-7}cycloalkyl, phenyl, hydroxyl, amino, C_{1-6}alkoxy, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfonyl, diC_{1-6}alkylamino, C_{1-6}alkoxycarbonylamino, monocyclic heterocycloalkyl, pyrazoyl or imidazolyl;

R^{12} is hydrogen or C_{1-6}alky;

R^{13} is hydrogen, C_{1-6}alkyl, phenyl-C_xH_{2x}-, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, benzoyl or monocyclic heterocycloalkyl, wherein

x is 1-6;

W is a bond, $C_yH_{2y}C(R^{15})(R^{16})C_zH_{2z}$ or $C_yH_{2y}CH(R^{15})CH(R^{16})C_zH_{2z}$, wherein R^{15} and R^{16} are independently selected from hydrogen, fluoro, hydroxy and C_{1-6}alkyl,

y is 0-6;

z is 0-6;

X is a bond; O; S; $S(O)_2$; or NR^{17}, wherein R^{17} is hydrogen, C_{1-6}alkyl;

or R^{13} and R^{17}, together with the nitrogen to which they are attached, form monocyclic heterocycloalkyl;

or pharmaceutically acceptable salts, or enantiomers thereof.

Particularly, the "HBsAg inhibitor" of the present invention relates to (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

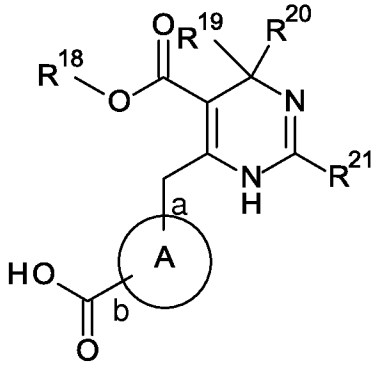
(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Unless otherwise indicated, an HBsAg inhibitor can include any one of the compounds of formula (I) and (II), in any pharmaceutically acceptable form, including any isomer (e.g., diastereomer or enantiomer), salt, solvate, polymorph, and the like.

In one embodiment of the present invention, the HBV capsid assembly inhibitor is a compound of formula (III):



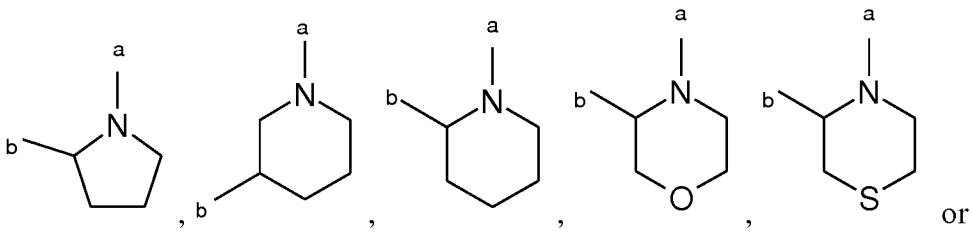
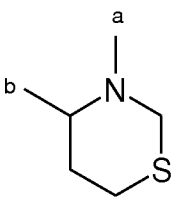
(III),

wherein

R^{18} is C_{1-6}alkyl or trifluoromethyl-C_sH_{2s}-, wherein s is 1, 2, 3, 4, 5 or 6;

One of R^{19} and R^{20} is phenyl, which is once or twice or three times substituted by C_{1-6}alkyl, cyano or halogen; and the other one is hydrogen or deuterium;

R^{21} is phenyl, thiazolyl, oxazolyl, imidazolyl, thienyl or pyridinyl, which is unsubstituted or substituted by C_{1-6}alkyl, C_{1-6}alkylsulfanyl, halogen or cycloalkyl, wherein C_{1-6}alkyl can be further optionally substituted with halogen;

A is  or , which is unsubstituted or substituted by groups selected from C_{1-6}alkyl, deuterium and halogen;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

More particularly the HBV capsid assembly inhibitor of the present invention relates to

(*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-Carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

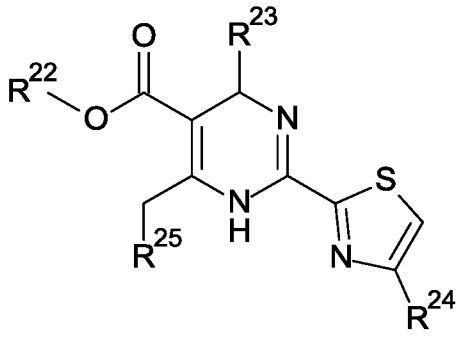
(2*R*,3*S*)-4-[(R)-6-(2-Chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

or any other compound disclosed in patent WO2014/037480;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Compounds of formula (III) and Compounds 7, 8 and 9 can be obtained according to the synthetic procedures disclosed in WO2014/037480.

In another embodiment of the present invention, the HBV capsid assembly inhibitor is a compound of formula (IV):



(IV)

wherein

R^{22} is C_{1-6}alkyl;

R^{23} is phenyl, which is once or twice or three times substituted by halogen or C_{1-6}alkyl;

R^{24} is hydrogen or C_{1-6}alkyl;

R^{25} is bicyclic bridged heterocyclyl;

or pharmaceutically acceptable salt, or tautomerism isomer, or enantiomer, or diastereomer thereof.

More particularly the HBV capsid assembly inhibitor of the present invention relates to

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

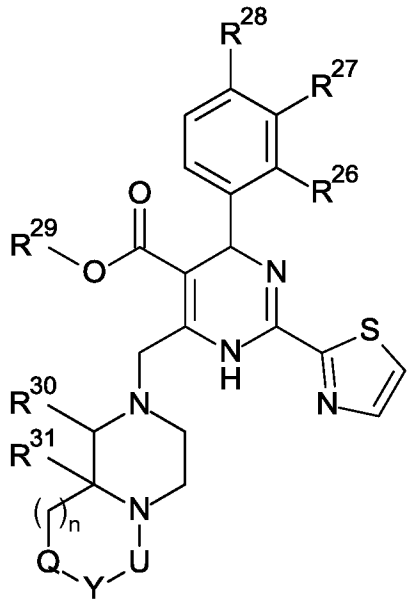
2-[(1S,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or any other compound disclosed in patent WO 2014/184328;

or pharmaceutically acceptable salt, or tautomerism isomer, or enantiomer, or diastereomer thereof.

Compounds of formula (IV) and Compounds 16 and 17 can be obtained according to the synthetic procedures disclosed in WO 2014/184328.

In another embodiment of the present invention, the HBV capsid assembly inhibitor is a compound of formula (V):



(V)

wherein

R^{26} is hydrogen, halogen or C_{1-6}alkyl;

R^{27} is hydrogen or halogen;

R^{28} is hydrogen or halogen;

R^{29} is C_{1-6}alkyl;

R^{30} is hydrogen, hydroxyC_{1-6}alkyl, aminocarbonyl, C_{1-6}alkoxycarbonyl or carboxy;

R^{31} is hydrogen, C_{1-6}alkoxycarbonyl or carboxy-C_mH_{2m}-;

U is carbonyl or sulfonyl;

Y is -CH_2-, -O- or -N(R^{32})-,

wherein R^{32} is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl-C_mH_{2m}-, C_{1-6}alkoxycarbonyl-C_mH_{2m}-,-C_tH_{2t}-COOH, -haloC_{1-6}alkyl-COOH, -(C_{1-6}alkoxy)C_{1-6}alkyl-COOH, -C_{1-6}alkyl-O-C_{1-6}alkyl-COOH, -C_{3-7}cycloalkyl-C_mH_{2m}-COOH, -C_mH_{2m}-C_{3-}

$_{7}$cycloalkyl-COOH, hydroxy-C_tH_{2t}-, carboxyspiro[3.3]heptyl or carboxyphenyl-C_mH_{2m}-, carboxypyridinyl-C_mH_{2m}-;

Q is -CH_2-, -$C(C_{1-6}alkyl)_2$-, -O- or carbonyl;

n is 0 or 1;

m is 0-7;

t is 1-7;

or pharmaceutically acceptable salt, or enantiomer or diastereomer thereof.

More particularly the HBV capsid assembly inhibitor of the present invention relates to 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

or any other compound disclosed in patent WO2015/132276;

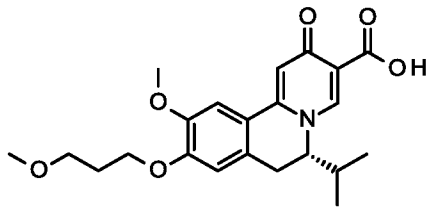
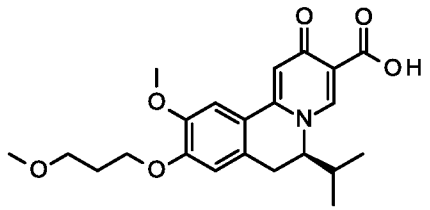
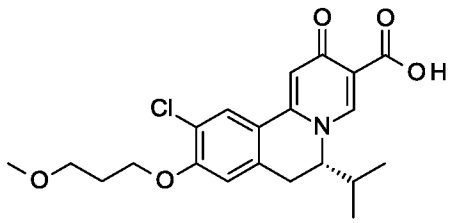
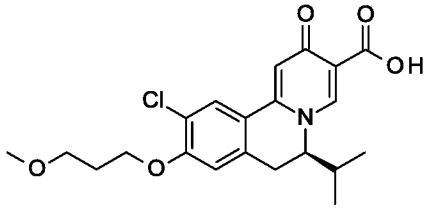
or pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

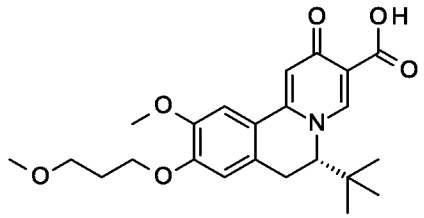
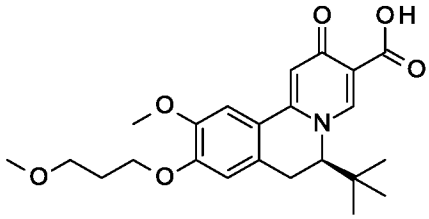
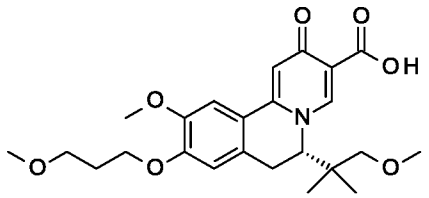
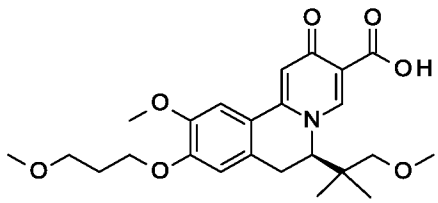
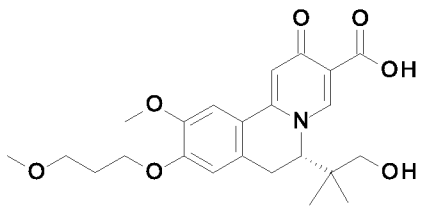
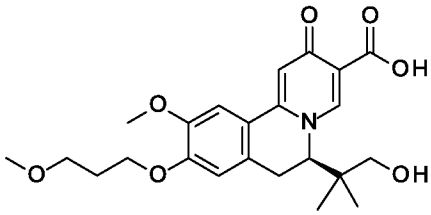
Compounds of formula (V) and Compounds 10 to 15 can be obtained according to the synthetic procedures disclosed in WO2015/132276.

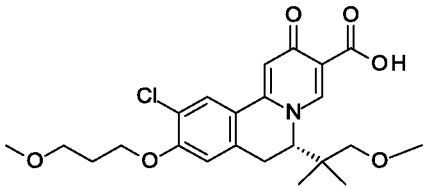
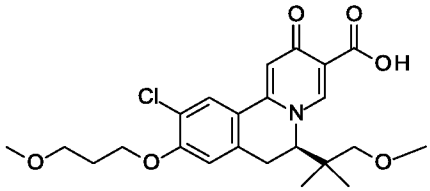
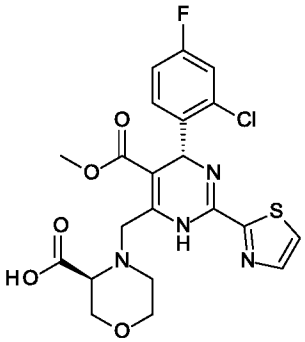
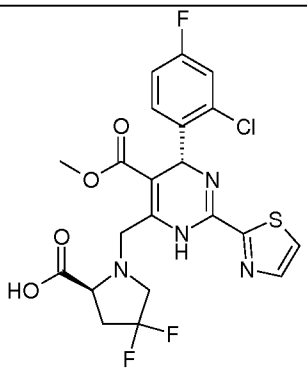
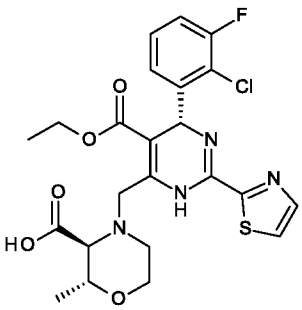
In another embodiment of the present invention, the HBV capsid assembly inhibitor is anyone of the compounds disclosed in WO2008154817, WO2008154819, WO2014029193, WO2015074546, CN103664897 and CN103664925.

