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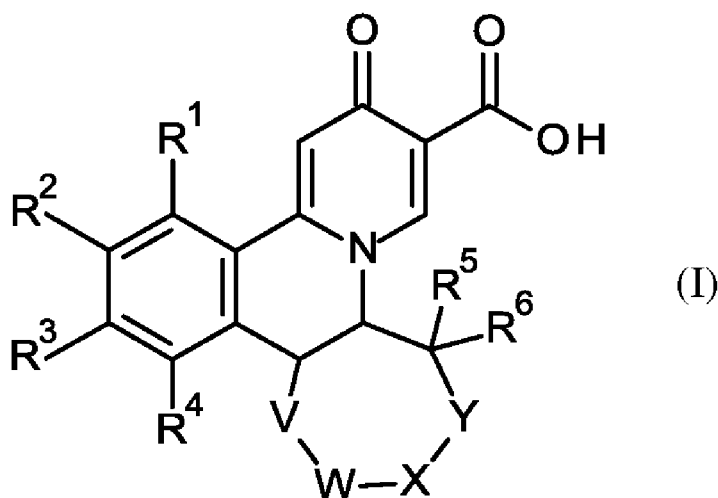
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(54) Title: NOVEL TETRACYCLIC 4-OXO-PYRIDINE-3-CARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT AND PROPHYLAXIS OF HEPATITIS B VIRUS INFECTION



(57) Abstract: The invention provides novel compounds having the general formula wherein R¹ to R⁶, V, W, X and Y are as described herein, compositions including the compounds and methods of using the compounds.

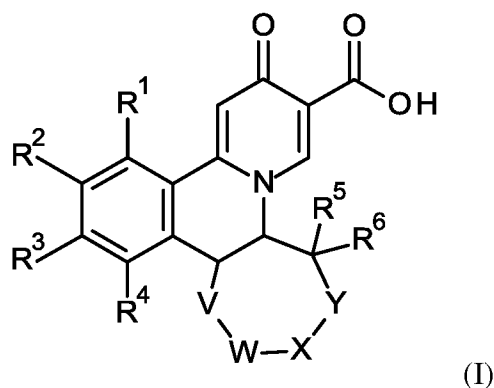
Novel tetracyclic 4-oxo-pyridine-3-carboxylic acid derivatives for the treatment and prophylaxis of hepatitis B virus infection

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to HBsAg (HBV Surface antigen) inhibitors and HBV DNA production inhibitors useful for treating HBV infection.

5 FIELD OF THE INVENTION

The present invention relates to novel tetracyclic 4-oxo-pyridine-3-carboxylic acid derivatives having pharmaceutical activity, their manufacture, pharmaceutical compositions containing them and their potential use as medicaments.

The present invention relates to compounds of formula I



wherein R¹ to R⁶, V, W, X and Y are as described below, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

The hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA virus. The compact 3.2 kb HBV genome consists of four overlapping open reading frames (ORF), which encode for the core, polymerase (Pol), envelope and X-proteins. The Pol ORF is the longest and the envelope ORF is located within it, while the X and core ORFs overlap with the Pol ORF. The lifecycle of HBV has two main events: 1) generation of closed circular DNA (cccDNA) from relaxed circular (RC DNA), and 2) reverse transcription of pregenomic RNA (pgRNA) to produce RC DNA. Prior to the infection of host cells, the HBV genome exists within the virion as RC DNA. It has been determined that HBV virions are able to gain entry into host cells by

non-specifically binding to the negatively charged proteoglycans present on the surface of human hepatocytes (Schulze, A., P. Gripon & S. Urban. *Hepatology*, 46, (2007), 1759-68) and via the specific binding of HBV surface antigens (HBsAg) to the hepatocyte sodium-taurocholate cotransporting polypeptide (NTCP) receptor (Yan, H. et al. *J Virol*, 87, (2013), 7977-91). Once the virion has entered the cell, the viral cores and the encapsidated RC DNA are transported by host factors, via a nuclear localization signal, into the nucleus through the Imp β /Imp α nuclear transport receptors. Inside the nucleus, host DNA repair enzymes convert the RC DNA into cccDNA. cccDNA acts as the template for all viral mRNAs and as such, is responsible for HBV persistence in infected individuals. The transcripts produced from cccDNA are grouped into two categories; Pregenomic RNA (pgRNA) and subgenomic RNA. Subgenomic transcripts encode for the three envelopes (L, M and S) and X proteins, and pgRNA encodes for Pre-Core, Core, and Pol proteins (Quasdorff, M. & U. Protzer. *J Viral Hepat*, 17, (2010), 527-36). Inhibition of HBV gene expression or HBV RNA synthesis leads to the inhibition of HBV viral replication and antigens production (Mao, R. et al. *PLoS Pathog*, 9, (2013), e1003494; Mao, R. et al. *J Virol*, 85, (2011), 1048-57). For instance, IFN- α was shown to inhibit HBV replication and viral HBsAg production by decreasing the transcription of pgRNA and subgenomic RNA from the HBV covalently closed circular DNA (cccDNA) minichromosome. (Belloni, L. et al. *J Clin Invest*, 122, (2012), 529-37; Mao, R. et al. *J Virol*, 85, (2011), 1048-57). All HBV viral mRNAs are capped and polyadenylated, and then exported to the cytoplasm for translation. In the cytoplasm, the assembly of new virions is initiated and nascent pgRNA is packaged with viral Pol so that reverse transcription of pgRNA, via a single stranded DNA intermediate, into RC DNA can commence. The mature nucleocapsids containing RC DNA are enveloped with cellular lipids and viral L, M, and S proteins and then the infectious HBV particles are then released by budding at the intracellular membrane (Locarnini, S. *Semin Liver Dis*, (2005), 25 Suppl 1, 9-19). Interestingly, non-infectious particles are also produced that greatly outnumber the infectious virions. These empty, enveloped particles (L, M and S) are referred to as subviral particles. Importantly, since subviral particles share the same envelope proteins and as infectious particles, it has been surmised that they act as decoys to the host immune system and have been used for HBV vaccines. The S, M, and L envelope proteins are expressed from a single ORF that contains three different start codons. All three proteins share a 226aa sequence, the S-domain, at their C-termini. M and L have additional pre-S domains, Pre-S2 and Pre-S2 and Pre-S1, respectively. However, it is the S-domain that has the HBsAg epitope (Lambert, C. & R. Prange. *Virol J*, (2007), 4, 45).

The control of viral infection needs a tight surveillance of the host innate immune system which could respond within minutes to hours after infection to impact on the initial growth of the virus and limit the development of a chronic and persistent infection. Despite the available current treatments based on IFN and nucleos(t)ide analogues, the Hepatitis B virus (HBV) infection remains a major health problem worldwide which concerns an estimated 350 million chronic carriers who have a higher risk of liver cirrhosis and hepatocellular carcinoma.

The secretion of antiviral cytokines in response to HBV infection by the hepatocytes and/or the intra-hepatic immune cells plays a central role in the viral clearance of infected liver. However, chronically infected patients only display a weak immune response due to various escape strategies adopted by the virus to counteract the host cell recognition systems and the subsequent antiviral responses.

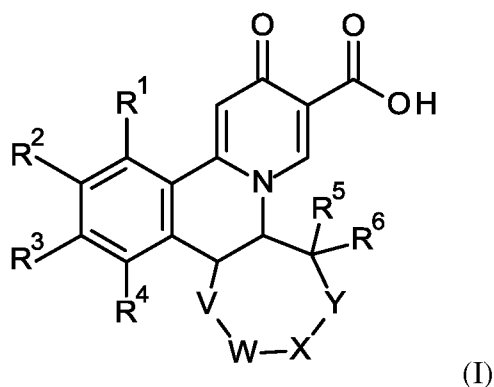
Many observations showed that several HBV viral proteins could counteract the initial host cellular response by interfering with the viral recognition signaling system and subsequently the interferon (IFN) antiviral activity. Among these, the excessive secretion of HBV empty subviral particles (SVPs, HBsAg) may participate to the maintenance of the immunological tolerant state observed in chronically infected patients (CHB). 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; Fiscaro 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 Gastroenterology*, (2013), Article ID 935295).

HBsAg quantification is a significant biomarker for prognosis and treatment response in chronic hepatitis B. However the achievement of HBsAg loss and seroconversion is rarely observed in chronically infected patients but remains the ultimate goal of therapy. Current therapy such as Nucleos(t)ide analogues are molecules that inhibit HBV DNA synthesis but are not directed at reducing HBsAg level. Nucleos(t)ide analogs, even with prolonged therapy, have demonstrated rates of HBsAg clearance comparable to those observed naturally (between -1%-2%) (Janssen et al. *Lancet*, (2005), 365, 123-9; Marcellin et al. *N. Engl. J. Med.*, (2004), 351, 1206-17; Buster et al. *Hepatology*, (2007), 46, 388-94). 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).

SUMMARY OF THE INVENTION

5 The present invention relates to compounds of formula I,



wherein

R^1 , R^2 , R^3 and R^4 are independently selected from hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, halogen, cyano, amino, C_{1-6} alkylamino, di C_{1-6} alkylamino, pyrrolidinyl and OR^7 ;

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

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

R^7 is hydrogen; C_{1-6} alkyl; halo C_{1-6} alkyl; C_{3-7} cycloalkyl C_{1-6} alkyl; phenyl C_{1-6} alkyl; cyano C_{1-6} alkyl; hydroxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; carboxy C_{1-6} alkyl; C_{1-6} alkoxycarbonyl C_{1-6} alkyl; C_{1-6} alkylsulfanyl C_{1-6} alkyl; C_{1-6} alkylsulfonyl C_{1-6} alkyl; amino C_{1-6} alkyl; C_{1-6} alkylamino C_{1-6} alkyl; di C_{1-6} alkylamino C_{1-6} alkyl; C_{1-6} alkylcarbonylamino C_{1-6} alkyl; C_{1-6} alkylsulfonylamino C_{1-6} alkyl; C_{1-6} alkoxycarbonylamino C_{1-6} alkyl; or heterocycloalkyl C_{1-6} alkyl, wherein heterocycloalkyl is *N*-containing monocyclic heterocycloalkyl;

One of V, W, X and Y is selected from CR^8R^9 , O, S, SO_2 and NR^{10} , the others of V, W, X and Y are independently selected from a bond and CR^8R^9 , wherein

20 R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

R¹⁰ is phenylC₁₋₆alkoxycarbonyl, phenylC₁₋₆alkylcarbonyl, phenylC₁₋₆alkylsulfonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyl, or C₁₋₆alkylsulfonyl; or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

5 **DETAILED DESCRIPTION OF THE INVENTION**

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, *tert*-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl, isopropyl and *tert*-butyl.

The term “C₃₋₇cycloalkyl”, alone or in combination, 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 “C₃₋₇cycloalkyl” groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term “C₁₋₆alkoxy” alone or in combination signifies a group C₁₋₆alkyl-O-, wherein the “C₁₋₆alkyl” is as defined above; examples for C₁₋₆alkoxy are methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy and the like. Particular “C₁₋₆alkoxy” groups are methoxy and ethoxy and more particularly methoxy.

The term “halogen” means fluorine, chlorine, bromine or iodine.

The term “haloC₁₋₆alkyl” denotes a C₁₋₆alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of “haloC₁₋₆alkyl” include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 3,3- difluoropropyl, 2-fluoroethyl, 2,2- difluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl or trifluoromethyl. Particular “haloC₁₋₆alkyl” group is difluoromethyl or trifluoromethyl.

The term “monocyclic heterocycloalkyl” is a monovalent saturated or partly unsaturated monocyclic ring system of 4 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, azetidiny, 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 piperidinyl, morpholinyl, 2-oxo-pyrrolidinyl, and pyrrolidinyl.

The term “*N*-containing monocyclic heterocycloalkyl” is a “monocyclic heterocycloalkyl” as defined above wherein at least one of the heteroatoms is N. Examples for “*N*-containing monocyclic heterocycloalkyl” are aziridinyl, azetidiny, pyrrolidinyl, 2-oxo-pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Particular “*N*-containing monocyclic heterocycloalkyl” groups are piperidinyl, morpholinyl, 2-oxo-pyrrolidinyl and pyrrolidinyl.

The term “amino” denotes a group of the formula -NR'R” wherein R' and R” are independently hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₇cycloalkyl, heteroC₃₋₇cycloalkyl, aryl or heteroaryl. Alternatively, R' and R”, together with the nitrogen to which they are attached, can form a heteroC₃₋₇cycloalkyl.