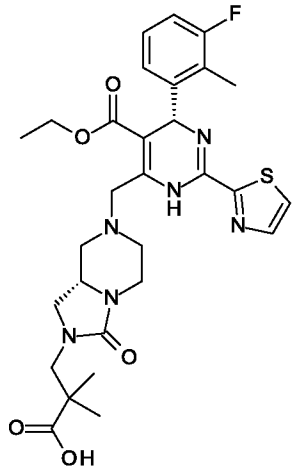
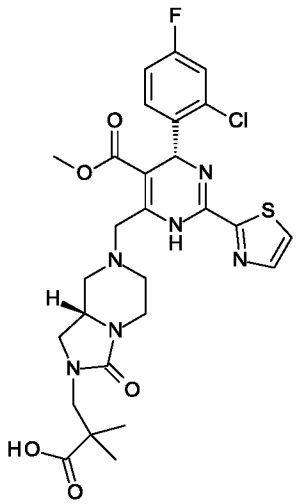
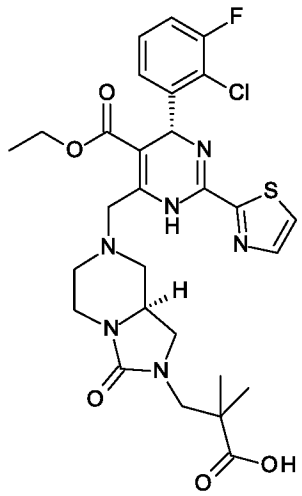
In one embodiment of the present invention, the pharmaceutical composition comprises an HBsAg inhibitor and HBV capsid assembly inhibitor, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor are independently selected from Table 1. Compounds 1A, 1B, 2A, 2B, 3A and 3B were first disclosed in WO 2015/113990; Compounds 7, 8 and 9 were first disclosed in WO2014/037480; Compounds 16 and 17 were disclosed in WO2014/184328; Compounds 10-15 were disclosed in WO2015/132276.

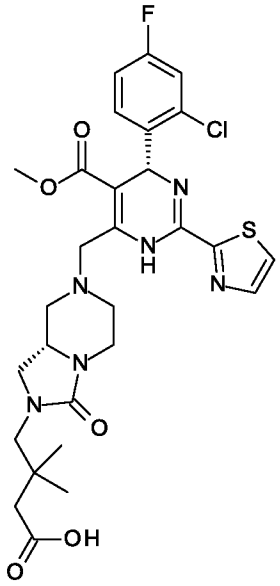
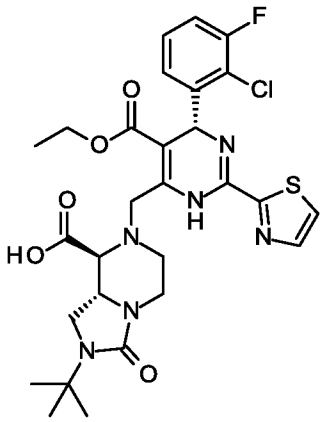
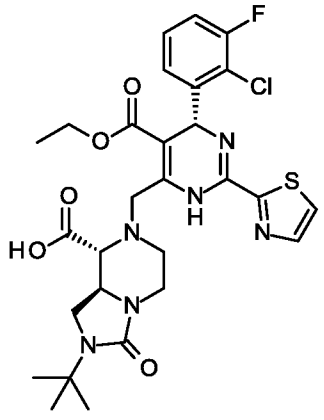
Table 1. List of HBsAg inhibitor and HBV capsid assembly inhibitor

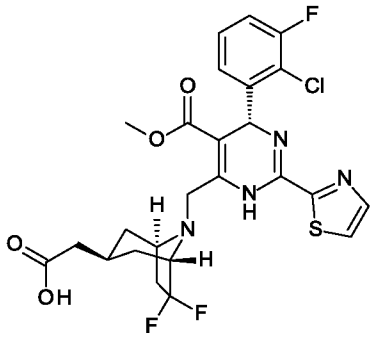
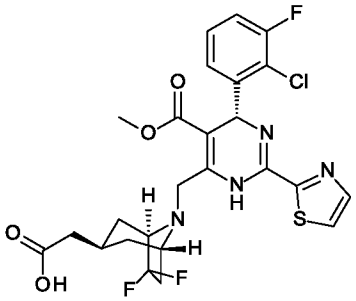
Compound Number	Class	Compound Name	Structure
1A	HBsAg inhibitor	(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
1B	HBsAg inhibitor	(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
2A	HBsAg inhibitor	(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
2B	HBsAg inhibitor	(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	

Compound Number	Class	Compound Name	Structure
3A	HBsAg inhibitor	(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
3B	HBsAg inhibitor	(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
4A	HBsAg inhibitor	(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
4B	HBsAg inhibitor	(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
5A	HBsAg inhibitor	(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
5B	HBsAg inhibitor	(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	

Compound Number	Class	Compound Name	Structure
6A	HBsAg inhibitor	(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
6B	HBsAg inhibitor	(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid	
7	HBV capsid assembly inhibitor	(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid	
8	HBV capsid assembly inhibitor	(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester	
9	HBV capsid assembly inhibitor	(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid	

Compound Number	Class	Compound Name	Structure
10	HBV capsid assembly inhibitor	3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid	
11	HBV capsid assembly inhibitor	3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid	
12	HBV capsid assembly inhibitor	3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid	

Compound Number	Class	Compound Name	Structure
13	HBV capsid assembly inhibitor	4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid	
14	HBV capsid assembly inhibitor	(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid	
15	HBV capsid assembly inhibitor	(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid	

Compound Number	Class	Compound Name	Structure
16	HBV capsid assembly inhibitor	2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid	
17	HBV capsid assembly inhibitor	2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid	

More particularly, the present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor which is selected from any one of the following combinations:

Compound 1A and Compound 7; Compound 1A and Compound 8;
Compound 1A and Compound 9; Compound 1A and Compound 10;
Compound 1A and Compound 11; Compound 1A and Compound 12;
Compound 1A and Compound 13; Compound 1A and Compound 14;
Compound 1A and Compound 15; Compound 1A and Compound 16;
Compound 1A and Compound 17; Compound 1B and Compound 7;
Compound 1B and Compound 8; Compound 1B and Compound 9;
Compound 1B and Compound 10; Compound 1B and Compound 11;
Compound 1B and Compound 12; Compound 1B and Compound 13;
Compound 1B and Compound 14; Compound 1B and Compound 15;
Compound 1B and Compound 16; Compound 1B and Compound 17;
Compound 2A and Compound 7; Compound 2A and Compound 8;
Compound 2A and Compound 9; Compound 2A and Compound 10;

Compound 2A and Compound 11; Compound 2A and Compound 12;
Compound 2A and Compound 13; Compound 2A and Compound 14;
Compound 2A and Compound 15; Compound 2A and Compound 16;
Compound 2A and Compound 17; Compound 2B and Compound 7;
Compound 2B and Compound 8; Compound 2B and Compound 9;
Compound 2B and Compound 10; Compound 2B and Compound 11;
Compound 2B and Compound 12; Compound 2B and Compound 13;
Compound 2B and Compound 14; Compound 2B and Compound 15;
Compound 2B and Compound 16; Compound 2B and Compound 17;
Compound 3A and Compound 7; Compound 3A and Compound 8;
Compound 3A and Compound 9; Compound 3A and Compound 10;
Compound 3A and Compound 11; Compound 3A and Compound 12;
Compound 3A and Compound 13; Compound 3A and Compound 14;
Compound 3A and Compound 15; Compound 3A and Compound 16;
Compound 3A and Compound 17; Compound 3B and Compound 7;
Compound 3B and Compound 8; Compound 3B and Compound 9;
Compound 3B and Compound 10; Compound 3B and Compound 11;
Compound 3B and Compound 12; Compound 3B and Compound 13;
Compound 3B and Compound 14; Compound 3B and Compound 15;
Compound 3B and Compound 16; Compound 3B and Compound 17;
Compound 4A and Compound 7; Compound 4A and Compound 8;
Compound 4A and Compound 9; Compound 4A and Compound 10;
Compound 4A and Compound 11; Compound 4A and Compound 12;
Compound 4A and Compound 13; Compound 4A and Compound 14;
Compound 4A and Compound 15; Compound 4A and Compound 16;
Compound 4A and Compound 17; Compound 4B and Compound 7;
Compound 4B and Compound 8; Compound 4B and Compound 9;
Compound 4B and Compound 10; Compound 4B and Compound 11;
Compound 4B and Compound 12; Compound 4B and Compound 13;
Compound 4B and Compound 14; Compound 4B and Compound 15;
Compound 4B and Compound 16; Compound 4B and Compound 17;
Compound 5A and Compound 7; Compound 5A and Compound 8;
Compound 5A and Compound 9; Compound 5A and Compound 10;

Compound 5A and Compound 11; Compound 5A and Compound 12;
Compound 5A and Compound 13; Compound 5A and Compound 14;
Compound 5A and Compound 15; Compound 5A and Compound 16;
Compound 5A and Compound 17; Compound 5B and Compound 7;
Compound 5B and Compound 8; Compound 5B and Compound 9;
Compound 5B and Compound 10; Compound 5B and Compound 11;
Compound 5B and Compound 12; Compound 5B and Compound 13;
Compound 5B and Compound 14; Compound 5B and Compound 15;
Compound 5B and Compound 16; Compound 5B and Compound 17;
Compound 6A and Compound 7; Compound 6A and Compound 8;
Compound 6A and Compound 9; Compound 6A and Compound 10;
Compound 6A and Compound 11; Compound 6A and Compound 12;
Compound 6A and Compound 13; Compound 6A and Compound 14;
Compound 6A and Compound 15; Compound 6A and Compound 16;
Compound 6A and Compound 17; Compound 6B and Compound 7;
Compound 6B and Compound 8; Compound 6B and Compound 9;
Compound 6B and Compound 10; Compound 6B and Compound 11;
Compound 6B and Compound 12; Compound 6B and Compound 13;
Compound 6B and Compound 14; Compound 6B and Compound 15;
Compound 6B and Compound 16; and Compound 6B and Compound 17;
in a pharmaceutically acceptable carrier.

Any one of Compounds 1A to 6A, 1B to 6B and 7- 15 of the aforementioned combinations can be replaced by its corresponding pharmaceutically acceptable salt, enantiomer or diastereomer, which is another aspect of this invention.

More particularly, the present invention relates to a pharmaceutical composition comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor which is selected from any one of the following combinations:

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-

thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-

phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-

fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-

methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(*4R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-

fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-

phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(*4R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-

5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-

phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-

fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-

phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; and

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-

1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-

phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; and

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

in a pharmaceutically acceptable carrier.

In one embodiment of the present invention, the pharmaceutical composition consists of an HBsAg inhibitor and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier. More particularly, the composition consists of:

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

in a pharmaceutically acceptable carrier.

In another embodiment of the present invention, other HBsAg inhibitors or HBV capsid assembly inhibitors can also be used in the pharmaceutical composition including small molecules or large molecules. Examples of other HBV capsid assembly inhibitors include, but not limited to, Bay 41-4109, Bay 38-7690, Bay 39-5493, GLS4, AT-61 and AT-130.

Typical dosages of an HBsAg inhibitor and/or an HBV capsid assembly inhibitor can be in various ranges, and where indicated by *in vitro* responses in an animal model, can be reduced by up to about one order of magnitude concentration or amount. Thus, the actual dosage will depend upon the judgment of the physician, the condition of the patient, and the effectiveness of the therapeutic method based on the *in vi*tro responsiveness of the appropriate animal models.

Another embodiment of the present invention relates to a method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor and an HBV capsid assembly inhibitor are used in the medicament.

A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor and an HBV capsid assembly inhibitor are co-administered in the same formulation or different formulation.

For purposes of the present invention, "co-administer" refers to any administration of an HBsAg inhibitor and an HBV capsid assembly inhibitor as the two active agents, either separately or together, where the two active agents are administered as part of an appropriate dose regimen designed to obtain the benefit of the combination therapy. Thus, the two active agents can be administered either as part of the same pharmaceutical composition or in separate pharmaceutical compositions. Also, the two active agents can be administered either at the same time, or sequentially.

The pharmaceutical composition of the HBsAg inhibitor and the HBV capsid assembly inhibitor can be administered with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozengens, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Administration of such dosage forms can be carried out in single or multiple doses. Carries include solid diluents of fillers, sterile aqueous media and various non-toxic organic solvents. Administration of such dosage forms can be carried out through, but not limited to, oral administration, parenteral administration, veterinary administration.

A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor and an HBV capsid assembly inhibitor are intended for administration to a subject by the same route or different routes.

A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor and an HBV capsid assembly inhibitor are intended for administration to a subject by parenteral or oral administration.

A further embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the administration of an HBsAg inhibitor and an HBV capsid assembly inhibitor to a subject is simultaneous or sequential. In any of the methods of the present invention, the administration of agents simultaneously can be performed by separately or sequentially administering agents at the

same time, or together as a fixed combination. Also, in any of the methods of the present invention, the administration of agents separately or sequentially can be in any order.

Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor is a compound of formula (I) or formula (II), or pharmaceutically acceptable salt, enantiomer or diastereomer thereof. Particularly, the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBV capsid assembly inhibitor is a compound of formula (III), formula (IV) or formula (V), or pharmaceutically acceptable salt, enantiomer or diastereomer thereof. Particularly, the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to the method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor and the HBV capsid assembly inhibitor used in the medicament are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

Another embodiment of the present invention relates to a kit comprising a container comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor, said kit can further comprise a sterile diluent.

A further embodiment of the present invention relates to the said kit, wherein the kit can further comprise a package insert comprising printed instructions directing the use of a combined treatment of an HBsAg inhibitor and an HBV capsid assembly inhibitor as a method for treatment or prophylaxis of hepatitis B virus infection.

Another embodiment of the present invention relates to the said kit, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to the said kit, wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to the said kit, characterized in that the HBsAg inhibitor and the HBV capsid assembly inhibitor used in the container are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an effective first amount of an HBsAg inhibitor, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and a second amount of an HBV capsid assembly inhibitor; or *vice versa*; wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an effective first amount of an HBsAg inhibitor, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and a second amount of an HBV capsid assembly inhibitor; or *vice versa*; wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the present invention relates to a method for the treatment or prophylaxis of hepatitis B virus infection, characterized in that the HBsAg inhibitor and the HBV capsid assembly inhibitor used are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

Another embodiment of the present invention relates to use of pharmaceutical composition herein mentioned above as an antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

Another embodiment of present invention relates to the use of an HBsAg inhibitor and an HBV capsid assembly inhibitor for the manufacture of pharmaceutical composition herein mentioned above as an antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.

EXAMPLES

The invention will be better understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

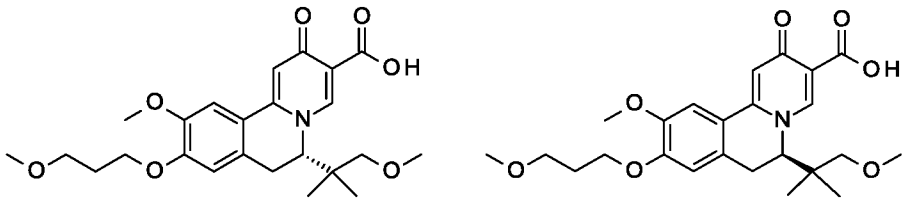
ABBREVIATIONS

3TC	Lamivudine
CI	Combination index
CTG	CellTiter-Glo®
FBS	Fetal Bovine Serum
GE	Genome equivalent
HBsAg	Hepatitis B surface antigen
μM	Micromolar
Min	Minute
nM	Nanomolar
PBS	Phosphate buffered saline
PEG	Polyethyleneglycol
qPCR	Real-time quantitative polymerase chain reaction
SD	Standard deviation
Sec	Second
UDG	Uracil DNA glycosylase

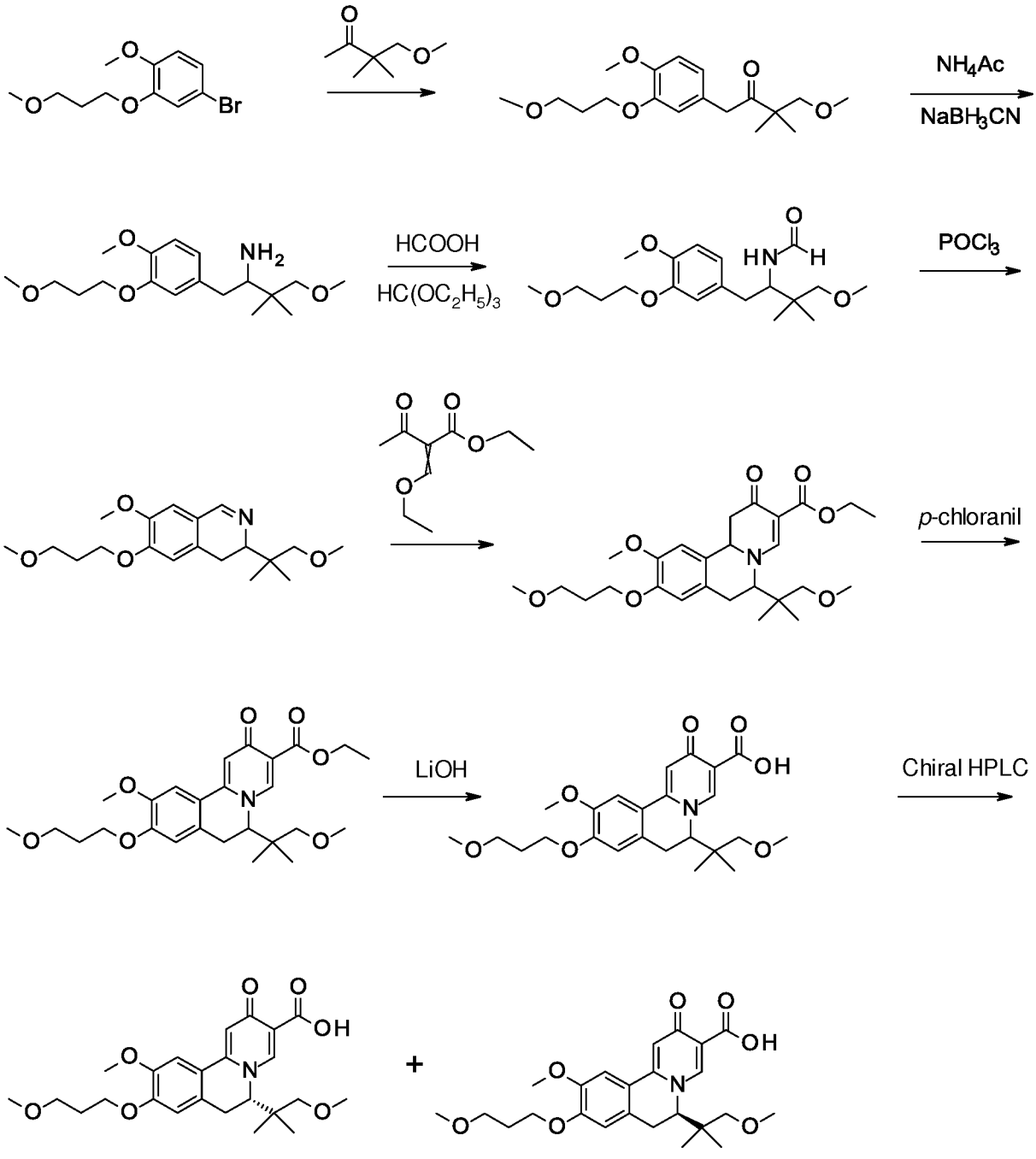
Example 1

Preparation of (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 4A) and (-)-10-methoxy-

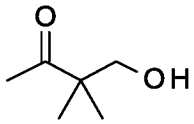
6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 4B)



Compound 4A and 4B was prepared through the following scheme:

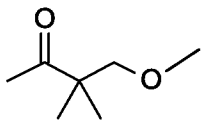


Step 1: Preparation of 4-hydroxy-3,3-dimethyl-butan-2-one



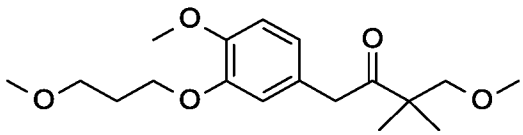
To a mixture of 3-methylbutan-2-one (400 g, 4.64 mol) in TFA (720 mL) was added paraformaldehyde (139.2 g, 4.64 mol). The resulting mixture was stirred at 80°C for 7 h. To this mixture was added $NaHCO_3$ aqueous solution (20 L) and the whole mixture was stirred at 25°C for 12 h. The reaction was conducted at 400 g scale three times in parallel. The combined reaction mixtures were extracted with DCM (7.5 L) 10 times, and the organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give 4-hydroxy-3,3-dimethyl-butan-2-one (1200 g).

Step 2: Preparation of 4-methoxy-3,3-dimethyl-butan-2-one



To a mixture of 4-hydroxy-3,3-dimethyl-butan-2-one (150 g, 1.3 mol) and dimethylsulfate (220 g, 1.75 mol) was added 20 N NaOH aqueous solution (88 mL, 1.75 mol) at 40°C. The mixture was stirred at 40°C for 16 h. The reaction was conducted at 150 g scale 8 times in parallel. The combined mixtures were quenched with water (8 L), and then extracted with methyl tertiary-butyl ether (16 L). The organic layer was washed with water (4 L) 10 times, dried over anhydrous Na_2SO_4 and concentrated to give 4-methoxy-3,3-dimethyl-butan-2-one (543 g) as a yellow oil.

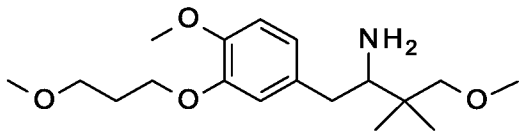
Step 3: Preparation of 4-methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one



To a solution of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (100 g, 0.37 mol) in dioxane (100 mL) was added 4-methoxy-3,3-dimethyl-butan-2-one (100 g, 0.73 mol), $Pd(OAc)_2$ (1.23 g, 5.5 mmol), XPhos (5.2 g, 11 mmol) and LiHMDS (850 mL, 1.3 M). The resulting mixture was stirred at 70 °C for 3 h under argon atmosphere. After being cooled to room temperature, the resulting suspension was poured into water and acidified to pH=3 with 2 M

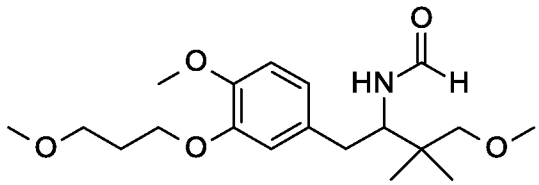
hydrochloride acid. The mixture was extracted with ethyl acetate (500 mL) 2 times. The combined organic layers were washed with water (200 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated to give crude 4-methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (120 g) as a yellow oil.

Step 4: Preparation of 4-methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine



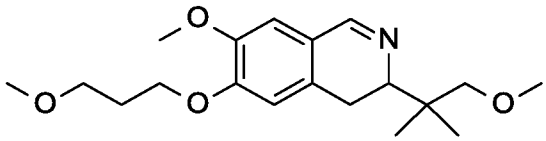
To a solution of crude 4- methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (120 g, 0.37 mol) in methanol (500 mL) was added ammonium acetate (280 g, 3.65 mol) and $NaBH_3CN$ (46 g, 0.73 mol). The resulting mixture was stirred for 12 h at 60 °C. The reaction was quenched with water, and then to the mixture was added 2.0 M NaOH aqueous solution (50 mL). The mixture was stirred for 1 h, adjusted to pH=1 with concentrated hydrochloric acid and then extracted with ethyl acetate (200 mL). The aqueous phase was adjusted to pH=12 with potassium hydroxide aqueous solution and extracted with ethyl acetate (500 mL) 2 times. The combined organic layers were washed with water (200 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give 4-methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (120 g).

Step 5: Preparation of *N*-[3-methoxy-1-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-2,2-dimethyl-propyl]formamide



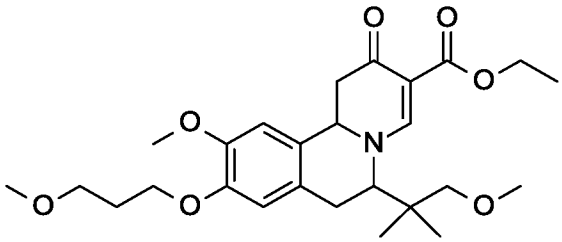
A mixture of 4-methoxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (120 g, 0.37 mol), formic acid (150 mL) and triethyl orthoformate (60 mL) in 1,4-dioxane (500 mL) was refluxed for 48 h and then concentrated. The residue was partitioned between ethyl acetate (500 mL) and water (200 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to give *N*-[3-methoxy-1-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-2,2-dimethyl-propyl]formamide (120 g).

Step 6: Preparation of 7-methoxy-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline



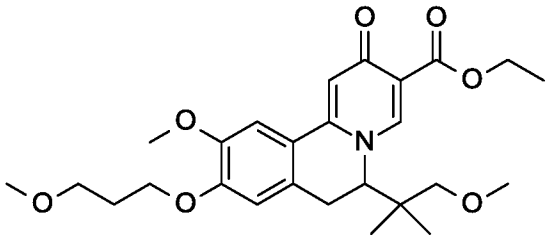
To a solution of *N*-[3-methoxy-1-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-2,2-dimethyl-propyl]formamide (120 g, 0.34 mol) in acetonitrile (500 mL) was added $POCl_3$ (64 mL, 0.68 mol) dropwise at 0-5 °C. The resulting mixture was heated at 60 °C for 1 h. After being cooled to rt, the mixture was concentrated. To the residue was added ethyl acetate (500 mL), then to the resulting mixture was added ammonia water to adjust the pH of the aqueous solution to around 11. The mixture was extracted with ethyl acetate (300 mL) 2 times. The organic layers were combined and concentrated. The residue was purified by column chromatography to 7-methoxy-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (89 g).

Step 7: Preparation of ethyl 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate



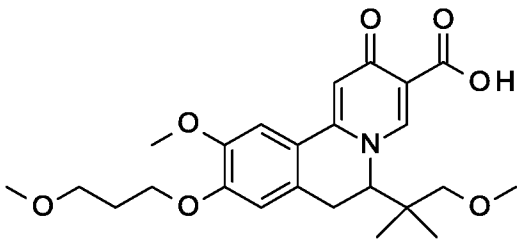
A mixture of 7-methoxy-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (87 g, 0.26 mol) and ethyl 2-(ethoxymethylene)-3-oxo-butanoate (144 g, 0.78 mol) in ethanol (500 mL) was refluxed 48 h. The mixture was concentrated to give crude ethyl 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate which was used in the next step without purification.

Step 8: Preparation of ethyl 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate



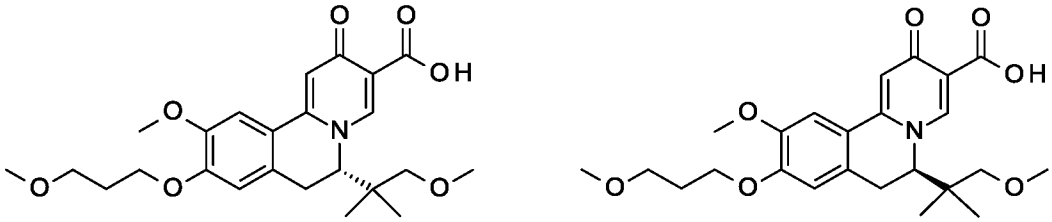
A mixture of crude ethyl 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate from step **5** and *p*-chloranil (50 g, 0.21mol) in DME (500 mL) was refluxed for 2 h. After being cooled to room temperature, the mixture was concentrated. The residue was dissolved in ethyl acetate (500 mL). And then the solution was washed with water (200 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give crude ethyl 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate which was used directly in the next step.