The term “carbonyl” alone or in combination refers to the group -C(O)-.

The term “cyano” alone or in combination refers to the group -CN.

The term “C₁₋₆alkylsulfanyl” denotes the group -S-R', wherein R' is a C₁₋₆alkyl group as defined above.

The term “C₁₋₆alkylsulfonyl” denotes a group -SO₂-R', wherein R' is a C₁₋₆alkyl group as defined above. Examples of C₁₋₆alkylsulfonyl include methylsulfonyl and ethylsulfonyl.

The term “enantiomer” denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term “diastereomer” denotes 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, and reactivities.

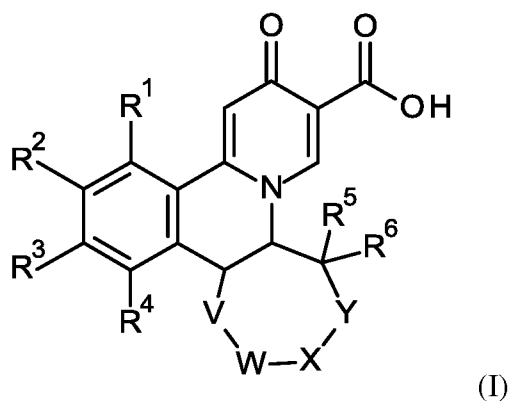
The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those

derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., *et al.*, Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., *et al.* Particular are the sodium salts of the compounds of formula I.

Compounds of the general formula I 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.

15 INHIBITORS OF HBsAg

The present invention provides (i) novel compounds having the general formula I,



wherein

R^1 , R^2 , R^3 and R^4 are independently selected from hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, halogen, cyano, amino, C_{1-6} alkylamino, di C_{1-6} alkylamino, pyrrolidinyl and OR^7 ;

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

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

R^7 is hydrogen; C_{1-6} alkyl; halo C_{1-6} alkyl; C_{3-7} cycloalkyl C_{1-6} alkyl; phenyl C_{1-6} alkyl; cyano C_{1-6} alkyl; hydroxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; carboxy C_{1-6} alkyl; C_{1-6} alkoxycarbonyl C_{1-6} alkyl;

C_{1-6} alkylsulfanyl C_{1-6} alkyl; C_{1-6} alkylsulfonyl C_{1-6} alkyl; amino C_{1-6} alkyl; C_{1-6} alkylamino C_{1-6} alkyl; di C_{1-6} alkylamino C_{1-6} alkyl; C_{1-6} alkylcarbonylamino C_{1-6} alkyl; C_{1-6} alkylsulfonylamino C_{1-6} alkyl;

C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl; or heterocycloalkylC₁₋₆alkyl, wherein heterocycloalkyl is *N*-containing monocyclic heterocycloalkyl;

One of V, W, X and Y is selected from CR⁸R⁹, O, S, SO₂ and NR¹⁰, the others of V, W, X and Y are independently selected from a bond and CR⁸R⁹, wherein

- 5 R⁸ is hydrogen or C₁₋₆alkyl;
 R⁹ is hydrogen or C₁₋₆alkyl;
 R¹⁰ is phenylC₁₋₆alkoxycarbonyl, phenylC₁₋₆alkylcarbonyl, phenylC₁₋₆alkylsulfonyl,
 C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyl, or C₁₋₆alkylsulfonyl;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

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Another embodiment of present invention is (ii) a compound of formula I, wherein

- R¹ is hydrogen;
 R² is halogen or C₁₋₆alkoxy;
 R³ is selected from C₁₋₆alkyl, pyrrolidinyl or OR⁷, wherein
 15 R⁷ is hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, phenylC₁₋₆alkyl,
 cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxyC₁₋₆alkyl, C₁₋₆
 alkoxycarbonylC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆
 alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆
 alkoxycarbonylaminoC₁₋₆alkyl, morpholinylC₁₋₆alkyl, pyrrolidinylC₁₋₆alkyl or (2-oxo-
 20 pyrrolidinyl)C₁₋₆alkyl;
 R⁴ is hydrogen;
 R⁵ is hydrogen or C₁₋₆alkyl;
 R⁶ is hydrogen or C₁₋₆alkyl;

V and Y are CH₂;

- 25 X is selected from a bond, CH₂, O, S, SO₂ and phenylC₁₋₆alkoxycarbonylamino when W is a
 bond; or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

- 30 A further embodiment of present invention is (iii) a compound of formula I, wherein

R¹ is hydrogen;
 R² is chloro or methoxy;
 R³ is selected from methyl, ethyl, propyl, pyrrolidinyl, hydroxy, methoxy, difluoroethoxy,

trifluoroethoxy, cyclopropylmethoxy, benzyloxy, cyanopropoxy, hydroxypropoxy, hydroxyhexyloxy, hydroxydimethylpropoxy, methoxyethoxy, methoxypropoxy, carboxypropoxy, ethoxycarbonylpropoxy, methylsulfanylpropoxy, methylsulfonylpropoxy, aminohexyloxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy, *tert*-

5 butoxycarbonylaminohexyloxy, morpholinylpropoxy, pyrrolidinylpropoxy and (2-oxo-pyrrolidinyl)propoxy;

R⁴ is hydrogen;

R⁵ is hydrogen or methyl;

R⁶ is hydrogen or methyl;

10 V and Y are CH₂;

X is selected from a bond, CH₂, O, S, SO₂ and phenylmethoxycarbonylamino when W is a bond; or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

15

Another embodiment of present invention is (iv) a compound of formula I, wherein

R¹ is hydrogen;

R² is C₁₋₆alkoxy;

R³ is selected from C₁₋₆alkyl, pyrrolidinyl or OR⁷, wherein R⁷ is hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, phenylC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxyC₁₋₆alkyl, C₁₋₆alkoxycarbonylC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl, morpholinylC₁₋₆alkyl, pyrrolidinylC₁₋₆alkyl or (2-oxo-pyrrolidinyl)C₁₋₆alkyl;

25 R⁴ is hydrogen;

R⁵ is C₁₋₆alkyl;

R⁶ is C₁₋₆alkyl;

V and Y are CH₂;

W is a bond;

30 X is a bond;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

A further embodiment of present invention is (v) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R² is methoxy, and all remaining substituents have the significances given herein before.

5 A further embodiment of present invention is (vi) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R³ is OR⁷, wherein R⁷ is C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl or morpholinylC₁₋₆alkyl; and all remaining substituents have the significances given herein before.

A further embodiment of present invention is (vii) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer, or diastereomer thereof, wherein R³ is selected from methoxy, difluoroethoxy, trifluoroethoxy, cyclopropylmethoxy, hydroxypropoxy, hydroxyhexyloxy, hydroxydimethylpropoxy, methoxyethoxy, methoxypropoxy, methylsulfanylpropoxy, methylsulfonylpropoxy, aminohexyloxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy, *tert*-butoxycarbonylaminohexyloxy or morpholinylpropoxy, and all remaining substituents have the significances given herein before.

A further embodiment of present invention is (viii) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R⁵ is methyl; R⁶ is methyl, and all remaining substituents have the significances given herein before.

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Another embodiment of present invention is (ix) a compound of formula I, wherein

- R¹ is hydrogen;
R² is halogen or C₁₋₆alkoxy;
R³ is OR⁷; wherein R⁷ is phenylC₁₋₆alkyl or C₁₋₆alkoxyC₁₋₆alkyl;
30 R⁴ is hydrogen;
R⁵ is hydrogen;
R⁶ is hydrogen;
V and Y are CH₂;

X is selected from CH₂, O, S, SO₂ and phenylC₁₋₆alkoxycarbonylamino when W is a bond; or
X is CH₂ when W is CH₂;
or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

- 5 A further embodiment of present invention is (x) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R² is chloro or methoxy, and all remaining substituents have the significances given herein before.

- 10 A further embodiment of present invention is (xi) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R³ is benzyloxy or methoxypropoxy, and all remaining substituents have the significances given herein before.

- 15 A further embodiment of present invention is (xii) a compound of formula I as defined above, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein X is CH₂ or S when W is a bond, or X is CH₂ when W is CH₂, and all remaining substituents have the significances given herein before.

- Another embodiment of present invention is (xiii) a compound of formula I, wherein
- 20 R¹ is hydrogen;
R² is halogen or C₁₋₆alkoxy;
R³ is selected from C₁₋₆alkyl, pyrrolidinyl or OR⁷, wherein R⁷ is haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl or morpholinylC₁₋₆alkyl;
- 25 R⁴ is hydrogen;
R⁵ is hydrogen or C₁₋₆alkyl;
R⁶ is hydrogen or C₁₋₆alkyl;
V and Y are CH₂;
X is a bond or S when W is a bond, or
- 30 X is CH₂ when W is CH₂;
or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

Another embodiment of present invention is (xiv) a compound of formula I, wherein

R¹ is hydrogen;

R² is chloro or methoxy;

R³ is selected from ethyl, pyrrolidinyl, difluoroethoxy, trifluoroethoxy,

5 hydroxydimethylpropoxy, methoxypropoxy, methylsulfonylpropoxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy and morpholinylpropoxy;

R⁴ is hydrogen;

R⁵ is hydrogen or methyl;

R⁶ is hydrogen or methyl;

10 V and Y are CH₂;

X is a bond or S when W is a bond, or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

15 A further embodiment of the present invention is (xv) *cis*-isomer of formula I, or pharmaceutically acceptable salts, or enantiomers or diastereomers thereof, wherein R¹ to R⁶, V, W, X and Y have the significances given herein before.

Another embodiment of the present invention is (xvi) *trans*-isomer of formula I, or
20 pharmaceutically acceptable salts, or enantiomers or diastereomers thereof, wherein R¹ to R⁶, V, W, X and Y have the significances given herein before.

Particular compounds of formula I according to the invention are the following:

Trans-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-
25 hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-
hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-
hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

30 (*3aS*, *12bR*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-
hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

(*3aR*, *12bS*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-
hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10,11-dimethoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

5 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

10 *Cis*-11-(cyclopropylmethoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-11-(2-methoxyethoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-(3-cyanopropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

15 *Cis*-11-(3-hydroxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

20 *Cis*-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(pyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(2-oxopyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

25 *Cis*-11-(4-ethoxy-4-oxobutoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-(3-carboxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

30 *Cis*-10-methoxy-3,3-dimethyl-11-(3-(methylthio)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-hydroxyhexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-((tert-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

5 *Cis*-11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

10 *Cis*-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Trans-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

Cis-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

15 *Trans*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1H-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid;

Cis-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1H-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid;

20 *Trans*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid;

Cis-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid;

25 *Cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

30 *Cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid 2,2-dioxide;

Cis-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

- 5 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-propyl-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;
- Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;
- or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

10

More particularly, the invention relates to the following compounds of formula I:

Trans-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

- 15 *Cis*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

- 20 *Cis*-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;
- Cis*-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

- 25 *Cis*-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

- 30 *Cis*-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

Cis-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

Cis-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

5 or pharmaceutically acceptable salts, or enantiomers thereof.

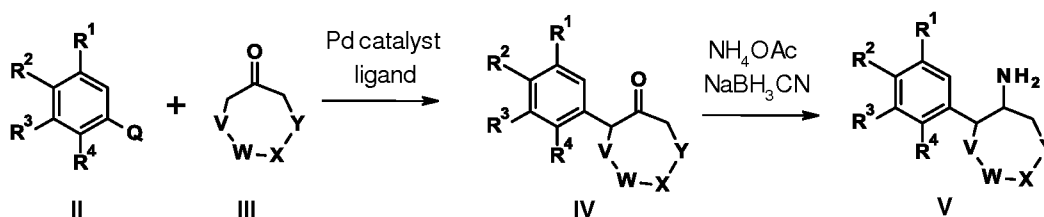
SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R¹ to R⁶, V, W, X and Y are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

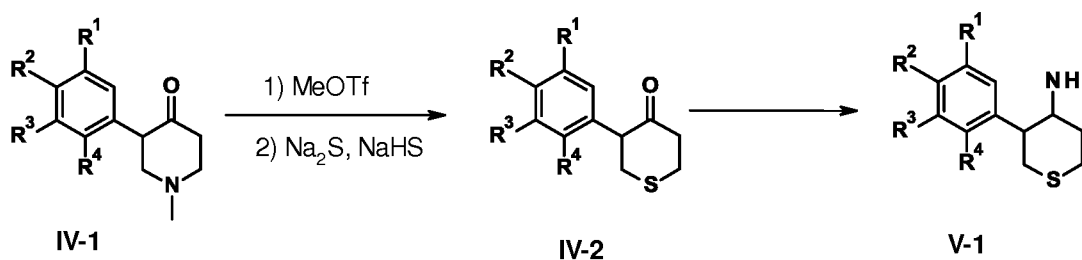
15 General synthetic route for intermediates (Scheme 1)

Scheme 1

Method 1)



Method 2)



20 Intermediates can be prepared according to Scheme 1, wherein Q is Br or I; None of V, W, X and Y is S.

By Method 1) Coupling reaction of Halide II with Ketone III affords Compound IV. The reaction can be carried out in the presence of a Pd catalyst such as Pd₂(dba)₃, Pd(PPh₃)₄ or PdCl₂(PPh₃)₂, a ligand such as Xantphos, and a suitable base such as *tert*-BuONa, Na₂CO₃ or

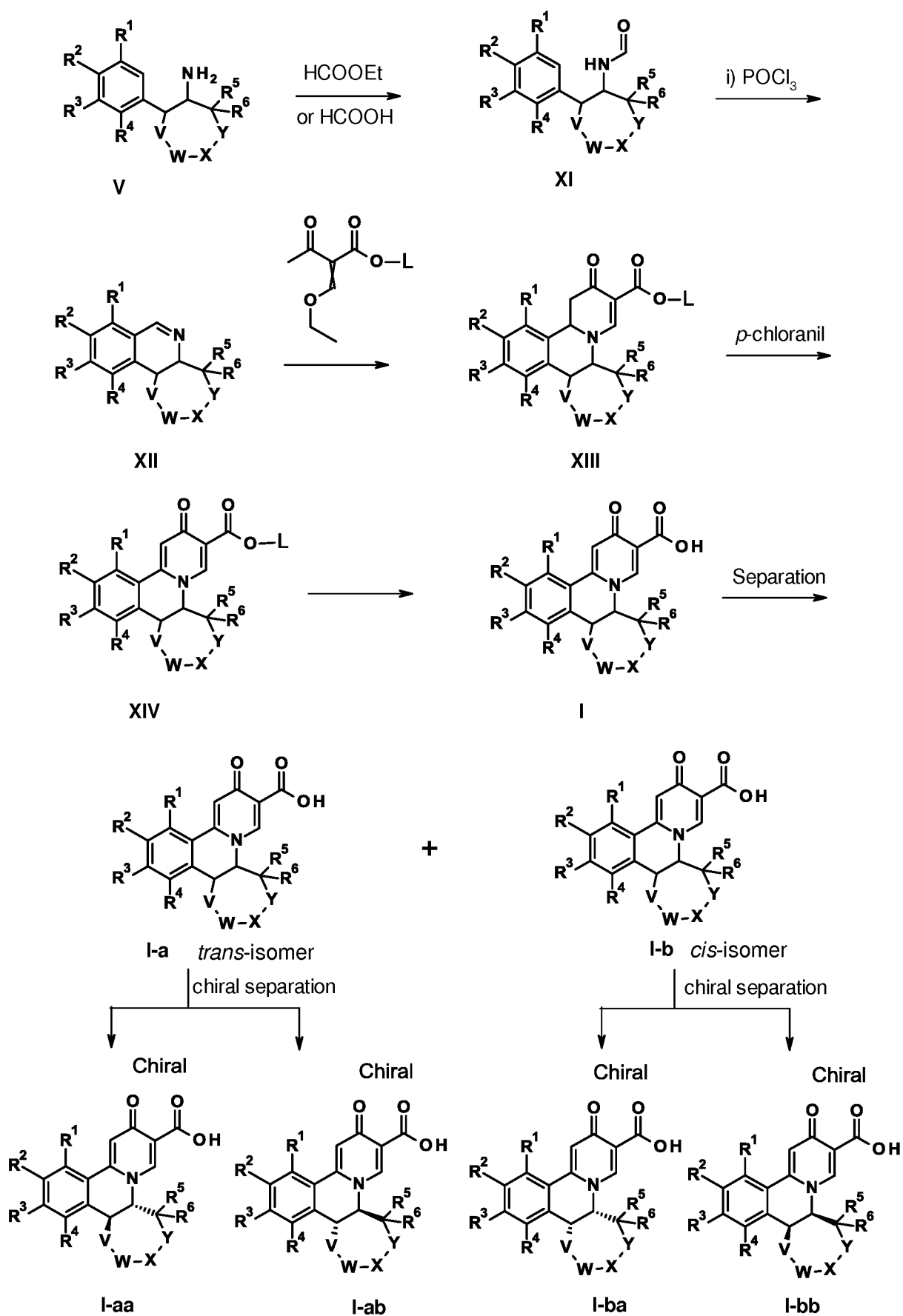
Cs₂CO₃, in a suitable solvent such as THF, toluene or 1,4-dioxane at a temperature between room temperature and 130 °C. Reductive amination of Compound **IV** affords Amine **V**. The reaction can be carried out by using NH₄OAc and NaBH₃CN in a suitable solvent such as methanol.

- 5 **By Method 2)**, quaternization of Compound **IV-1** with methyl trifluoromethanesulfonate followed by heating with NaHS, Na₂S and water affords Compound **IV-2**. The quaternization reaction can be carried out in a suitable solvent such as isobutyl methylketone at 0 °C to room temperature. Reductive amination of Compound **IV-2** by using NH₄OAc and NaBH₃CN affords Compound **V-1**.

10

General synthetic route for Compounds **I**, **Ia**, **Ib**, **Iaa**, **Iab**, **Iba** and **Ibb** (Scheme 2)

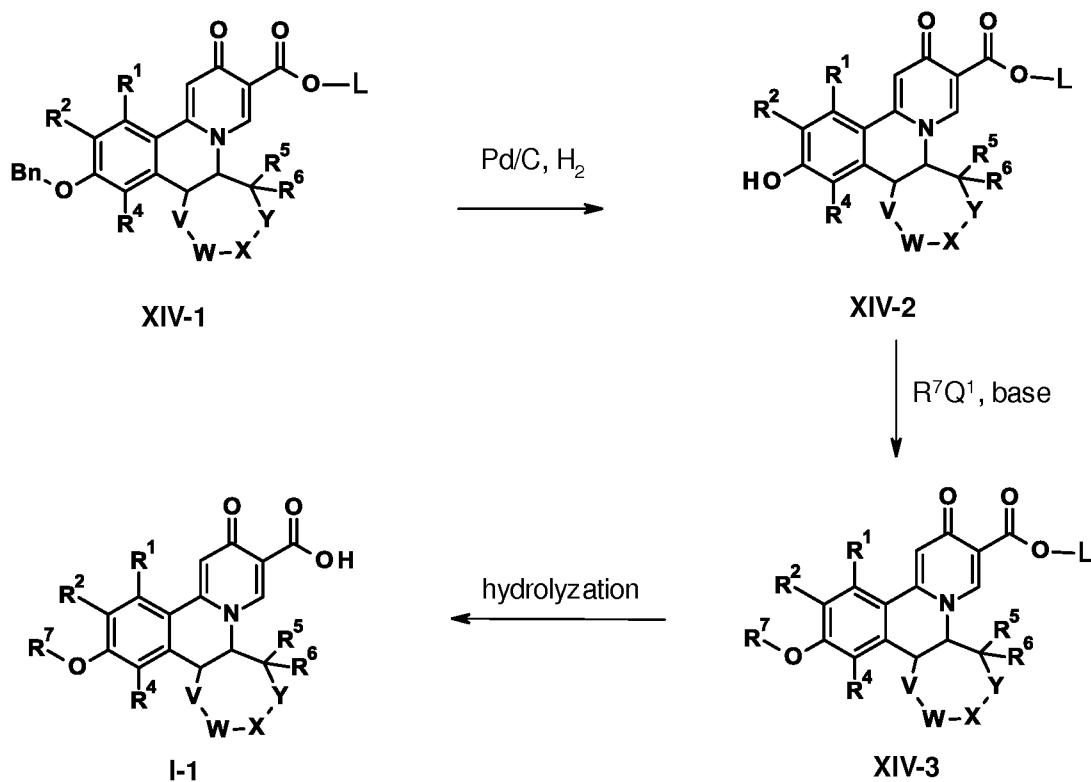
Scheme 2



The compound of formula **I**, **Ia**, **Ib**, **Iaa**, **Iab**, **Iba** and **Ibb** can be prepared according to Scheme 2, wherein L is C₁₋₆alkyl. Compound **V** is heated with ethyl formate or formic acid in a solvent such as ethanol or dioxane to afford Compound **XI**. Compound **XI** is treated with POCl₃ in a suitable solvent such as acetonitrile or DCM at a temperature between room temperature and 100 °C to give Compound **XII**. Compound **XII** reacts with C₁₋₆alkyl 2-(ethoxymethylene)-3-oxo-butanoate in a solvent such as ethanol to give Compound **XIII**. After dehydrogenation of **XIII** by *p*-chloranil, compound **XIV** is obtained. Hydrolyzation of **XIV** by lithium hydroxide or sodium hydroxide in a suitable solvent such as THF/H₂O, EtOH/H₂O or MeOH/H₂O affords Compound **I**. Compound **I** can be separated by crystallization, or column chromatography, or preparative HPLC to give **Ia** and **Ib**, which can be further separated by chiral HPLC to give Compounds **Iaa**, **Iab** and **Iba**, **Ibb** respectively.

General synthetic route for Compounds **I-1** (Scheme 3)

Scheme 3



15

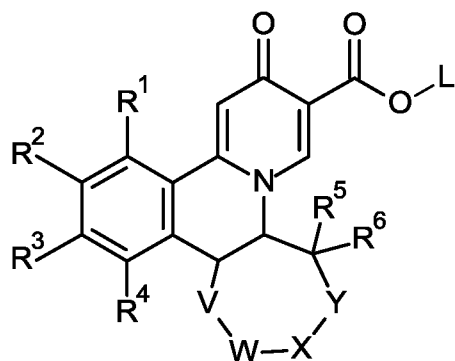
The compound of formula **I-1** can be prepared according to Scheme 3, wherein Q¹ is halogen, -O-S(O)₂CH₃ or -O-S(O)₂-(4-CH₃-Ph); L is C₁₋₆alkyl. Debenzylation of Compound **XIV-1** by hydrogenation is carried out in the presence of Pd/C in a solvent such as ethanol, THF, methanol to afford **XIV-2**. Then **XIV-2** reacts with halide, mesylate or tosylate in the presence of a base such as K₂CO₃ in a solvent such as acetone or DMF to give Compound **XIV-3**.

20

Hydrolyzation of **XIV-3** by lithium hydroxide or sodium hydroxide in a suitable solvent such as THF/H₂O, EtOH/H₂O or MeOH/H₂O affords **I-1**.

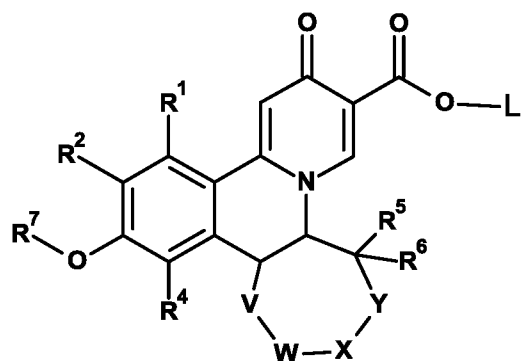
This invention also relates to a process for the preparation of a compound of formula I comprising

(a) hydrolysis of a compound of formula (A) by using a base,



(A); or

(b) hydrolysis of a compound of formula (B) by using a base,



(B);

10 wherein R¹ to R⁷, V, W, X and Y are defined above unless otherwise indicated, L is C₁₋₆alkyl.

In step (a) and (b) a base is for example lithium hydroxide or sodium hydroxide.

A compound of formula I when manufactured according to the above process is also an object of the invention.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

The invention also relates to a compound of formula I for use as therapeutically active substance.

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at
5 the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another
10 embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being
15 treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit HBsAg. For example, such amount may be below the
20 amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01 to 100 mg/kg, alternatively about 0.01 to 100 mg/kg of patient body weight per day, with the typical initial range of
25 compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 0.1 to about 1000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including
30 oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components
5 conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art
10 and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical
15 Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or
pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product
20 (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 0.1 to 1000 mg of the compound of the invention compounded with about 0 to 2000 mg anhydrous lactose, about 0 to 2000 mg sodium croscarmellose, about 0 to 2000 mg polyvinylpyrrolidone (PVP) K30, and
25 about 0 to 2000 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 0.1 to 1000 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a
30 tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

The following example A and B illustrate typical compositions of the present invention, but serve merely as representative thereof.