Step 9: Preparation of 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid



To a solution of crude ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate from step 6 in THF (200 mL) and ethanol (200 mL) was added 2.0 M LiOH aqueous solution (200 mL) at rt. The resulting mixture was stirred for 4 h, and then acidified to pH=1-2 with 2 M hydrochloric acid. The mixture was extracted with DCM (500 mL) 2 times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (50 g) as white solid.

Step 10: preparation of (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 4A) and (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 4B)



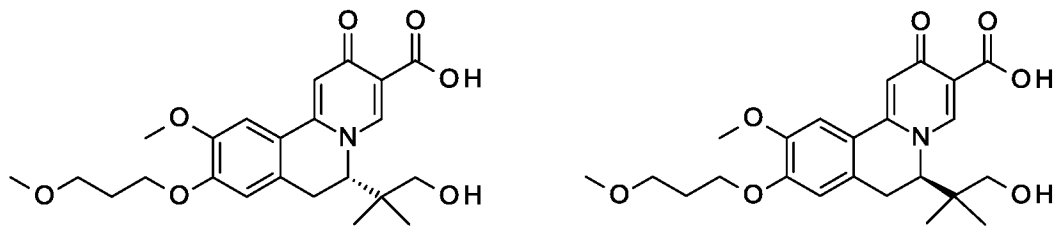
Separation of the racemic 10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (50 g) by chiral HPLC afforded (+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a] quinolizine-3-carboxylic acid (22 g, Compound 4A) and (-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (22 g, Compound 4B).

Compound 4A: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.56 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 7.08 (s, 1H), 4.64 (m, 1H), 4.01-4.19 (m, 2H), 3.87 (s, 3H), 3.48 (m, 2H), 3.26 (s, 3H), 3.18-3.24 (m, 2H), 2.80-3.01 (m, 2H), 1.99 (m, 2H), 0.87 (s, 3H), 0.46 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 446. $[\alpha]_D^{20}$ = +89.314° (0.063%, CH_3CN).

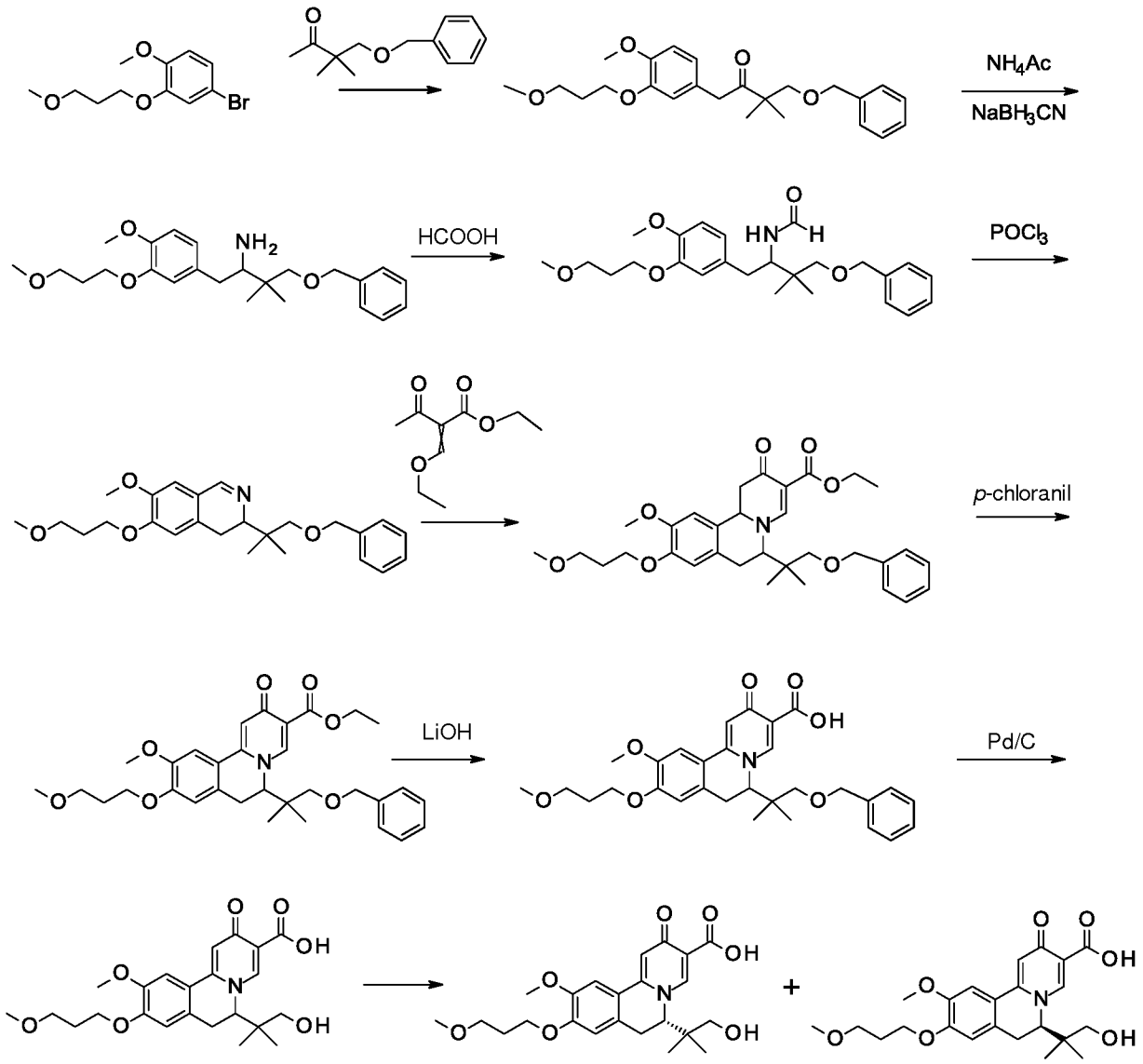
Compound 4B: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.56 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 7.08 (s, 1H), 4.64 (m, 1H), 4.01-4.19 (m, 2H), 3.87 (s, 3H), 3.48 (m, 2H), 3.26 (s, 3H), 3.18-3.24 (m, 2H), 2.80-3.01 (m, 2H), 1.99 (m, 2H), 0.87 (s, 3H), 0.46 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 446.

Example 2

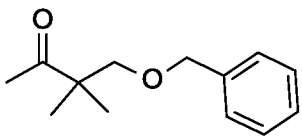
Preparation of (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 5A) and (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 5B)



Compound 5A and 5B was prepared through the following scheme:

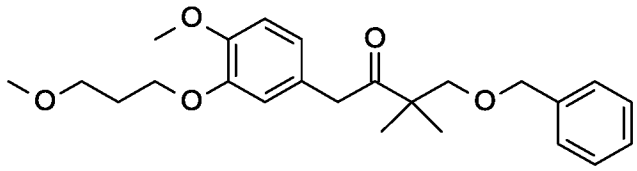


Step 1: Preparation of 4-benzyloxy-3,3-dimethyl-butan-2-one



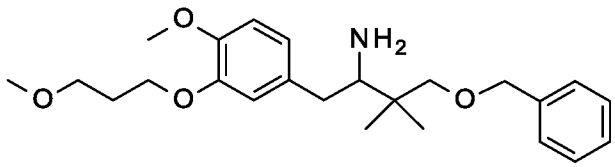
A mixture of 4-hydroxy-3,3-dimethyl-butan-2-one (16.6 g, 0.14 mol) and bromomethylbenzene (37 g, 0.28 mol) in DIPEA (28 g, 0.28 mol) was heated at 150 °C for 1 h. After being cooled to rt, the mixture was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH= 1-2 with 2 M hydrochloride acid. Then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give 4-benzyloxy-3,3-dimethyl-butan-2-one (10 g).

Step 2: Preparation of 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one



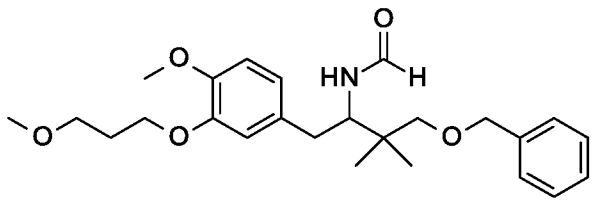
To a solution of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (3.65 g, 13.3 mmol) in dioxane (30 mL) was added 4-benzyloxy-3,3-dimethyl-butan-2-one (5.5 g, 26.6 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol), XPhos (191 mg, 0.4 mmol) and LiHMDS (30 mL, 1.3 M). The resulting mixture was stirred at 70 °C for 3 h under argon atmosphere. After being cooled to rt, the resulting suspension was poured into water and acidified to pH=3 with 2 M hydrochloride acid. The mixture was extracted with ethyl acetate (100 mL) 2 times. The combined organic layers were washed with water (100 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated to give crude 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (9 g) as a yellow oil.

Step 3: Preparation of 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine



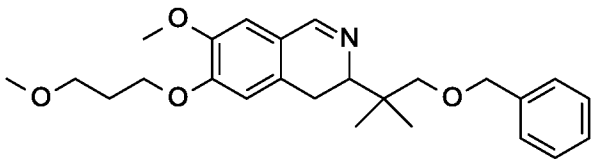
To a solution of crude 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (9 g, 13.3 mmol) in methanol (150 mL) was added ammonium acetate (15 g, 200 mmol) and $NaBH_3CN$ (1.7 g, 26.6 mmol). The resulting mixture was stirred for 12 h at 60 °C. The reaction was quenched with water, and then to the mixture was added 2.0 M NaOH aqueous solution (50 mL). The resulting mixture was stirred for 1 h, and then extracted with ethyl acetate (150 mL). The organic layer was washed with water (100 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (5 g) which was used in the next step without further purification.

Step 4: Preparation of *N*-[3-benzyloxy-1-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-2,2-dimethyl-propyl]formamide



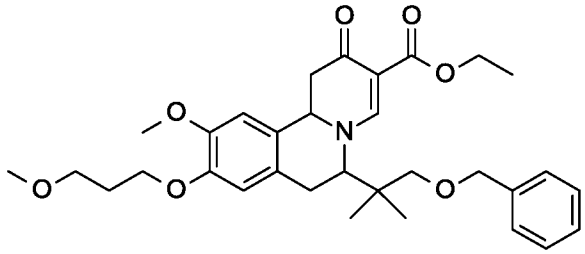
A mixture of 4-benzyloxy-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (5 g, 12.4 mmol) and formic acid (1.2 g, 25 mmol) in 1,4-dioxane (30 mL) was refluxed for 12 h. Then the mixture was concentrated under reduced pressure to give a red oil, which was then dissolved in ethyl acetate (30 mL). The solution was washed with water (30 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give *N*-[3-benzyloxy-1-[[4-methoxy-3-(3-methoxypropoxy) phenyl]methyl]-2,2-dimethyl-propyl]formamide (6 g), which was used in the next step without further purification.

Step 5: Preparation of 3-(2-benzyloxy-1,1-dimethyl-ethyl)-7-methoxy-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline



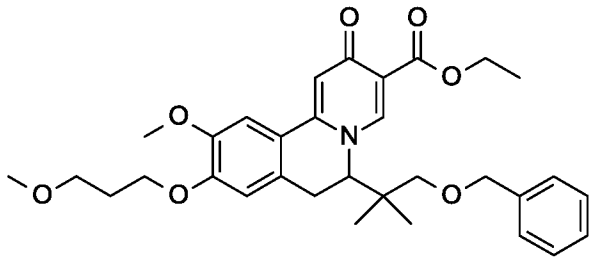
To a solution of *N*-[3-benzyloxy-1-[[4-methoxy-3-(3-methoxypropoxy) phenyl]methyl]-2,2-dimethyl-propyl]formamide (5.3 g, 12.3 mmol) in acetonitrile (50 mL) was added $POCl_3$ (2.3 mL, 24.6 mmol) dropwise at 0-5 °C. The resulting mixture was heated to 60 °C and maintained at 60 °C for 1 h. After being cooled to rt, the mixture was concentrated. To the residue was added ethyl acetate (50 mL). Then to the resulting mixture was added ammonia water to adjust the pH of the aqueous phase to around 11. The mixture was extracted with ethyl acetate (50 mL) 2 times, and the organic layers were combined and concentrated. The residue was purified by column chromatography to give 3-(2-benzyloxy-1,1-dimethyl-ethyl)-7-methoxy-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (2.7 g).

Step 6: Preparation of ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate



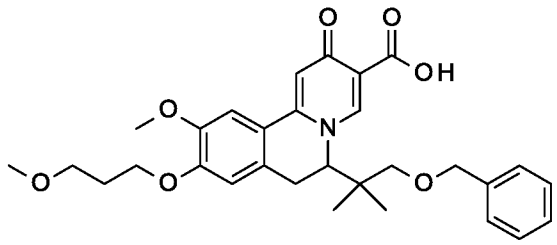
A mixture of 3-(2-benzyloxy-1,1-dimethyl-ethyl)-7-methoxy-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (2.65 g, 6.4 mmol) and ethyl 2-(ethoxymethylene)-3-oxo-butanoate (3.4 g, 19.3 mmol) in ethanol (50 mL) was refluxed overnight. Then the mixture was concentrated to give crude ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate as a dark brown oil which was used in the next step without purification.

Step 7: Preparation of ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate



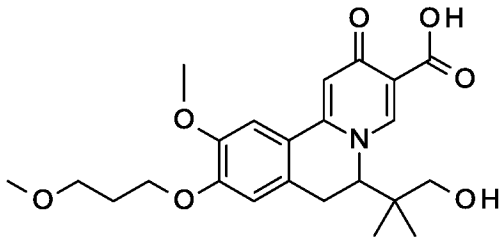
A mixture of crude ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate from step **6** and *p*-chloranil (1.6 g, 6.4 mmol) in DME (50 mL) was refluxed for 2 h. After being cooled to room temperature, the mixture was concentrated. The residue was dissolved in ethyl acetate (50 mL). The solution was washed with water (50 mL) 2 times and then washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give crude ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate which was used directly in the next step.

Step 8: Preparation of 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid



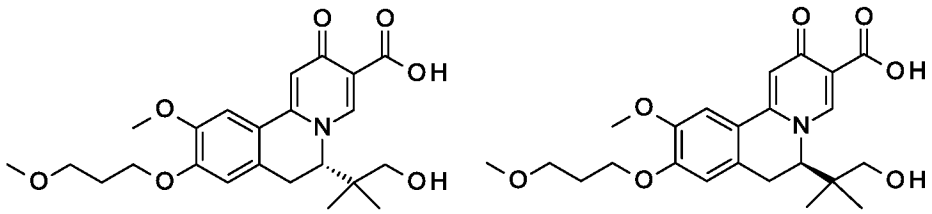
To a solution of crude ethyl 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate from step **7** in THF (10 mL) and methanol (15 mL) was added 2.0 M LiOH aqueous solution (10 mL) at rt. The resulting mixture was stirred for 4 h, and then acidified to pH=1-2 with 2 M hydrochloric acid. The mixture was extracted with DCM (30 mL) 2 times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (1.5 g) as a white solid.

Step 9: Preparation of 6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid



To a mixture of 6-(2-benzyloxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (100 mg) and Pd/C (10 mg) in ethanol (10 mL) was added Et_3SiH (1 mL). The mixture was heated at 80 °C for 3 h, and then additional Et_3SiH (1 mL) was added. After that, the mixture was heated at 80 °C overnight and then filtered. The filtrate was concentrated and the residue was purified by prep-HPLC to give 6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (50 mg) as a white solid.

Step 10: Preparation of (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 5A) and (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 5B)



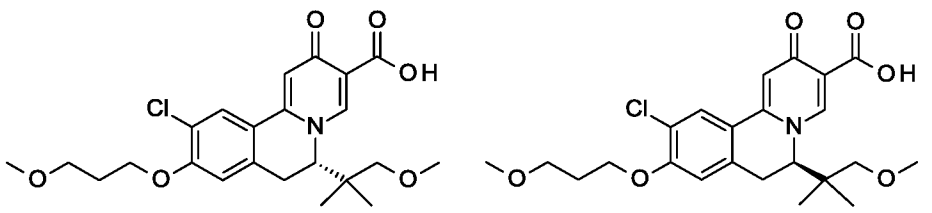
Separation of the racemic 6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (100 mg) by chiral HPLC afforded (+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo [a]quinolizine-3-carboxylic acid (30 mg, Compound 5A) and (-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (28 mg, Compound 5B).

Compound 5A: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.68 (s, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 7.08 (s, 1H), 5.08 (m, 1H), 4.67 (m, 1H), 4.10 (m, 2H), 3.87 (s, 3H), 3.48 (m, 2H), 3.33 (s, 3H), 3.19-3.25 (m, 2H), 2.96-3.11 (m, 2H), 1.99 (m, 2H), 0.76 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI^+) [$(M+H)^+$]: 432. $[\alpha]_D^{20}$ = +90.00° (0.100%, CH_3CN).

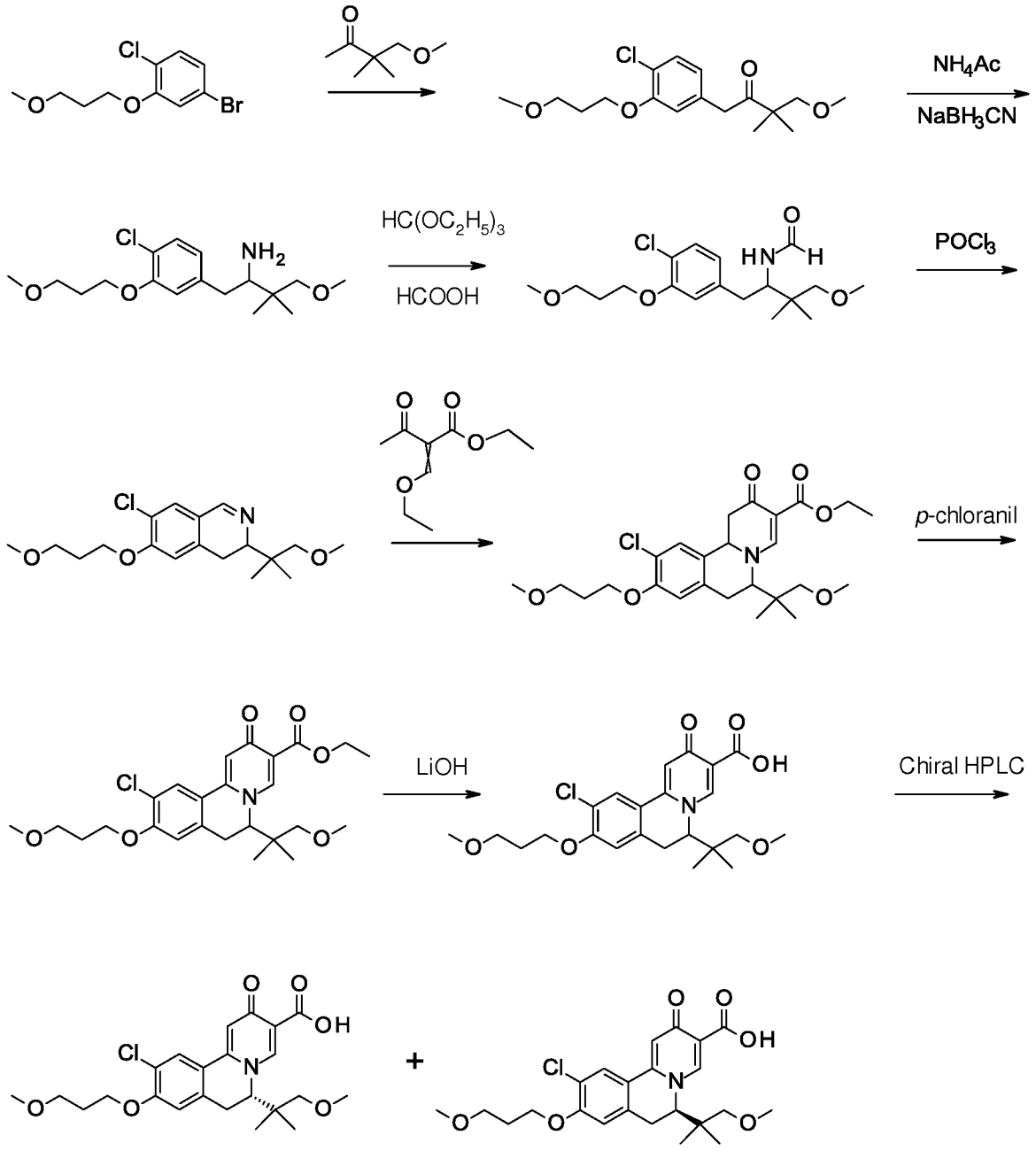
Compound 5B: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.68 (s, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 7.08 (s, 1H), 5.08 (m, 1H), 4.67 (m, 1H), 4.10 (m, 2H), 3.87 (s, 3H), 3.48 (m, 2H), 3.33 (s, 3H), 3.19-3.25 (m, 2H), 2.96-3.11 (m, 2H), 1.99 (m, 2H), 0.76 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI^+) [$(M+H)^+$]: 432.

Example 3

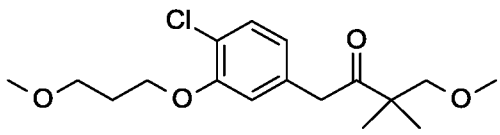
Preparation of (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 6A) and (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 6B)



Compound 6A and 6B was prepared through the following scheme:



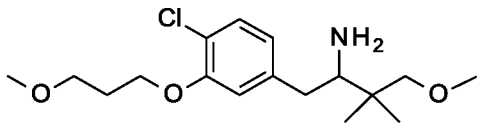
Step 1: Preparation of 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one



To a solution of 4-bromo-1-chloro-2-(3-methoxypropoxy)benzene (20 g, 72 mmol) in dioxane (50 mL) was added 4-methoxy-3,3-dimethyl-butan-2-one (19 g, 144 mmol), $Pd(OAc)_2$

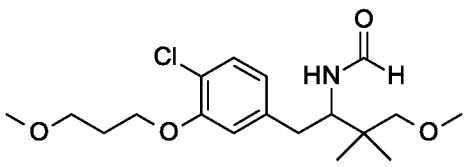
(0.24 g, 1 mmol), XPhos (1 g, 2.16 mmol) and LiHMDS (166 mL, 1.3 M). The resulting mixture was stirred at 70 °C for 3 h under argon atmosphere. After being cooled to room temperature, the suspension was poured into water. The mixture was acidified to pH=3 with 2 M hydrochloride acid, and then extracted with ethyl acetate (200 mL) 2 times. The combined organic layers were washed with water (80 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated to give crude 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (24 g) as a yellow oil.

Step 2: Preparation of 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine



To a solution of crude 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-one (24 g, 72 mmol) in methanol (200 mL) was added ammonium acetate (55 g, 720 mmol) and $NaBH_3CN$ (9 g, 144 mmol). The resulting mixture was stirred for 12 h at 60 °C. The reaction was quenched with water, and then to the mixture was added 2.0 M NaOH aqueous solution (20 mL). The mixture was stirred for 1 h, and then adjusted to pH=1 with concentrated hydrochloric acid. After being washed with ethyl acetate (100 mL) to remove impurities, the separated aqueous phase was adjusted to pH=12 with potassium hydroxide and then extracted with ethyl acetate (200 mL) 2 times. The combined organic layers were washed with water (80 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (25 g).

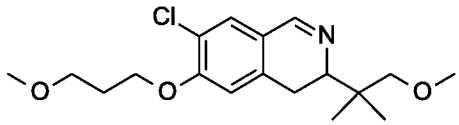
Step 3: Preparation of *N*-[1-[[4-chloro-3-(3-methoxypropoxy)phenyl]methyl]-3-methoxy-2,2-dimethyl-propyl]formamide



A mixture of 4-chloro-1-[4-methoxy-3-(3-methoxypropoxy)phenyl]-3,3-dimethyl-butan-2-amine (25 g, 72 mmol), formic acid (30 mL) and triethyl orthoformate (10 mL) in 1,4-dioxane

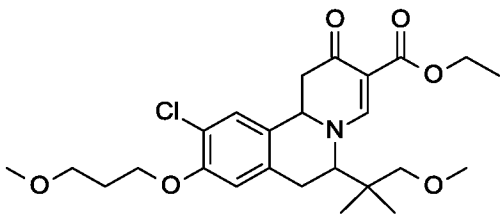
(200 mL) was refluxed for 48 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (200 mL) and water (50 mL). The separated organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to give *N*-[1-[[4-chloro-3-(3-methoxypropoxy)phenyl] methyl]-3-methoxy-2,2-dimethyl-propyl]formamide (25 g) which was used in the next step without further purification.

Step 4: Preparation of 7-chloro-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline



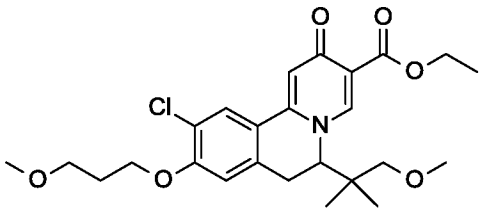
To a solution of *N*-[1-[[4-chloro-3-(3-methoxypropoxy)phenyl] methyl]-3-methoxy-2,2-dimethyl-propyl]formamide (24g, 72 mmol) in acetonitrile (200 mL) was added $POCl_3$ (14 mL, 144 mmol) dropwise at 0-5 °C. The resulting mixture was warmed at 60 °C for 1 h. After being cooled to rt, the mixture was concentrated. To the residue ethyl acetate (200mL) was added, then to the mixture was added ammonia water to adjust the pH of the aqueous solution to around 11. The mixture was extracted with ethyl acetate (200 mL) 2 times. The organic layers were combined and concentrated. The residue was purified by column chromatography to 7-chloro-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (21 g).

Step 5: Preparation of ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate



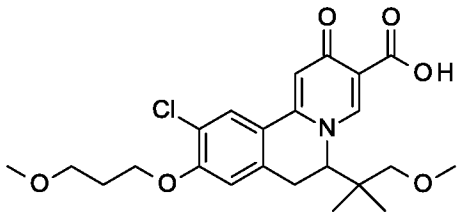
A mixture of 7-chloro-3-(2-methoxy-1,1-dimethyl-ethyl)-6-(3-methoxypropoxy)-3,4-dihydroisoquinoline (21 g, 62 mmol) and ethyl 2-(ethoxymethylene)-3-oxo-butanoate (34 g, 185 mmol) in ethanol (100 mL) was refluxed for 24 h. The mixture was concentrated to give crude ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate as a dark brown oil which was used in the next step without purification.