Example A

A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	<u>Per capsule</u>
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention can inhibit HBsAg production or secretion and inhibit HBV gene expression. Accordingly, the compounds of the invention are useful for the treatment or prophylaxis of HBV infection.

5 The invention relates to the use of a compound of formula I for the inhibition of HBsAg production or secretion.

The invention relates to the use of a compound of formula I for the inhibition of HBV DNA production.

The invention relates to the use of a compound of formula I for the inhibition of HBV gene expression.

10 The invention relates to the use of a compound of formula I for the treatment or prophylaxis of HBV infection.

The use of a compound of formula I for the preparation of medicaments useful in the treatment or prophylaxis diseases that are related to HBV infection is an object of the invention.

15 The invention relates in particular to the use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

Another embodiment includes a method for the treatment or prophylaxis of HBV infection, which method comprises administering an effective amount of a compound of Formula I, a stereoisomer, tautomer, prodrug, conjugates or pharmaceutically acceptable salt thereof.

20 **BRIEF DESCRIPTION OF THE FIGURE**

Figure 1. X-ray structure of Example 4

EXAMPLES

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

Abbreviations used herein are as follows:

μL:	microliter
μm:	micrometer
30 μM:	micromoles per liter

	CDCl ₃ :	deuterated chloroform
	DME:	1,2-dimethoxyethane
	DMSO- <i>d</i> ₆ :	deuterated dimethylsulfoxide
	g:	gram
5	h:	hour
	hrs:	hours
	IC ₅₀ :	the half maximal inhibitory concentration
	HPLC:	high performance liquid chromatography
	LC/MS:	liquid chromatography/mass spectrometry
10	LiOH·H ₂ O:	lithium hydroxide monohydrate
	M:	molarity
	mg:	milligram
	MHz:	megahertz
	min:	minute
15	mM:	millimoles per liter
	mm:	millimeter
	mmol:	millimole
	MS (ESI):	mass spectroscopy (electron spray ionization)
	NaOH:	sodium hydroxide
20	Na ₂ SO ₄ :	sodium sulfate
	NaBH ₃ CN:	sodium cyanotrihydroborate
	NaHCO ₃ :	sodium hydrogen carbonate
	nM:	nanomoles per liter
	nm:	nanometer
25	NMR:	nuclear magnetic resonance
	obsd.	observed
	rt:	room temperature
	Pd/C:	palladium on activated carbon
	Pd(PPh ₃) ₄ :	tetrakis(triphenylphosphine)palladium(0)
30	Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ :	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
	prep-HPLC:	preparative high performance liquid chromatography
	POCl ₃ :	phosphorus oxychloride

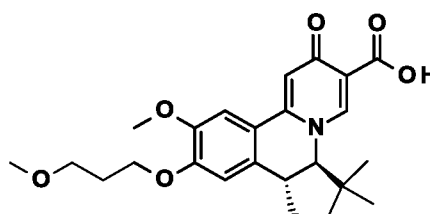
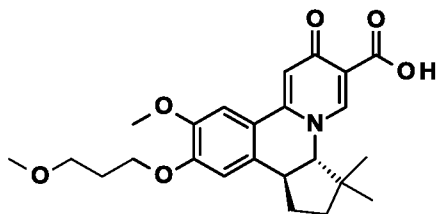
TFA: trifluoroacetic acid
 δ : chemical shift

GENERAL EXPERIMENTAL CONDITIONS

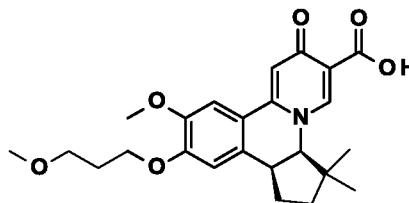
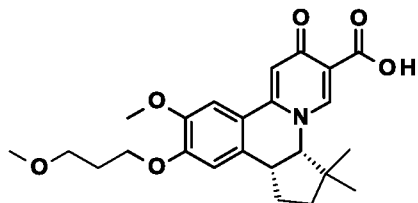
- 5 Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 μ M; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.
- 10 Intermediates and final compounds were purified by preparative HPLC on reversed phase column using X BridgeTM Perp C₁₈ (5 μ m, OBDTM 30 $\times$ 100 mm) column or SunFireTM Perp C₁₈ (5 μ m, OBDTM 30 $\times$ 100 mm) column.
- Chiral separation was carried out on a preparative SFC 80Q using AD-H, 250 $\times$ 20mm I.D. column. Condition: A: CO₂; B: 0.5% diethyl amine in MeOH; gradient: B 40%.
- 15 LC/MS spectra were obtained using an Acquity Ultra Performance LC - 3100 Mass Detector or Acquity Ultra Performance LC - SQ Detector. Standard LC/MS conditions were as follows (running time 3 minutes):
- Acidic condition: A: 0.1% formic acid in H₂O; B: 0.1% formic acid in acetonitrile;
Basic condition: A: 0.05% NH₃·H₂O in H₂O; B: acetonitrile;
- 20 Neutral condition: A: H₂O; B: acetonitrile.
- Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion (M+H)⁺.
- The microwave assisted reactions were carried out in a Biotage Initiator Sixty or CEM Discover.
- 25 NMR Spectra were obtained using Bruker Avance 400MHz.
- A single crystal was mounted in a loop and cooled to 160 K in a nitrogen stream. Data were collected on a Gemini R Ultra diffractometer (Oxford Diffraction, UK) with Cu-K-alpha-radiation (1.54178Å) and processed with the CrysAlis-package. Structure solution and refinement was performed using the ShelXTL software (Bruker AXS, Karlsruhe).
- 30 All reactions involving air-sensitive reagents were performed under an argon atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

Example 1 and 2: *Trans*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid and *cis*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

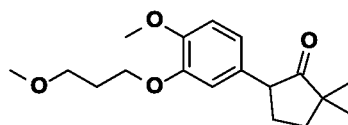


Example 1



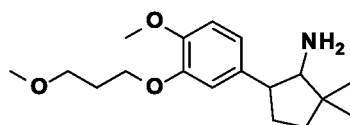
Example 2

Step 1: Preparation of 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentanone



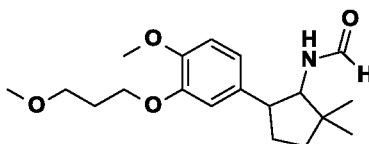
To a mixture of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (2.74 g, 10 mmol), tris(dibenzylideneacetone)dipalladium(0) (92 mg, 0.1 mmol), 2-dicyclohexylphosphino-2'-methylbiphenyl (73 mg, 0.2 mmol) and *t*-BuONa (1.92 g, 20 mmol) in THF (20 mL) was added 2,2-dimethylcyclopentanone (2.24 g, 20 mmol). The resulting mixture was heated at 50 °C for 1 hr under microwave irradiation and argon atmosphere. After being cooled to rt, the mixture was filtered. The filter cake was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentanone (2.23 g) as a yellow oil, which was directly used in the next step without further purification.

Step 2: Preparation of 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentanamine



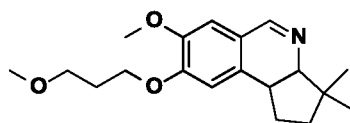
To a mixture of crude 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-
 5 cyclopentanone (2.51 g, 7.3 mmol) and ammonium acetate (8.43 g, 109.5 mmol) in ethanol (30 mL) was added NaBH₃CN (920 mg, 14.6 mmol). The resulting mixture was heated at 100 °C with stirring for 30 hrs under argon atmosphere. The reaction mixture was diluted with water, then basified with 1 M NaOH aqueous solution to pH=10-12. The resulting mixture was stirred at rt for 30 min, then extracted with CH₂Cl₂ for three times. The combined organic layers were
 10 washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give crude 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentanamine (2.17 g) as a yellow oil, which was directly used in the next step without further purification.

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



15 A solution of crude 5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentanamine (2.17 g, 7.1 mmol) and formic acid (0.3 mL) in ethyl formate (30 mL) was heated at 90 °C for 6 hrs. The mixture was concentrated under reduced pressure to give crude *N*-[5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-cyclopentyl]formamide (2.47 g) as a
 20 yellow oil which was directly used in the next step without further purification.

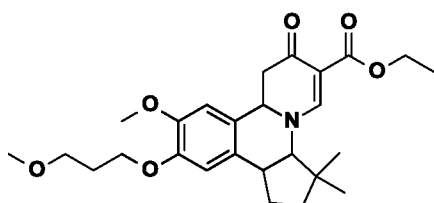
Step 4: Preparation of 7-methoxy-8-(3-methoxypropoxy)-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline



To a solution of crude *N*-[5-[4-methoxy-3-(3-methoxypropoxy)phenyl]-2,2-dimethyl-
 25 cyclopentyl]formamide (2.47 g, 7.1 mmol) in CH₃CN (20 mL) was added POCl₃ (1.09 g, 7.1 mmol). The reaction mixture was stirred at rt for 14 hrs, then concentrated under reduced pressure. The residue was dissolved in CH₃CN and then basified with ammonium hydroxide to

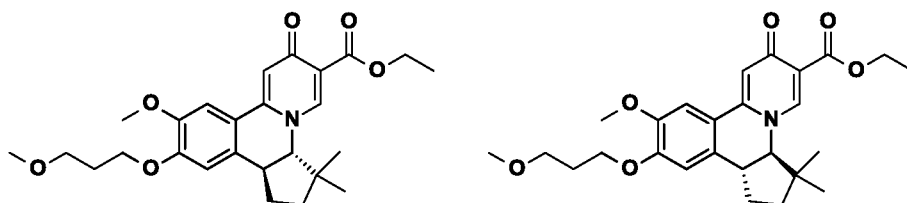
pH=10 at 0 °C. The mixture was allowed to warm to rt and stirred for 1 hr at rt. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 7-methoxy-8-(3-methoxypropoxy)-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline (1.98 g) as a yellow oil which was directly used in the next step without further purification.

Step 5: Preparation of ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate

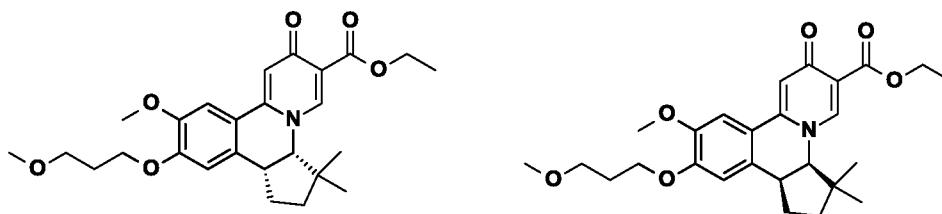


A mixture of crude 7-methoxy-8-(3-methoxypropoxy)-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline (1.98 g, 6.25 mmol) and ethyl 2-(ethoxymethylene)-3-oxobutanoate (3.49 g, 18.75 mmol) in ethanol (20 mL) was heated at 100 °C with stirring for 16 hrs. The mixture was concentrated under reduced pressure to give crude ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (5.16 g) as a brown oil which was directly used in the next step without further purification.

Step 6: Preparation of *trans*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate and *cis*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate



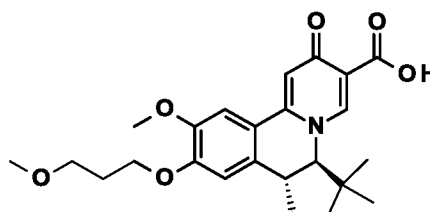
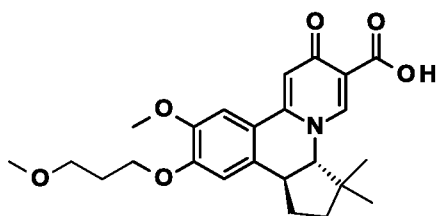
trans configuration



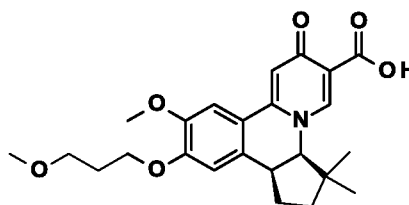
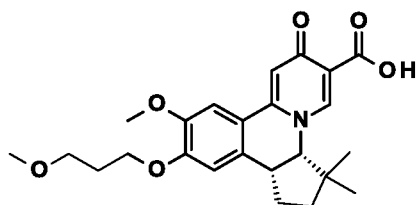
cis configuration

A mixture of crude ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (5.16 g, 6.25 mmol) and *p*-chloranil (1.54 g, 6.25 mmol) in DME (20 mL) was heated at 70 °C for 3 hrs under argon atmosphere. After being cooled to rt, the mixture was filtered. The filter cake was dried to give *trans*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (930 mg) as a yellow solid. The filtrate was concentrated to give crude *cis*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (6.13 g) as a brown oil which was directly used in the next step without further purification.