Step 6: Preparation of ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate



A mixture of crude ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-1,6,7,11b-tetrahydrobenzo[a]quinolizine-3-carboxylate from step **5** and *p*-chloranil (15 g, 62 mmol) in DME (100 mL) was refluxed for 2 h. After being cooled to rt, the mixture was concentrated. The residue was dissolved in ethyl acetate (500 mL). The solution was washed with water (200 mL) 2 times and brine, dried over anhydrous Na_2SO_4 and concentrated to give crude ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate which was used directly in the next step.

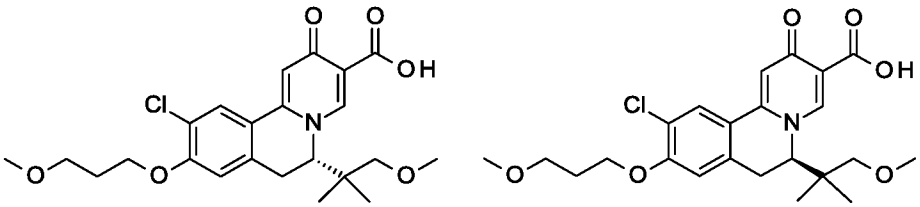
Step 7: Preparation of 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid



To a solution of crude ethyl 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylate in THF (50 mL) and ethanol (50 mL) was added 2.0 M LiOH aqueous solution (50 mL) at rt. The resulting mixture was stirred for 4 h, and then acidified to pH=1-2 with 2 M hydrochloric acid. The mixture was extracted with DCM (100 mL) 2 times. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (4.1 g) as a white solid.

Step 8: Preparation of (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 6A)

and (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (Compound 6B)



Separation of the racemic 10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (2 g) by chiral HPLC afforded (+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a] quinolizine-3-carboxylic acid (750 mg, Compound 6A) and (-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid (680 mg, Compound 6B).

Compound 6A: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.56 (s, 1H), 8.15 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 4.68 (m, 1H), 4.13-4.32 (m, 2H), 3.52 (m, 2H), 3.27 (s, 3H), 3.12 (s, 3H), 2.94 (s, 1H), 2.90 (s, 1H), 2.82 (m, 1H), 2.00-2.12 (m, 2H), 1.97-2.09 (m, 3H), 1.69-1.83 (m, 1H), 0.88 (s, 3H), 0.47 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 450. $[\alpha]_D^{20}$ =+ 96.000° (0.100%, CH_3CN).

Compound 6B: ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.56 (s, 1H), 8.15 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 4.68 (m, 1H), 4.13-4.32 (m, 2H), 3.52 (m, 2H), 3.27 (s, 3H), 3.12 (s, 3H), 2.94 (s, 1H), 2.90 (s, 1H), 2.82 (m, 1H), 2.00-2.12 (m, 2H), 1.97-2.09 (m, 3H), 1.69-1.83 (m, 1H), 0.88 (s, 3H), 0.47 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 450.

Example 4

HBsAg Assay to test capacity of HBsAg inhibitor to inhibit HBsAg

The capacity of Compounds 4A, 4B, 5A, 5B, 6A and 6B to inhibit HBsAg was tested in the HBsAg Assay described below. Results of HBsAg assay are given in Table 2.

Materials and methods

HBV cell line

HepG2.2.15 cells (Acs et al. *Proc Natl Acad Sci U S A,* 84, (1987), 4641-4), a constitutively HBV-expressing cell line were cultured in DMEM+Glutamax-I medium (Invitrogen, Carlsbad, CA, USA, Catalog number: 11320082), supplemented with 10% fetal

bovine serum (Invitrogen, Catalog number: 10099141) and G418 (Invitrogen, Catalog number: 10131027) at a final concentration of 200 mg/L and maintained in 5% CO_2 at 37°C.

HBsAg Assay

HepG2.2.15 cells were seeded in duplicate into white, 96-well plates at 1.5 x 10^4 cells/well. The cells were treated with a three-fold serial dilution series of the compounds in DMSO. The final DMSO concentration in all wells was 1% and DMSO was used as no drug control.

The HBsAg chemiluminescence immunoassay (CLIA) kit (Autobio Diagnostics Co., Zhengzhou, China, Catalog number: CL0310-2) was used to measure the levels of secreted HBV antigens semi-quantitatively. For the detection 50 µL/well culture supernatant was used and HBsAg was quantified using HBsAg chemiluminescence immunoassay (CLIA) kit (Autobio Diagnostics Co., Zhengzhou, China, Catalog number: CL0310-2), 50 µL of the supernatant was transferred to the CLIA assay plate and 50 µL of enzyme conjugate reagent was added into each well. The plates were sealed and gently agitated for 1 hour at room temperature. The supernatant-enzyme-mixture was discarded and wells were washed 6 times with 300 µL of PBS. The residual liquid was removed by plating the CLIA plate right side down on absorbent tissue paper. 25 µL of substrates A and B were added to each well. Luminance was measured using a luminometer (Mithras LB 940 Multimode Microplate Reader) after 10 minutes incubation. Dose-response curves were generated and the IC_{50} value was extrapolated by using the E-WorkBook Suite (ID Business Solutions Ltd., Guildford, UK). The IC_{50} was defined as the compound concentration (or conditioned media log dilution) at which HBsAg secretion was reduced by 50% compared to the no drug control.

Table 2. Activity data of HBsAg inhibitors

Compound Number	IC_{50} (µM)
4A	0.003
4B	0.396
5A	0.002
5B	0.084
6A	0.003
6B	8.27

Example 5

Combination of an HBsAg inhibitor and an HBV capsid assembly inhibitor in HBV infected HepaRG cells

Material and Methods

Virus and cells

HepG2.2.15 cells were cultured in DMEM+Glutamax I (Gibco, #21885) supplemented with 10% FBS, 1% Pen/Strep (Gibco, #15140) and G-418 (250 μg/mL) and used for production of infectious HBV (genotype D). 90% confluent cells from three T175 flasks were trypsinized and transferred into one collagen coated hyperflask (550 mL). Once the cells are confluent, medium was changed to DMEM+Glutamax I with 1% DMSO and 2.5% FBS. Once the cells were slightly over confluent, medium was changed to DMEM/F12+Glutamax I (Gibco, #31331) supplemented with MEM non-essential amino acids (6 mL, Gibco, #11140), Pen/Strep (6 mL), sodium pyruvate (6 mL), DMSO (9 mL) and FBS (10 mL) (all per 500mL medium). Medium was changed every 3 days and supernatants were harvested for 2 weeks. Virus was concentrated from supernatants by PEG precipitation and the titer (genome equivalent (GE) / mL) was determined by qPCR. Briefly, supernatants were mixed with 40% PEG solution at a ratio of 4:1, incubated on a shaker at 4°C overnight and then centrifuged using 50 mL falcon tubes at 4°C for one hour at 3724 g (RCF). The supernatant was discarded and the centrifugation step was repeated with new supernatant reusing the tubes until all PEG-precipitated supernatant was processed. The pellets were re-suspended in William's E Medium (Gibco, #22551) at a concentration of 10^7-10^9 genome equivalents (GE) per mL and frozen at -80°C. DNA copy number calculation was based on a standard curve generated from HBV plasmid dilutions with known concentrations.

HepaRG cells (Biopredic International, Saint-Gregoire, France) were cultured in working growth medium (500 mL Willams E Medium with 50 mL HepaRG Growth supplement from Biopredic, 5 mL Glutamax-I (Gibco, #35050) and 5 mL Pen/Strep) for 2 weeks. After 2 weeks medium was changed to differentiation medium containing 1.8% DMSO (500 mL Willams E Medium with 50 mL HepaRG Growth supplement from Biopredic, 5 mL Pen/Strep, 5 mL Glutamax-I and 9 mL DMSO). Medium was changed twice a week up to 2 weeks. Once fully differentiated, cells were trypsinized and seeded into collagenated 96 well plates (50,000 cells/well in 100 μL) in differentiation medium. Cells were cultured at least 5 days in the 96 well plates before they were infected with HBV.

Infection and compound treatment of HepaRG cells

For HBV infection of differentiated HepaRG cells, medium was removed and new differentiation medium (120 µL/well) containing 4% PEG-8000 and virus stock (20 to 30 GE/cell) was added. Cells were cultured at 37°C for 16 to 20 h before medium was removed, cells were washed 4 times with PBS and new differentiation medium (120 µL/well) was added. At day 4 post infection, medium was removed and 100 µL new differentiation medium was added to each well. 3-fold serial dilutions (5 µL compound to 10 µL DMSO) of drug A and drug B were prepared in 100% DMSO starting with 15 µL undiluted compound solution (400-fold concentration of highest test concentration). 5 µL of drug A and B dilutions were then added to 990 µL medium (containing 0.8% DMSO) in a 96 deep well plate in a fashion according to the design shown in Table 3. 100 µL thereof were added to the HepaRG cells with a final DMSO concentration of 1.8%. Drug A tested is **Compound 7** or **Compound 10**, Drug B tested is **Compound 1A**. The concentration ranges tested were 300 nM to 0.4 nM for **Compound 7**, 150 nM to 0.2 nM for **Compound 10**, and 30 nM to 0.37 nM for **Compound 1A**. Medium was replaced by new medium with compound at day 7 post infection and at day 11 post infection cell supernatants were harvested and directly used for HBV DNA extraction or stored at -20°C. Cell viability of the cells was determined using the cell viability assay described below.

Table 3. Plate layout for combinations of Drug A and Drug B

	1	2	3	4	5	6	7	8	9	10	11	12
a	X	X	X	X	X	X	X	X	X	X	X	X
b	X	A1	**A1+B7**	**A1+B6**	**A1+B5**	A1+B4	A1+B3	A1+B2	A1+B1	VC	ETV	CC
c	X	A2	A2+B7	**A2+B6**	**A2+B5**	**A2+B4**	A2+B3	A2+B2	A2+B1	VC	ETV	CC
d	X	A3	A3+B7	A3+B6	**A3+B5**	**A3+B4**	**A3+B3**	A3+B2	A3+B1	VC	ETV	CC
e	X	A4	A4+B7	A4+B6	A4+B5	**A4+B4**	**A4+B3**	**A4+B2**	A4+B1	VC	ETV	CC
f	X	A5	A5+B7	A5+B6	A5+B5	A5+B4	**A5+B3**	**A5+B2**	**A5+B1**	VC	ETV	CC
g	X	VC	B7	B6	B5	B4	B3	B2	B1	VC	ETV	CC
h	X	X	X	X	X	X	X	X	X	X	X	X

X: PBS

CC: cell control (uninfected)

VC: virus control

ETV: reference control (200nM Entecavir)

A1-5: serial dilution of drug A

B1-7: serial dilution of drug B

A1+B7: example of combination of drug A and B at different ratios

DNA extraction

HBV DNA from HepaRG cell supernatants was extracted using the MagNA Pure 96 (Roche) robot. 100 µL of the supernatants were mixed in a processing cartridge with 200 µL MagNA Pure 96 external lysis buffer (Roche, Cat. No. 06374913001) and incubated for 10 minutes. DNA was then extracted using the "MagNA Pure 96 DNA and Viral Nucleic Acid Small Volume Kit" (Roche, Cat. No. 06543588001) and the "Viral NA Plasma SV external lysis 2.0" protocol. DNA elution volume was 50 µL.

qPCR

Quantification of extracted HBV DNA was performed using a Taqman qPCR machine (ViiA7, life technologies). Each DNA sample was tested in duplicate in the PCR. 5 µL of DNA sample were added to 15 µL of PCR mastermix containing 10 µL TaqMan Gene Expression Master Mix (Applied Biosystems, Cat. No. 4369016), 0.5 µL PrimeTime XL qPCR Primer/Probe (IDT, Leuven, Belgium) and 4.5 µL distilled water in a 384 well plate and the PCR was performed using the following settings: UDG Incubation (2 min, 50°C), Enzyme Activation (10min, 95°C) and PCR (40 cycles with 15sec, 95° for Denaturing and 1min, 60°C for annealing and extension). DNA copy numbers were calculated from C_t values based on a HBV plasmid DNA standard curve by the ViiA7 software.

Sequences for TaqMan primers and probes (IDT):

Forward core primer (F3_core): CTG TGC CTT GGG TGG CTT T

Reverse primer (R3_core): AAG GAA AGA AGT CAG AAG GCA AAA

Taqman probe (P3_core): 56-FAM/AGC TCC AAA /ZEN/TTC TTT ATA AGG GTC GAT GTC CAT G/3IABkFQ

Cell viability assay

Cell viability of the HBV infected and treated HepaRG cells was determined at day 11 post infection using the CellTiter-Glo® (CTG) Luminescent Cell Viability Assay (Promega, Cat. No. G7572). 100 µL of CTG reagent were added to each well of the cells, incubated for 10 min and

80 µL of each well were transferred to a new white 96 well plate. Luminescence (0.2 sec) was measured using an Envision reader (PerkinElmer).

Data Analysis

Isobologram model

The combination experimental results were analyzed using the model described by Craig *et al.* (Craig J, Duncan I, Whittaker L and Roberts N. (1990). Antiviral synergy between inhibitors of HIV proteinase and reverse transcriptase. *Antiviral Chem. Chemother.* 4:161-166). EC_{50} values were obtained for compounds used alone and in combination with others. To relate these two values and describe the degree of synergy/additivity/antagonism between them, the Fractional Inhibitory Concentration (FIC) was first calculated and used to generate isobolograms. Briefly, the FIC is the ratio of the EC_{50} of the drug in combination to the EC_{50} of the drug on its own:

$$FIC = \text{ratio } [EC_{50\,\text{combination}} : EC_{50\,\text{alone}}]$$

The Combination Index (CI), obtained by adding the FICs of the two compounds, was then used to describe the effect between compounds used in the combinations. A CI < 1 means synergism, a CI = 1 means additivity and a CI > 1 means antagonism.

CalcuSyn model

Each experiment was performed in at least triplicate and performed independently 3 times. Mean percent inhibition of HBV replication based on DNA copy number was calculated from all experiments and analyzed using the Calcusyn software (CalcuSyn Version 2.11, Biosoft, Cambridge, UK) based on the Loewe additivity model described by Chou and Talalay (Chou TC (2006). Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol. Rev., 58:_621-681). For the CalcuSyn evaluation, data from three diagonal lanes with a constant concentration ratio for the drug combinations of each lane from the checkerboard plate were used (marked in bold in Table 3). In a first step, this program converts the dose-effect curves for each drug or drug combination to median effect plots. A combination index (CI) for each experimental combination was then calculated by the following equation (for mutually nonexclusive interactions):

$$[(D)_1/(Dx)_1]+[(D)_2/(Dx)_2]+[(D)_1(D)_2/(Dx)_1(Dx)_2]$$

where $(Dx)_1$ and $(Dx)_2$ are the doses of drug 1 and drug 2 that have x effect when each drug is used alone, and $(D)_1$ and $(D)_2$ are the doses of drug 1 and drug 2 that have the same x effect when they are used in combination, respectively. The software calculates the CIs at 50%, 75%

and 90% antiviral effect of combinations. Combination effect assessment was based on overall CI values as follows: CI value <0.7 as synergy, 0.7 to 0.9 as slight to moderate synergy, 0.9 to 1.1 as additive, 1.1 to 1.5 as slight to moderate antagonism and >1.5 as antagonism (Chou TC (2006). Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol. Rev., 58:621-681). Drug combinations were analyzed at three different fixed drug ratios spanning and including the approximate ratio of their EC_{50}s.

Results

Combination of **Compound 1**A with **Compound 7**, and combination of **Compound 1**A with **Compound 10** were tested for anti-HBV activity in HBV infected differentiated HepaRG cells. Combination of **Lamivudine** with **Lamivudine** was set as the control combination. The single compound inhibitory activites (EC_{50}) obtained in the combination studies were determined (Table 4). The concentration ranges chosen were also confirmed below the cytotoxic concentrations for each of the compounds (Table 5) and had no significant cytotoxic effect that could interfere with the antiviral activity.

Table 4. Mean EC_{50} ± SD values for the individual compounds used in the combination studies

Drug A	**Drug B**	**EC_{50} ± SD (n) Drug A**	**EC_{50} ± SD (n) Drug B**
Lamivudine	Lamivudine	12.9 nM ± 6.4 (3)	13.7 nM ± 1.0 (3)
Compound 1A	Compound 7	5.5 nM ± 0.7 (3)	16.9 nM ± 3.4 (3)
Compound 1A	Compound 10	5.7 nM ± 1.4 (3)	9.1 nM ± 3.0 (3)

Table 5. Cytotoxicity analysis for the individual compounds used in the combination studies

Drug A	**Drug B**	**Percentage of cell viability at max concentration ± SD (n^a) Drug A**	**Percentage of cell viability at max concentration ± SD (n^a) Drug B**
Lamivudine	Lamivudine	86.4 ± 2.6 (3)	104.5 ± 2.6 (3)
Compound 1A	Compound 7	90.1 ± 3.4 (3)	102.5 ± 5.8 (3)
Compound 1A	Compound 10	94.6 ± 7.5 (3)	96.8 ± 1.2 (3)

[a)] number of independent experiments

The interaction between **Compound 1A** and **Compound 7** was analyzed using the CalcuSyn software (Table 6). The overall CI for three different concentration ratios was between 0.65 and 0.80, thus the combination of **Compound 1A** and **Compound 7** is synergistic.

The interaction between **Compound 1A** and **Compound 7** was also analyzed using the Isobologram model (Figure 1). The FIC values for the combination of **Compound 1A** and **Compound 7** were plotted one against the other for each of the experiments. The analysis showed that the CI values were < 1. Therefore, the combination of **Compound 1A** and **Compound 7** is synergistic.

The interaction between **Compound 1A** and **Compound 10** was analyzed using the CalcuSyn software (Table 6). The overall CI for three different concentration ratios was between 0.48 and 0.64, thus the combination of **Compound 1A** and **Compound 10** is synergistic.

The interaction between Compound **1A** and Compound **10** was also analyzed using the Isobologram model (Figure 2). The FIC values for the combination of Compound 1A and Compound 10 were plotted one against the other for each of the experiments. The analysis showed that the CI values were < 1. Therefore, the combination of Compound 1A and Compound 10 is synergistic.

None of the combinations had a significant effect on cell viability.

Table 6 CalcuSyn based combination indices for the pair-wise checkerboard combinations (HBV DNA)

Drug combination	**n[a]**	**Molar ratio**	**CI values at the following levels of HBV inhibition**				**Assessment[b]**
			50%	**75%**	**90%**	**Overall CI**	
Lamivudine and Lamivudine	3	1 : 0.3	1.12 ± 0.24	1.05 ± 0.16	1.02 ± 0.11	1.06 ± 0.16	additivity
		1 : 1	0.98 ± 0.12	1.00 ± 0.14	1.06 ± 0.11	1.02 ± 0.11	
		1 : 3	1.02 ± 0.22	1.03 ± 0.22	1.08 ± 0.21	1.04 ± 0.19	
Compound 1A and Compound 7	3	1 : 1.1	0.68 ± 0.06	0.64 ± 0.04	0.62 ± 0.13	0.65 ± 0.07	synergism
		1 : 3.3	0.84 ± 0.15	0.77 ± 0.14	0.77 ± 0.23	0.80 ± 0.16	
		1 : 10	0.88 ± 0.10	0.75 ± 0.03	0.66 ± 0.04	0.77 ± 0.11	
Compound 1A and Compound 10	3	1 : 0.5	0.50 ± 0.03	0.45 ± 0.10	0.48 ± 0.24	0.48 ± 0.13	synergism
		1 : 1.6	0.60 ± 0.05	0.55 ± 0.14	0.60 ± 0.30	0.58 ± 0.17	
		1 : 5	0.64 ± 0.09	0.61 ± 0.17	0.68 ± 0.42	0.64 ± 0.23	

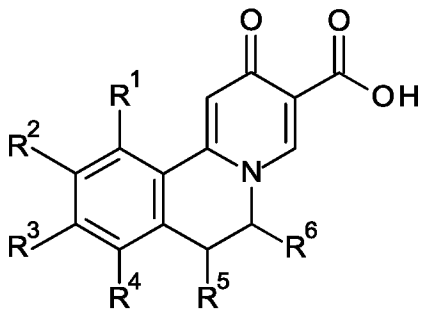
[a)] number of independent experiments

[b)] Assessment was based on CI values determined by the CalcuSyn software.

CLAIMS

1. A pharmaceutical composition comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1, wherein the HBsAg inhibitor is a compound of formula (I):



(I)

wherein

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkylamino or C_{1-6}alkoxy;

R^2 is hydrogen; halogen; C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C_{1-6}alkoxy, which is unsubstituted or once, twice or three times substituted by fluoro; cyano; C_{3-7}cycloalkyl; hydroxy or phenyl-C_xH_{2x}-O-;

R^3 is hydrogen;

halogen;

C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro;

cyano;

pyrrolidinyl;

amino;

phenyl-C_xH_{2x}-*N*(C_{1-6}alkyl)-;

C_{1-6}alkoxycarbonylpiperazinyl;

or R^7-O- , wherein R^7 is hydrogen; C_{1-6}alkyl, which is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy and C_{2-6}alkenyl; C_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkyl; aminoC_{1-8}alkyl; C_{1-6}alkylcarbonylaminoC_{1-8}alkyl; C_{1-6}alkylsulfonylaminoC_{1-8}alkyl; C_{1-6}alkylsulfanylC_{1-6}alkyl; C_{1-6}alkylsulfonylC_{1-6}alkyl; cyanoC_{1-6}alkyl; C_{3-7}cycloalkylC_{1-6}alkyl; cyanoC_{3-7}cycloalkylC_{1-6}alkyl; phenylC_{1-6}alkyl; pyrrolidinylcarbonylC_{1-6}alkyl; C_{2-6}alkynyl; hydroxyC_{1-6}alkylC_{2-6}alkynyl; aminoC_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkoxyC_{1-6}alkyl; diC_{1-6}alkylaminoC_{1-6}alkoxyC_{1-6}alkyl; carboxyC_{1-6}alkyl; or C_{1-6}alkoxycarbonylaminoC_{1-8}alkyl;

heteroarylC_{1-6}alkyl, wherein heteroaryl is *N*-containing monocyclic heteroaryl; or heterocycloalkylC_{1-6}alkyl, wherein heterocycloalkyl is monocyclic heterocycloalkyl;

R^4 is hydrogen, halogen, C_{1-6}alkyl, cyano or C_{1-6}alkoxy;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is hydrogen; C_{1-6}alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C_{3-7}cycloalkyl, which is unsubstituted or once, twice or three times substituted by fluoro or C_{1-6}alkyl; or phenyl-C_xH_{2x}-;

x is 1-6;

or a pharmaceutically acceptable salt, or enantiomer thereof.

3. The pharmaceutical composition according to claim 1, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

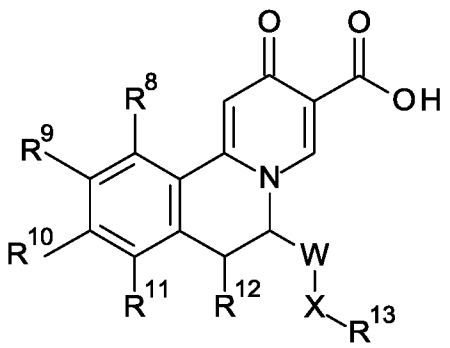
(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ,

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, or

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

4. The pharmaceutical composition according to claim 1, wherein the HBsAg inhibitor is a compound of formula (II):



(II)

wherein

R^8, R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, C_{1-6}alkyl, diC_{1-6}alkylamino, cyano, *N*-containing monocyclic heterocycloalkyl and OR^{14}, wherein

R^{14} is hydrogen; C_{1-6}alkyl; or C_{1-6}alkyl which is substituted once or more times by fluoro, C_{3-7}cycloalkyl, phenyl, hydroxyl, amino, C_{1-6}alkoxy, C_{1-6}alkylsulfanyl, C_{1-6}alkylsulfonyl, diC_{1-6}alkylamino, C_{1-6}alkoxycarbonylamino, monocyclic heterocycloalkyl, pyrazoyl or imidazolyl;

R^{12} is hydrogen or C_{1-6}alky;

R^{13} is hydrogen, C_{1-6}alkyl, phenyl-C_xH_{2x}-, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, benzoyl or monocyclic heterocycloalkyl, wherein

x is 1-6;

W is a bond, $C_yH_{2y}C(R^{15})(R^{16})C_zH_{2z}$ or $C_yH_{2y}CH(R^{15})CH(R^{16})C_zH_{2z}$, wherein

R^{15} and R^{16} are independently selected from hydrogen, fluoro, hydroxy and C_{1-6}alkyl,

y is 0-6;

z is 0-6;

X is a bond; O; S; $S(O)_2$; or NR^{17}, wherein R^{17} is hydrogen, C_{1-6}alkyl;

or R^{13} and R^{17}, together with the nitrogen to which they are attached, form monocyclic heterocycloalkyl;

or a pharmaceutically acceptable salts, or enantiomers thereof.

5. The pharmaceutical composition according to claim 1 or 4, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid ,

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

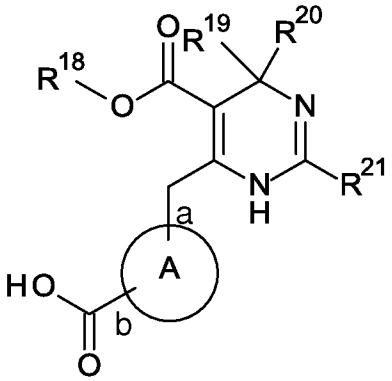
(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid, or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid,

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the HBV capsid assembly inhibitor is a compound of formula (III),



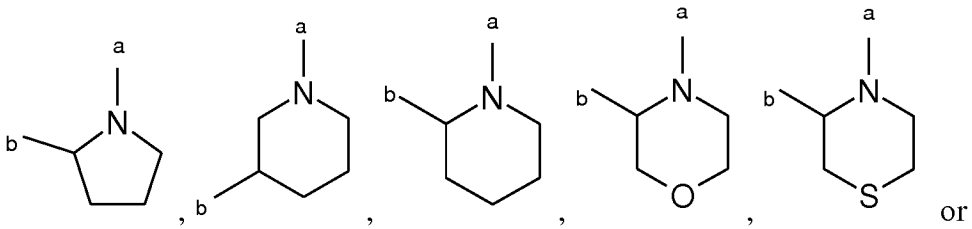
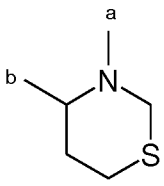
(III),

wherein

R^{18} is C_{1-6}alkyl or trifluoromethyl-C_sH_{2s}-, wherein s is 1, 2, 3, 4, 5 or 6;

One of R^{19} and R^{20} is phenyl, which is once or twice or three times substituted by C_{1-6}alkyl, cyano or halogen; and the other one is hydrogen or deuterium;

R^{21} is phenyl, thiazolyl, oxazolyl, imidazolyl, thienyl or pyridinyl, which is unsubstituted or substituted by C_{1-6}alkyl, C_{1-6}alkylsulfanyl, halogen or cycloalkyl, wherein C_{1-6}alkyl can be further optionally substituted with halogen;