Step 7: Preparation of *trans*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid and *cis*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



Example 1



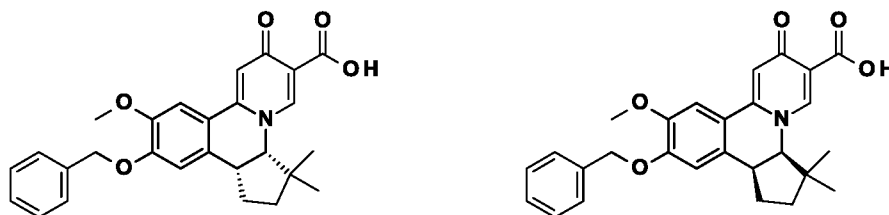
Example 2

To a solution of crude *trans*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (930 mg, 2 mmol) in methanol (8 mL) and H₂O (2 mL) was added LiOH·H₂O (672 mg, 16 mmol). The resulting mixture was stirred at rt for 3 hrs, then acidified with 1 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was treated with diethyl ether to afford *trans*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (290 mg, Example 1) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆): δ ppm

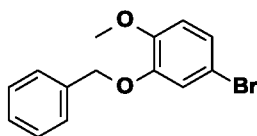
8.59 (s, 1H), 7.50 (s, 2H), 6.85 (s, 1H), 4.13 (m, 2H), 3.90 - 3.82 (m, 4H), 3.50 - 3.44 (m, 3H), 3.26 (s, 3H), 2.32 - 2.19 (m, 1H), 1.99 (quin, 2H), 1.94 - 1.77 (m, 3H), 1.47 (s, 3H), 1.24 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 428.

To a solution of crude *cis*-ethyl 10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (6.13 g, 2 mmol) in methanol (16 mL) and H₂O (4 mL) was added LiOH·H₂O (2.02 g, 48 mmol). The resulting mixture was stirred at rt for 5 hrs, then acidified with 1 M hydrochloric acid to pH=2-3, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was treated with diethyl ether to afford *cis*-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (309 mg, Example 2) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆): δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.52 (s, 1H), 7.01 (s, 1H), 4.63 (d, 1H), 4.20 - 4.06 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 3.48 (t, 2H), 3.26 (s, 3H), 2.33 - 2.19 (m, 2H), 1.98 (quin, 2H), 1.63 - 1.53 (m, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 428.

Example 3: *Cis*-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

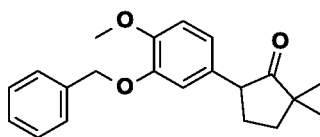


Step 1: Preparation of 2-benzyloxy-4-bromo-1-methoxy-benzene



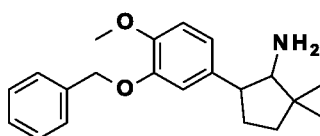
To a mixture of 5-bromo-2-methoxy-phenol (40.6 g, 200 mmol), K₂CO₃ (55.2 g, 400 mmol) in CH₃CN (300 mL) and DMF (100 mL) was added benzyl bromide (35.9 g, 210 mmol). The mixture was stirred at rt overnight, then partitioned between CH₂Cl₂ and water. The separated aqueous layer was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 2-benzyloxy-4-bromo-1-methoxy-benzene (62.6 g) as a yellow solid which was directly used in the next step without further purification.

Step 2: Preparation of 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanone



To a mixture of 2-benzyloxy-4-bromo-1-methoxy-benzene (53.5 g, 183 mmol),
 5 tris(dibenzylideneacetone)dipalladium(0) (3.4 g, 3.7 mmol), 2-dicyclohexylphosphino-2'-methylbiphenyl (2.7 g, 7.4 mmol) and *t*-BuONa (22.8 g, 238 mmol) in THF (600 mL) was added 2,2-dimethylcyclopentanone (24.6 g, 220 mmol). The resulting mixture was heated at 60 °C for 3.5 hrs under argon atmosphere. After being cooled to rt, the mixture was filtered. The filtrate was diluted with water and acidified with 2 M hydrochloric acid. The resulting mixture was
 10 extracted with diethyl ether for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanone (58.5 g) as a brown oil which was directly used in the next step without further purification.

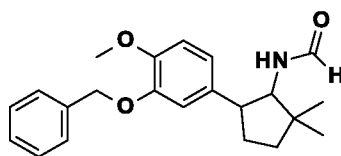
Step 3: Preparation of 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanamine



To a mixture of crude 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanone (58.5 g, 181 mmol) and ammonium acetate (209 g, 2720 mmol) in ethanol (500 mL) was added NaBH₃CN (22.8 g, 362 mmol). The resulting mixture was heated at 90 °C for 16 hrs under argon
 20 atmosphere, then to the reaction mixture were added additional ammonium acetate (69 g, 896 mmol) and NaBH₃CN (5.7 g, 90 mmol) successively. The resulting mixture was heated at 100 °C for additional 40 hrs. After being cooled to rt, the mixture was diluted with water, then basified with 2 M NaOH aqueous solution to pH=10-12, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and
 25 concentrated under reduced pressure to give crude 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanamine (60.0 g) as a yellow oil which was directly used in the next step without further purification.

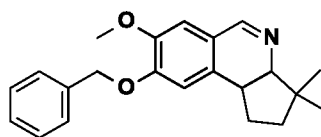
Step 4: Preparation of *N*-[5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentyl]formamide

-33-



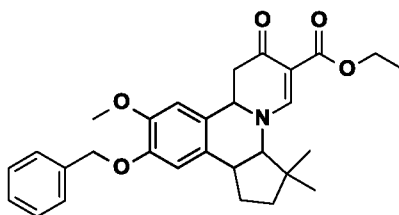
A solution of crude 5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentanamine (60.0 g, 181 mmol) and formic acid (3 mL) in ethyl formate (300 mL) was heated at 90 °C for 16 hrs. The mixture was concentrated under reduced pressure to give crude *N*-[5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentyl]formamide (61.9 g) as a yellow oil which was directly used in the next step without further purification.

Step 5: Preparation of 8-benzyloxy-7-methoxy-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline



To a solution of crude *N*-[5-(3-benzyloxy-4-methoxy-phenyl)-2,2-dimethyl-cyclopentyl]formamide (61.9 g, 175 mmol) in CH₃CN (400 mL) was added POCl₃ (26.8 g, 175 mmol). The reaction mixture was stirred at rt for 20 hrs under argon atmosphere, then concentrated under reduced pressure. The residue was dissolved in CH₃CN and then basified with ammonium hydroxide to pH=10 at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt for 1 hr, and then extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 8-benzyloxy-7-methoxy-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline (42.5 g) as a brown oil which was directly used in the next step without further purification.

Step 6: Preparation of ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate

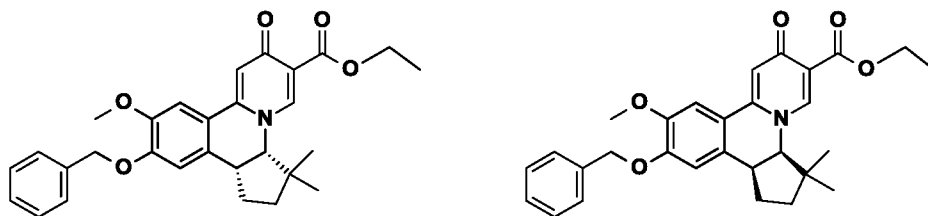


A mixture of crude 8-benzyloxy-7-methoxy-3,3-dimethyl-1,2,3a,9b-tetrahydrocyclopenta[c]isoquinoline (42.5 g, 127 mmol) and ethyl 2-(ethoxymethylene)-3-oxobutanoate (70.9 g, 381 mmol) in ethanol (400 mL) was heated at 100 °C for 48 hrs under argon

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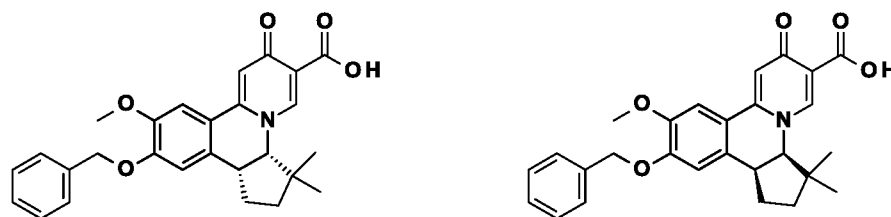
atmosphere. The mixture was concentrated under reduced pressure to give crude ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (126.8 g) as a red oil which was directly used in the next step without further purification.

5 **Step 7: Preparation of *cis*-ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate**



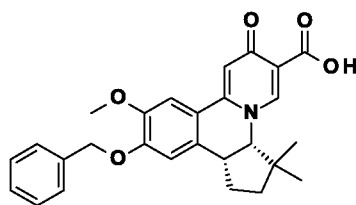
A mixture of crude ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,8,8a,12b-octahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (126.8 g, 127 mmol) and *p*-chloranil (31.2 g, 127 mmol) in DME (200 mL) was heated at 70 °C for 4 hrs. The resulting mixture was concentrated under reduced pressure, and the residue was dissolved in DME (100 mL). The resulting solution was stirred at rt for 1 h, and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in 2-methyltetrahydrofuran (300 mL). To the above solution was added saturated NaHCO₃ aqueous solution (200 mL). The resulting mixture was stirred for 30 min. The separated organic layer was washed with saturated NaHCO₃ aqueous solution (200 mL) twice and 4 M hydrochloric acid (75 mL) for three times. The combined acidic aqueous layers were basified with 4 M NaOH aqueous to pH=9 at 0 °C, and then extracted with CH₂Cl₂ (200 mL) for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give *cis*-ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (9.87 g) as a brown solid which was directly used in the next step without further purification.

20 **Step 8: Preparation of *cis*-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**

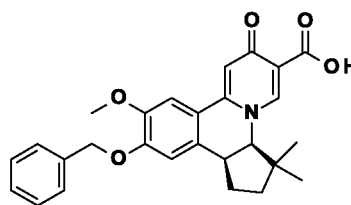


To a solution of crude *cis*-ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (2.17 g, 4.6 mmol) in methanol (16 mL) and H₂O (4 mL) was added LiOH·H₂O (773 mg, 18.4 mmol). The resulting mixture was stirred at rt for 3 hrs, then diluted with water and acidified with 1 M hydrochloric acid to pH=2-3. The resulting mixture was stirred at rt for 30 min and filtered. The filter cake was washed with water, dried and purified by prep-HPLC to afford *cis*-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (420 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆): δ ppm 8.54 (s, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 7.50 - 7.45 (m, 2H), 7.42 (t, 2H), 7.38 - 7.33 (m, 1H), 7.12 (s, 1H), 5.30 - 5.16 (m, 2H), 4.63 (d, 1H), 3.90 (s, 3H), 3.75 (t, 1H), 2.24 (t, 2H), 1.56 (ddd, 1H), 1.30 (td, 1H), 1.16 (s, 3H), 0.38 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 446.

Example 4 and 5: (3*aS*,12*bR*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid and (3*aR*,12*bS*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



Example 4



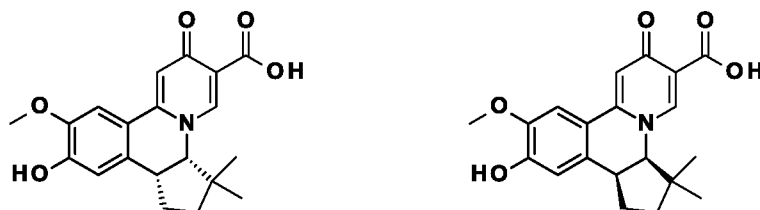
Example 5

Separation of the two enantiomers from *cis*-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid by chiral HPLC afforded (3*aS*,12*bR*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid and (3*aR*,12*bS*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid.

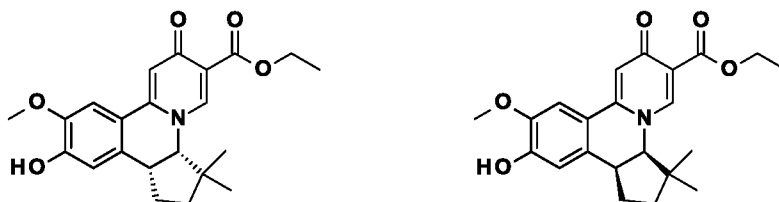
Example 4: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.50 - 7.45 (m, 2H), 7.42 (t, 2H), 7.38 - 7.33 (m, 1H), 7.12 (s, 1H), 5.31 - 5.15 (m, 2H), 4.62 (d, 1H), 3.89 (s, 3H), 3.75 (br. s., 1H), 2.23 (m, 2H), 1.63 - 1.50 (m, 1H), 1.36 - 1.24 (m, 1H), 1.15 (s, 3H), 0.37 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 446. The absolute stereochemistry was determined by the X-ray diffraction study (Figure 1).

Example 5: ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm 8.54 (s, 1H), 7.61 - 7.33 (m, 7H), 7.11 (s, 1H), 5.32 - 5.14 (m, 2H), 4.62 (m, 1H), 3.89 (s, 3H), 3.75 (br. s., 1H), 2.24 (m, 2H), 1.60 - 1.48 (m, 1H), 1.35 - 1.23 (m, 1H), 1.15 (s, 3H), 0.37 (s, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 446.

5 **Example 6: *Cis*-11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid**



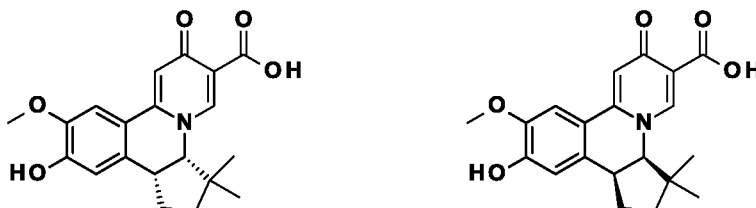
Step 1: Preparation of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate



10

A mixture of *cis*-ethyl 11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (7.7 g, 16.3 mmol) and 10 wt.% palladium on carbon (770 mg) in ethanol (300 mL) was stirred at rt for 64 hrs under hydrogen atmosphere by using a hydrogen balloon. The reaction mixture was filtered, and then the filtrate
15 was concentrated under reduced pressure to give crude *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (6.3 g) as a dark brown oil which was directly used in the next step without further purification.

Step 2: Preparation of *cis*-11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid

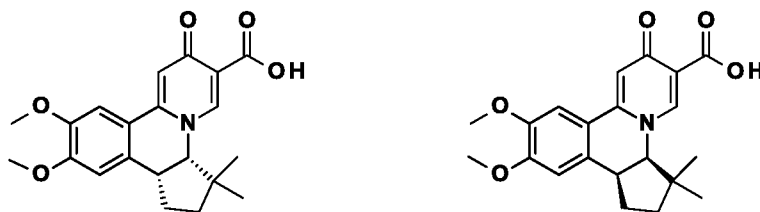


20

To a solution of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (76 mg, 0.2 mmol) in methanol (3 mL) and H_2O (1 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (34 mg, 0.8 mmol). The mixture was stirred at rt

overnight, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (9 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.51 (s, 1H), 7.53 (s, 1H), 7.51 (s, 1H), 6.85 (s, 1H), 4.59 (d, 1H), 3.89 (s, 3H), 3.75 - 3.65 (m, 1H), 2.28 - 2.08 (m, 2H), 1.63 - 1.52 (m, 1H), 1.42 - 1.30 (m, 1H), 1.15 (s, 3H), 0.39 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 356.

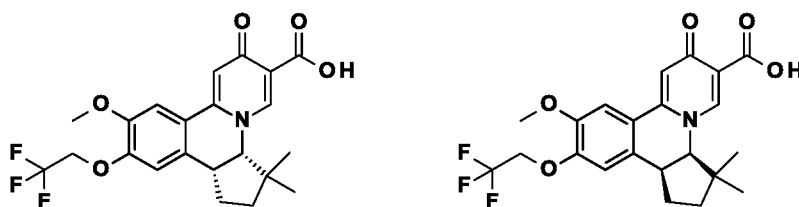
Example 7: *Cis*-10,11-dimethoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added iodomethane (207 mg, 1.8 mmol). The mixture was stirred at rt overnight. To the above mixture was added LiOH aqueous solution (0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 2 hrs, then acidified with 2 M hydrochloric acid to pH=2-3, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10,11-dimethoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (22 mg) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.59 (s, 1H), 7.52 (s, 1H), 7.01 (s, 1H), 4.64 (d, 1H), 3.90 - 3.88 (m, 3H), 3.88 - 3.86 (m, 3H), 3.81 - 3.74 (m, 1H), 2.37 - 2.21 (m, 2H), 1.59 (ddd, 1H), 1.37 (td, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 370.

Example 8: *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

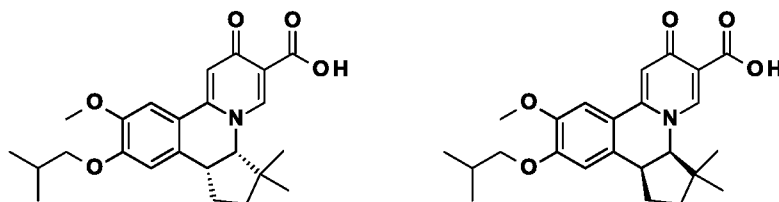
-38-



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DMF (2 mL) was added 1,1,1-trifluoro-2-iodo-ethane (315 mg, 1.5 mmol).

- 5 The resulting mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The reaction mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3, and extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified
- 10 by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (13 mg) as a white solid. ^1H NMR (400MHz, $DMSO-d_6$) δ ppm 8.56 (s, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.17 (s, 1H), 5.00 - 4.79 (m, 2H), 4.65 (d, 1H), 3.93 (s, 3H), 3.76 (t, 1H), 2.41 - 2.30 (m, 1H), 2.28 - 2.17 (m, 1H), 1.59 (ddd, 1H), 1.36 (td, 1H), 1.17 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI^+)
- 15 $[(M+H)^+]$: 438.

Example 9: *Cis*-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

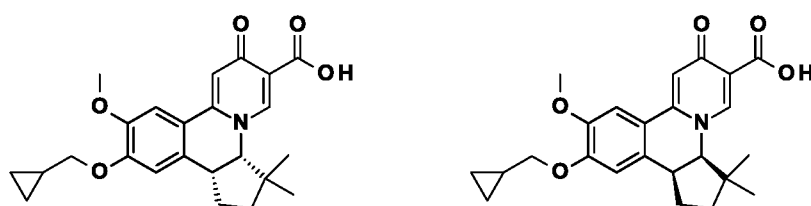


- 20 To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DMF (2 mL) was added 1-iodo-2-methyl-propane (166 mg, 0.9 mmol). The resulting mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting
- 25 mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified

by prep-HPLC to afford *cis*-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (21 mg) as a yellow solid.

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.58 (s, 1H), 7.52 (s, 1H), 6.99 (s, 1H), 4.63 (d, 1H), 3.89 (s, 3H), 3.88 - 3.80 (m, 2H), 3.76 (t, 1H), 2.37 - 2.20 (m, 2H), 2.13 - 1.99 (m, 1H), 1.58 (ddd, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 1.01 (d, 3H), 0.99 (d, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 412.

Example 10: *Cis*-11-(cyclopropylmethoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

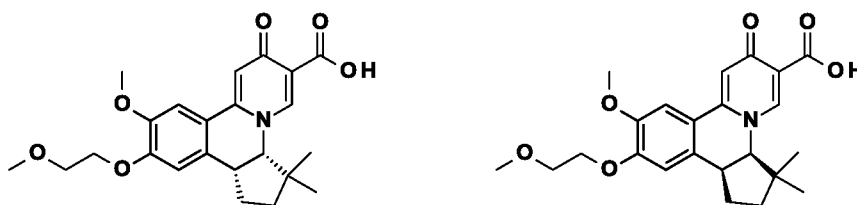


To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added bromomethylcyclopropane (122 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(cyclopropylmethoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (27 mg) as a yellow solid.

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 6.96 (s, 1H), 4.62 (d, 1H), 3.96 - 3.91 (m, 2H), 3.90 (s, 3H), 3.78 - 3.71 (m, 1H), 2.34 - 2.17 (m, 2H), 1.57 (ddd, 1H), 1.35 (td, 1H), 1.29 - 1.20 (m, 1H), 1.16 (s, 3H), 0.60 (dd, 2H), 0.40 (s, 3H), 0.35 (q, 2H). MS obsd. (ESI⁺) [(M+H)⁺]: 410.

Example 11: *Cis*-10-methoxy-11-(2-methoxyethoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

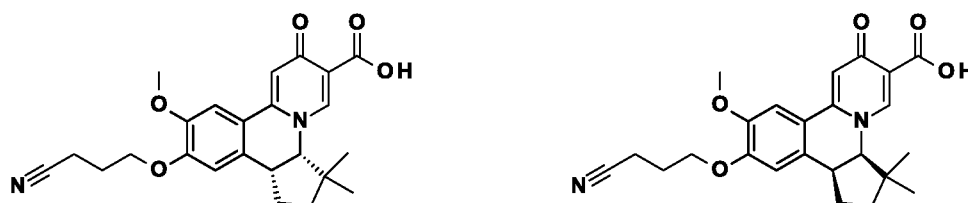
-40-



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 1-bromo-2-methoxy-ethane (292 mg, 2.1 mmol).

- 5 The mixture was stirred at rt for 40 hrs. To the above mixture was added LiOH·H₂O (50 mg, 1.2 mmol) and H₂O (1 mL). The resulting mixture was stirred at rt for 2 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-11-(2-methoxyethoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (26 mg) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.59 (s, 1H), 7.52 (s, 1H), 7.03 (s, 1H), 4.63 (d, 1H), 4.29 - 4.15 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 3.69 (t, 2H), 3.32 (s, 3H), 2.37 - 2.18 (m, 2H), 1.58 (ddd, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 414.

15 **Example 12: *Cis*-11-(3-cyanopropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**

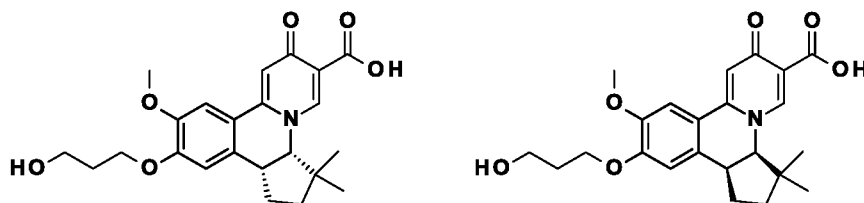


- To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 4-bromobutanenitrile (133 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(3-cyanopropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (24 mg) as a yellow solid.

^1H NMR (400MHz, $\text{DMSO-}d_6$) δ ppm 8.54 (s, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 7.05 (s, 1H), 4.64 (d, 1H), 4.24 - 4.09 (m, 2H), 3.90 (s, 3H), 3.81 - 3.73 (m, 1H), 2.66 (t, 2H), 2.37 - 2.19 (m, 2H), 2.07 (quin, 2H), 1.58 (ddd, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 423.

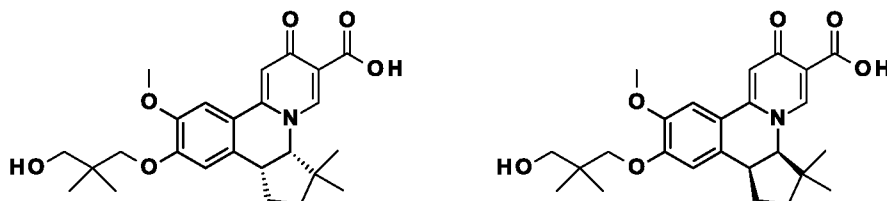
5

Example 13: *Cis*-11-(3-hydroxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-bromopropan-1-ol (167 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(3-hydroxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (13 mg) as a yellow solid. ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.01 (s, 1H), 4.63 (m, 2H), 4.23 - 4.09 (m, 2H), 3.89 (s, 3H), 3.81 - 3.72 (m, 1H), 3.57 (t, 2H), 2.35 - 2.18 (m, 2H), 1.89 (quin, 2H), 1.63 - 1.52 (m, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 414.