A is , , which is unsubstituted or substituted by groups selected from C_{1-6}alkyl, deuterium and halogen;

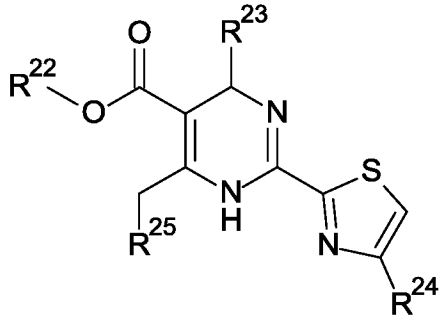
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-Carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester; or
(2*R*,3*S*)-4-[(R)-6-(2-Chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

8. The pharmaceutical composition according to any one of claims 1 to 5, wherein the HBV capsid assembly inhibitor is a compound of formula (IV),



(IV)

wherein

R^{22} is C_{1-6}alkyl;

R^{23} is phenyl, which is once or twice or three times substituted by halogen or C_{1-6}alkyl;

R^{24} is hydrogen or C_{1-6}alkyl;

R^{25} is bicyclic bridged heterocyclyl;

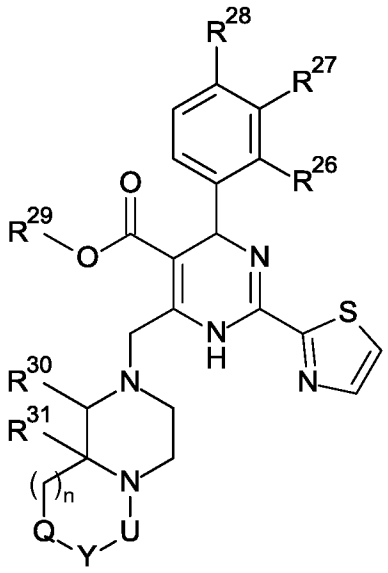
or pharmaceutically acceptable salt, or tautomerism isomer, or enantiomer, or diastereomer thereof.

9. The pharmaceutical composition according to any one of claims 1 to 5 and 8, wherein the HBV capsid assembly inhibitor is

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1S,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;
or pharmaceutically acceptable salt, or tautomerism isomer, or enantiomer, or diastereomer thereof.

10. The pharmaceutical composition according to any one of claims 1 to 5, wherein the HBV capsid assembly inhibitor is a compound of formula (V),



(V)

wherein

R^{26} is hydrogen, halogen or C_{1-6}alkyl;

R^{27} is hydrogen or halogen;

R^{28} is hydrogen or halogen;

R^{29} is C_{1-6}alkyl;

R^{30} is hydrogen, hydroxyC_{1-6}alkyl, aminocarbonyl, C_{1-6}alkoxycarbonyl or carboxy;

R^{31} is hydrogen, C_{1-6}alkoxycarbonyl or carboxy-C_mH_{2m}-;

U is carbonyl or sulfonyl;

Y is $-CH_2-$, -O- or $-N(R^{32})-$,

wherein R^{32} is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl-C_mH_{2m}-, C_{1-6}alkoxycarbonyl-C_mH_{2m}-,-C_tH_{2t}-COOH, -haloC_{1-6}alkyl-COOH, -(C_{1-6}alkoxy)C_{1-6}alkyl-COOH, -C_{1-6}alkyl-O-C_{1-6}alkyl-COOH, -C_{3-7}cycloalkyl-C_mH_{2m}-COOH, -C_mH_{2m}-C_{3-7}cycloalkyl-COOH, hydroxy-C_tH_{2t}-, carboxyspiro[3.3]heptyl or carboxyphenyl-C_mH_{2m}-, carboxypyridinyl-C_mH_{2m}-;

Q is $-CH_2-$, $-C(C_{1-6}alkyl)_2-$, -O- or carbonyl;

n is 0 or 1;

m is 0-7;

t is 1-7;

or pharmaceutically acceptable salt, or enantiomer or diastereomer thereof.

11. The pharmaceutical composition according to any one of claims 1 to 5 and 10, wherein the HBV capsid assembly inhibitor is

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid; or

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

or pharmaceutically acceptable salt, or enantiomer or diastereomer thereof.

12. The pharmaceutical composition according to claim 1, wherein the composition consists of an HBsAg inhibitor and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 1 or 12, wherein the composition consists of

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(*4R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(*4R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; and

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid ;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*S*,8*aR*)-2-tert-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

in a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 1 or 12, wherein the composition consists of

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;
in a pharmaceutically acceptable carrier.

15. A method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that an HBsAg inhibitor and an HBV capsid assembly inhibitor are used in the medicament.

16. The method according to claim 15, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor are co-administered in the same formulation or different formulation.

17. The method according to claim 15 or 16, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor are intended for administration to a subject by the same route or different routes.

18. The method according to any one of claims 15 to 17, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor are intended for administration to a subject by parenteral or oral administration.

19. The method according to any one of claims 15 to 18, wherein the administration is simultaneous or sequential.

20. The method according to any one of claims 15 to 19, wherein the HBsAg inhibitor is a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

21. The method according to any one of claims 15 to 20, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

22. The method according to any one of claims 15 to 21, wherein the HBV capsid assembly inhibitor is a compound of formula (III), formula (IV) or formula (V), or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

23. The method according to any one of claims 15 to 22, wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

24. The method according to any one of claims 15 to 23, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor used in the medicament are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-

fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

25. A kit comprising a container comprising an HBsAg inhibitor and an HBV capsid assembly inhibitor.

26. The kit according to claim 25, further comprising a sterile diluent.

27. The kit according to claim 25 or 26, further comprising a package insert comprising printed instructions directing the use of a combined treatment of an HBsAg inhibitor and an HBV capsid assembly inhibitor as a method for treatment or prophylaxis of hepatitis B virus infection.

28. The kit according to any one of claims 25 to 27, wherein the HBsAg inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

29. The kit according to any one of claims 25 to 28, wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

30. The kit according to any one of claims 25 to 29, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor used in the container are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

31. A method for the treatment or prophylaxis of hepatitis B virus infection, comprising administration to a subject with an effective first amount of an HBsAg inhibitor, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and a second amount of an HBV capsid assembly inhibitor, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof; or *vice versa*.

32. The method according to claim 31, wherein the HBsAg n inhibitor is

(+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-chloro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-*tert*-butyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-10-methoxy-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(-)-6-(2-hydroxy-1,1-dimethyl-ethyl)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

(+)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; or

(-)-10-chloro-6-(2-methoxy-1,1-dimethyl-ethyl)-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

33. The method according to claim 31 or 32, wherein the HBV capsid assembly inhibitor is

(*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

(*R*)-6-((*S*)-2-carboxy-4,4-difluoro-pyrrolidin-1-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(2*R*,3*S*)-4-[(*R*)-6-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-2-methyl-morpholine-3-carboxylic acid;

3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

4-[(8*aS*)-7-[[(4*R*)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-3,3-dimethyl-butanoic acid;

(8*S*,8*aR*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

(8*R*,8*aS*)-2-*tert*-butyl-7-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazine-8-carboxylic acid;

2-[(1*R*,3*S*,5*S*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or

2-[(1*S*,3*R*,5*R*)-8-[[(4*R*)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

34. The method according to any one of claim 31 to 33, wherein the HBsAg inhibitor and the HBV capsid assembly inhibitor used are (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and (*S*)-4-[(*R*)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or (+)-10-methoxy-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid and 3-[(8*aS*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1*H*-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid.

35. The use of pharmaceutical composition according to claim 1 to 14 as an antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

36. The use of an HBsAg inhibitor and an HBV capsid assembly inhibitor for the manufacture of pharmaceutical composition according to claim 1 to 14 as an antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.

37. The invention as hereinbefore described.

Case 33202

Figure 1.

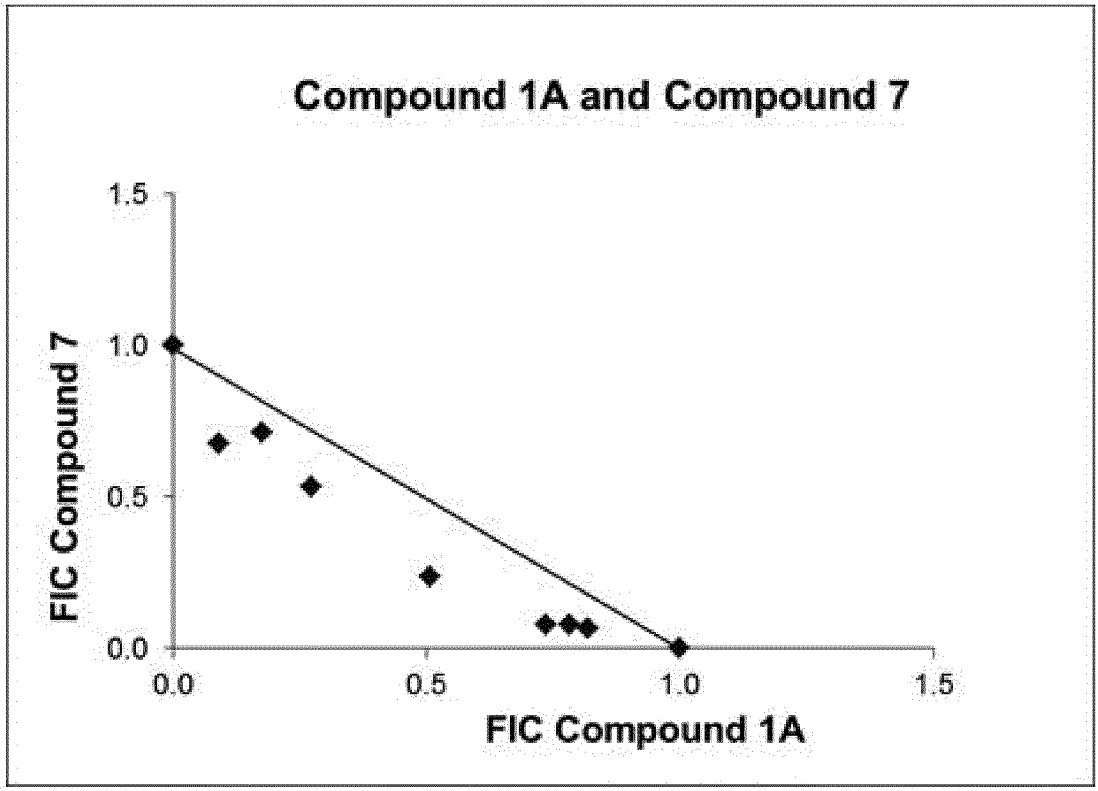
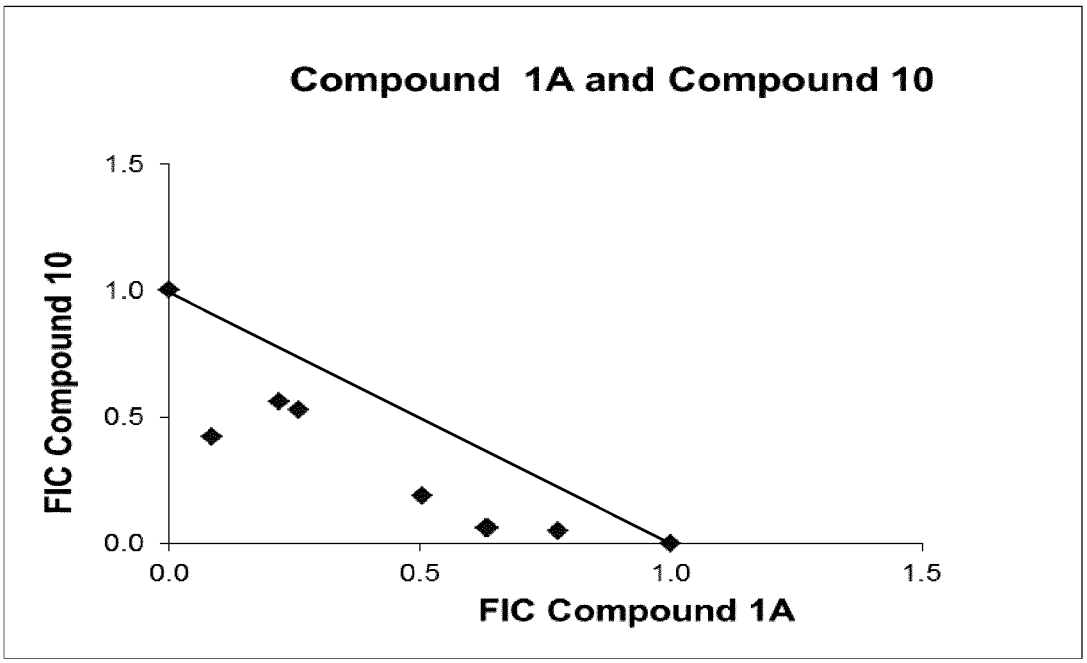


Figure 2.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/081556

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [ ] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

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      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081556

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4375 A61K31/506 A61K31/5377 A61P31/12 A61P31/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/113990 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 6 August 2015 (2015-08-06) the whole document, in particular 'Field of the Invention' 'Summary of the Invention' page 8 et seqq. 'Inhibitors of HBsAg' page 47 'Combination Therapy' Examples Claims ----- -/--	1-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2017	04/04/2017

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/037480 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 13 March 2014 (2014-03-13) the whole document, in particular 'Field of the Invention' 'Summary of the Invention' page 5 et seqq. 'Inhibitors of HBV' table 1 Examples Claims	1-37
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International application No
PCT/EP2016/081556

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