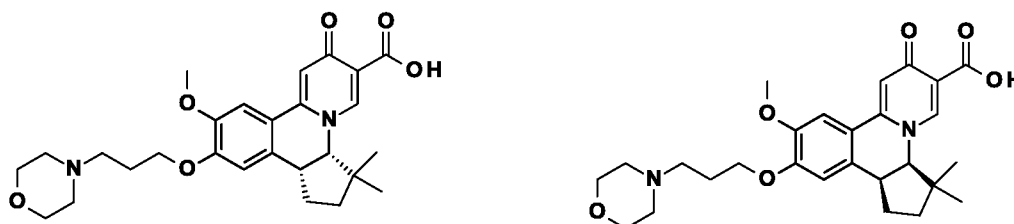
Example 14: *Cis*-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-bromo-2,2-dimethyl-propan-1-ol (150 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the
 5 above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with 2 M hydrochloric acid to pH=2-3 and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-
 10 oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid (8 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.58 (s, 1H), 7.52 (s, 1H), 7.00 (s, 1H), 4.63 (m, 2H), 3.90 (s, 3H), 3.87 - 3.81 (m, 1H), 3.80 - 3.74 (m, 2H), 3.30 (s, 2H), 2.35 - 2.19 (m, 2H), 1.64 - 1.52 (m, 1H), 1.36 (td, 1H), 1.16 (s, 3H), 0.95 (s, 6H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 442.

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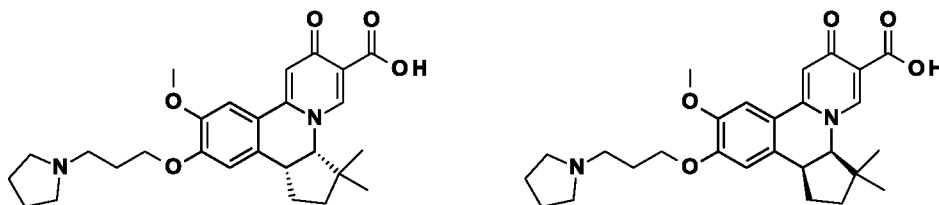
Example 15: *Cis*-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 4-(3-chloropropyl)morpholine (145 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, and then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The
 25 combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid (23 mg) as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ ppm 8.42 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 6.85 (s, 1H), 4.22 -

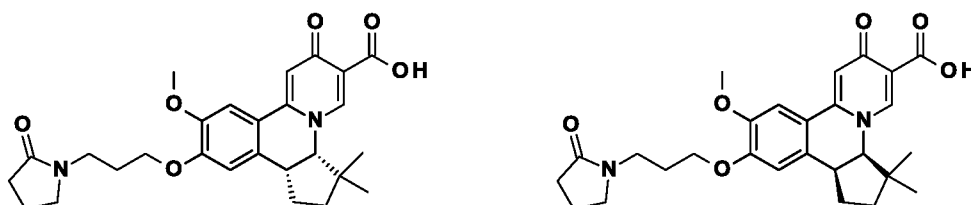
4.13 (m, 3H), 3.94 (s, 3H), 3.84 - 3.75 (m, 5H), 2.68 - 2.55 (m, 6H), 2.38 - 2.26 (m, 2H), 2.19 - 2.08 (m, 2H), 1.75 - 1.64 (m, 1H), 1.56 - 1.47 (m, 1H), 1.28 (s, 3H), 0.54 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 483.

5 **Example 16: *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(pyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**



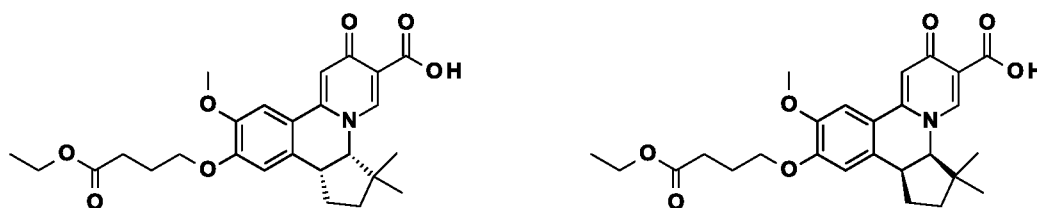
To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (124 mg, 0.9 mmol) in DMF (2 mL) was added 1-(3-chloropropyl)pyrrolidine hydrochloride (166 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, and then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(pyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (10 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.01 (s, 1H), 4.63 (d, 1H), 4.18 - 4.09 (m, 2H), 3.89 (s, 3H), 3.80 - 3.72 (m, 1H), 2.56 - 2.50 (m, 2H), 2.48 - 2.40 (m, 4H), 2.31 - 2.23 (m, 2H), 1.95 - 1.87 (m, 2H), 1.70 - 1.65 (m, 4H), 1.62 - 1.54 (m, 1H), 1.41 - 1.34 (m, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 467.

25 **Example 17: *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(2-oxopyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-(2-oxopyrrolidin-1-yl)propyl 4-methylbenzenesulfonate (178 mg, 0.6 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(2-oxopyrrolidin-1-yl)propoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid (20 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.59 (s, 1H), 7.52 (s, 1H), 6.98 (s, 1H), 4.63 (d, *J*=8.5 Hz, 1H), 4.17 - 4.01 (m, 2H), 3.90 (s, 3H), 3.80 - 3.72 (m, 1H), 3.40 - 3.35 (m, 2H), 2.34 - 2.16 (m, 4H), 1.99 - 1.88 (m, 4H), 1.64 - 1.53 (m, 1H), 1.36 (td, *J*=7.8, 12.8 Hz, 1H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 481.

Example 18: *Cis*-11-(4-ethoxy-4-oxobutoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid

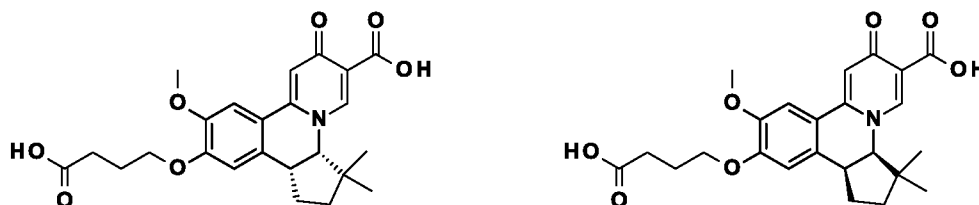


To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added ethyl 4-bromobutanoate (176 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(4-ethoxy-4-oxobutoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid (15 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.59 (s, 1H), 7.52 (s, 1H), 7.01 (s, 1H), 4.63 (d, 1H), 4.17 - 4.02 (m, 4H), 3.89

(s, 3H), 3.82 - 3.72 (m, 1H), 2.49 - 2.44 (m, 2H), 2.35 - 2.18 (m, 2H), 2.00 (quin, 2H), 1.63 - 1.53 (m, 1H), 1.35 (td, 1H), 1.22 - 1.14 (m, 6H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 470.

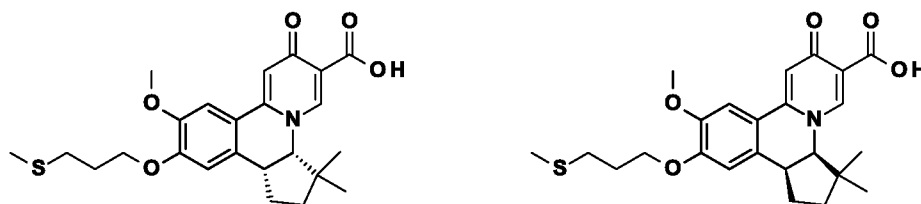
Example 19: *Cis*-11-(3-carboxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-

5 1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added ethyl 4-bromobutanoate (176 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford desired *cis*-11-(3-carboxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (25 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.02 (s, 1H), 4.62 (d, 1H), 4.18 - 4.02 (m, 2H), 3.89 (s, 3H), 3.82 - 3.72 (m, 1H), 2.40 (t, 2H), 2.35 - 2.20 (m, 2H), 1.96 (quin, 2H), 1.58 (ddd, 1H), 1.35 (td, 1H), 1.16 (s, 3H), 0.39 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 442.

Example 20: *Cis*-10-methoxy-3,3-dimethyl-11-(3-(methylthio)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

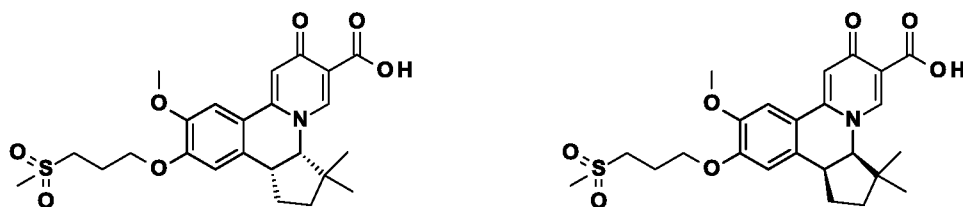


To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-methylsulfanylpropyl 4-methylbenzenesulfonate

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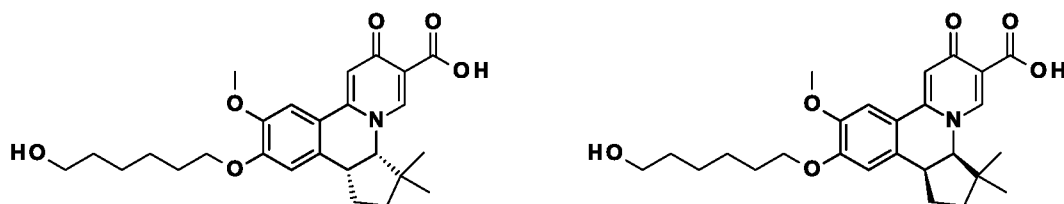
(156 mg, 0.6 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford desired *cis*-10-methoxy-3,3-dimethyl-11-(3-(methylthio)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (14 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.02 (s, 1H), 4.62 (d, 1H), 4.24 - 4.08 (m, 2H), 3.89 (s, 3H), 3.81 - 3.71 (m, 1H), 2.62 (m, 2H), 2.32 - 2.22 (m, 2H), 2.07 (s, 3H), 2.01 (quin, 2H), 1.64 - 1.53 (m, 1H), 1.35 (td, 1H), 1.16 (s, 3H), 0.39 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 444.

Example 21: *Cis*-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K₂CO₃ (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-methylsulfonylpropyl 4-methylbenzenesulfonate (175 mg, 0.6 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (13 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.02 (s, 1H), 4.63 (d, 1H), 4.30 - 4.14 (m, 2H), 3.90 (s, 3H), 3.81 - 3.73 (m, 1H), 3.31 - 3.25 (m, 2H), 3.04 (s, 3H), 2.35 - 2.12 (m, 4H), 1.64 - 1.53 (m, 1H), 1.35 (td, 1H), 1.16 (s, 3H), 0.39 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 476.

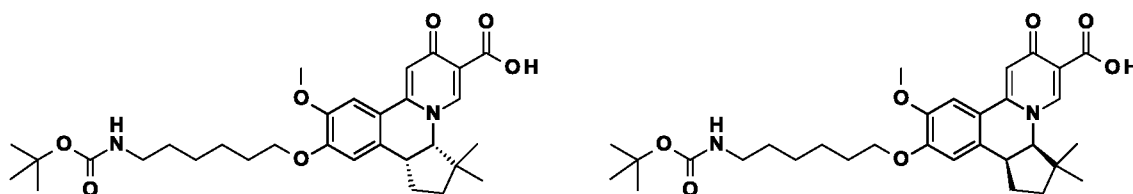
Example 22: *Cis*-11-((6-hydroxyhexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



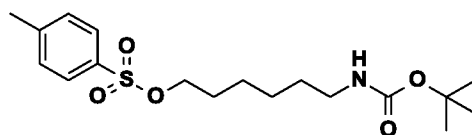
To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (115 mg, 0.3 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DMF (2 mL) was added 3-methylsulfonylpropyl 4-methylbenzenesulfonate (163 mg, 0.9 mmol). The mixture was heated at 120 °C with stirring for 4 hrs, and then cooled to rt. To the above mixture was added LiOH aqueous solution (2.4 M, 0.5 mL, 1.2 mmol). The resulting mixture was stirred at rt for 16 hrs, then acidified with acetic acid and extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-((6-hydroxyhexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (21 mg) as a yellow solid.

^1H NMR (400MHz, $DMSO-d_6$) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.00 (s, 1H), 4.63 (d, 1H), 4.37 (br. s., 1H), 4.15 - 3.99 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 3.40 (br. s., 2H), 2.36 - 2.18 (m, 2H), 1.74 (quin, 2H), 1.58 (ddd, 1H), 1.50 - 1.30 (m, 7H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 456.

Example 23: *Cis*-11-((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

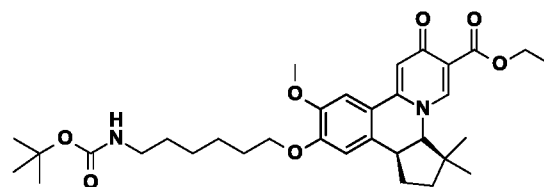
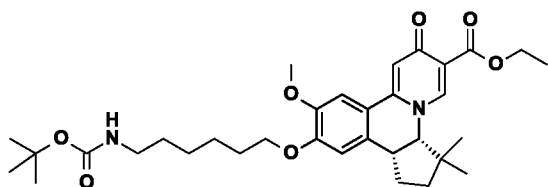


Step 1: Preparation of 6-((*tert*-butoxycarbonyl)amino)hexyl 4-methylbenzenesulfonate



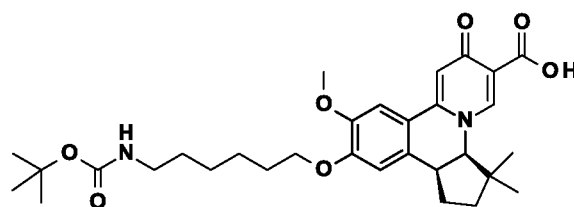
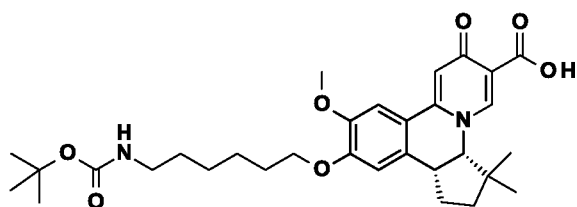
A mixture of *tert*-butyl *N*-(6-hydroxyhexyl)carbamate (5.38 g, 24.8 mmol), triethylamine (5.01 g, 49.6 mmol) and 4-dimethylaminopyridine (151 mg, 1.24 mmol) in CH₂Cl₂ (60 mL) was stirred at 0 °C for 30 min, then *p*-tolylsulfonylchloride (4.71 g, 24.8 mmol) was added in portions at 0 °C. The resulting mixture was allowed to warm to rt and stirred at rt overnight. The mixture was diluted with water, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with 1 M hydrochloric acid for three times, then washed with saturated NaHCO₃ aqueous solution and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give 6-(*tert*-butoxycarbonylamino)hexyl 4-methylbenzenesulfonate (8.30 g) as a yellow oil which was directly used in the next step without further purification.

Step 2: *Cis*-ethyl 11-((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate



To a mixture of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (460 mg, 1.2 mmol) and K₂CO₃ (331 mg, 2.4 mmol) in DMF (8 mL) was added 6-(*tert*-butoxycarbonylamino)hexyl 4-methylbenzenesulfonate (1.33 g, 3.6 mmol). The mixture was heated at 120 °C with stirring for 3 hrs. After being cooled to rt, the mixture was partitioned between CH₂Cl₂ and water. The separated aqueous layer was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude *cis*-ethyl 11-((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (1.48 g) as a brown oil which was directly used in the next step without further purification.

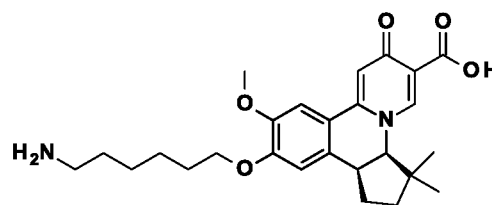
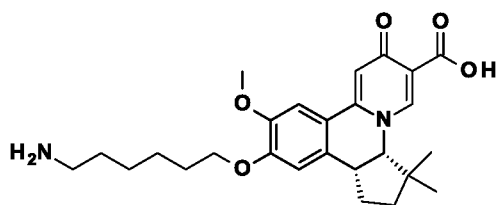
Step 3: Preparation of *cis*-11-((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid



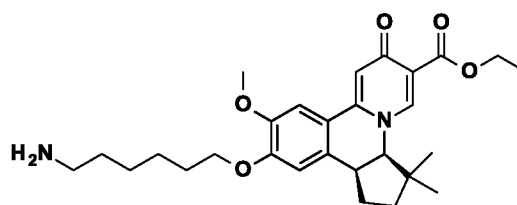
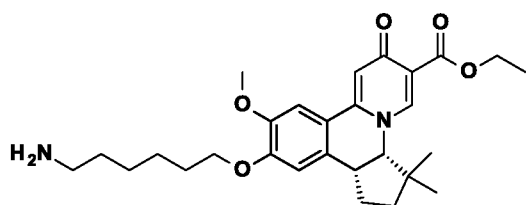
To a solution of crude *cis*-ethyl 11-(((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (370 mg, 0.3 mmol) in methanol (3 mL) and H₂O (1 mL) was added LiOH·H₂O (50 mg, 1.2 mmol). The mixture was stirred at rt overnight, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-(((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid (28 mg) as a yellow solid.

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 6.99 (s, 1H), 6.79 (m, 1H), 4.63 (d, 1H), 4.16 - 4.00 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 2.96 - 2.85 (m, 2H), 2.35 - 2.18 (m, 2H), 1.79 - 1.65 (m, 2H), 1.64 - 1.51 (m, 1H), 1.45 - 1.22 (m, 17H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 555.

Example 24: *Cis*-11-(((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid

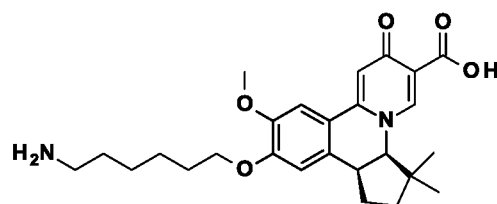
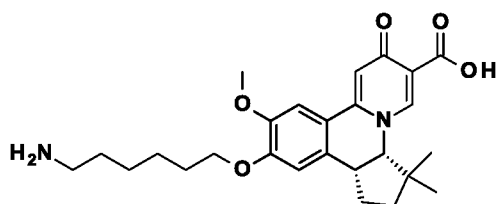


Step 1: Preparation of *cis*-ethyl 11-(((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate



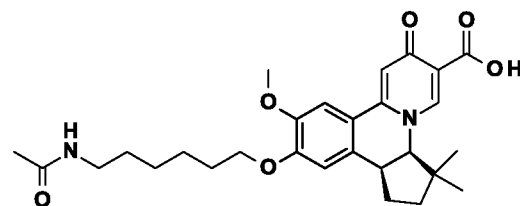
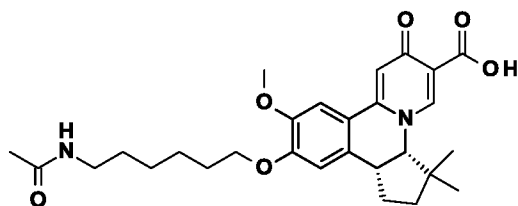
To a solution of crude *cis*-ethyl 11-(((6-((*tert*-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (1.11 g, 0.9 mmol) in CH₂Cl₂ (10 mL) was added trifluoroacetic acid (2 mL). The resulting mixture was stirred at rt overnight, then concentrated under reduced pressure to give crude *cis*-ethyl 11-(((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylate (2.10 g) as a brown oil which was directly used in the next step without further purification.

Step 2: Preparation of *cis*-11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

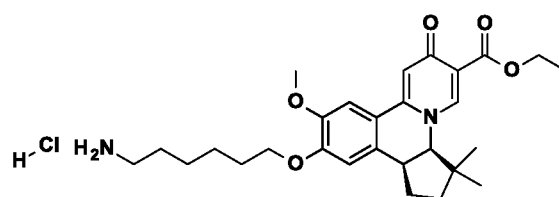
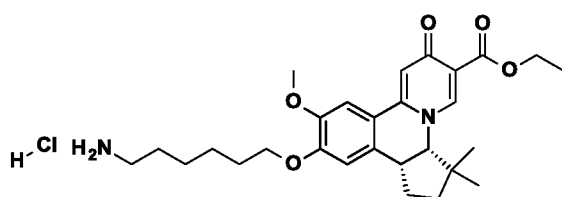


To a solution of crude *cis*-ethyl 11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (700 mg, 0.3 mmol) in methanol (3 mL) and H₂O (1 mL) was added LiOH·H₂O (252 mg, 6 mmol). The mixture was stirred at rt for 2 hrs, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (6 mg) as a colorless oil. MS obsd. (ESI⁺) [(M+H)⁺]: 455.

Example 25: *Cis*-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



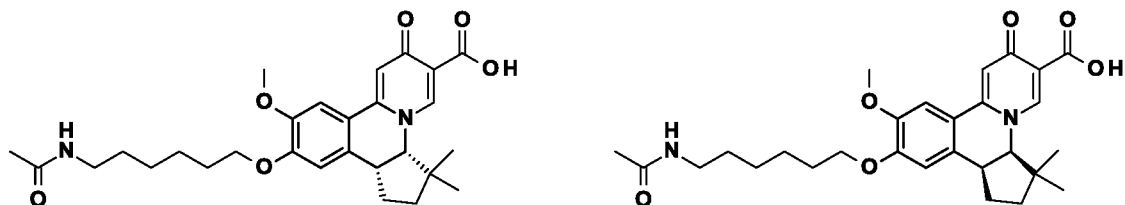
Step 1: Preparation of *cis*-ethyl 11-((6-((tert-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate hydrochloride



A mixture of *cis*-ethyl 11-((6-((tert-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (510 mg, 0.6 mmol) and 1 M HCl in EtOAc solution (15 mL) stirred at rt overnight. The

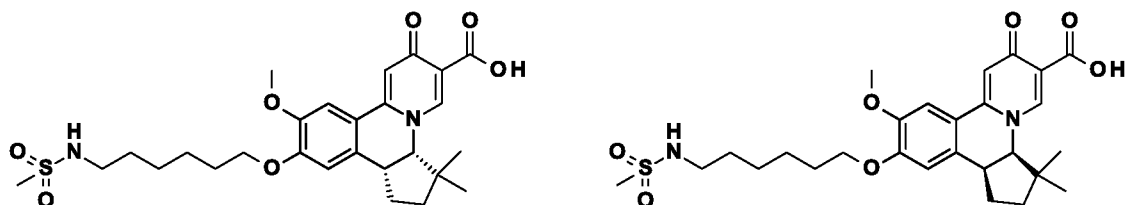
resulting mixture was concentrated under reduced pressure to give crude *cis*-ethyl 11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate hydrochloride (454 mg) as a brown oil which was directly used in the next step without further purification.

5 Step 2: Preparation of *cis*-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



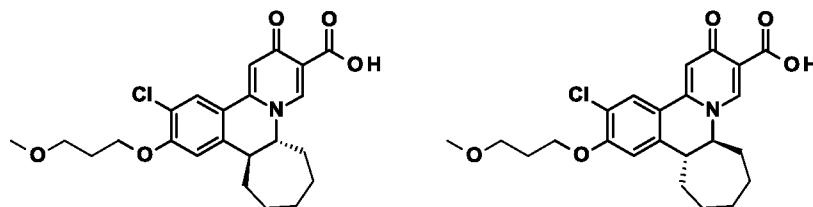
To a solution of *cis*-ethyl 11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate hydrochloride (227 mg, 0.3 mmol) and *N,N*-diisopropylethylamine (194 mg, 1.5 mmol) in CH₂Cl₂ (3 mL) was added acetyl chloride (70 mg, 0.9 mmol). The resulting mixture was stirred at rt for 1 h, and then concentrated under reduced pressure. The residue was dissolved in methanol (3 mL) and H₂O (1 mL), then to the solution was added LiOH·H₂O (101 mg, 2.4 mmol). The resulting mixture was stirred at rt for 16 hrs, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (27 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.54 (s, 1H), 7.80 (t, 1H), 7.58 (s, 1H), 7.51 (s, 1H), 7.00 (s, 1H), 4.63 (d, 1H), 4.15 - 4.00 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 3.02 (q, 2H), 2.35 - 2.19 (m, 2H), 1.78 (s, 3H), 1.77 - 1.69 (m, 2H), 1.58 (ddd, 1H), 1.47 - 1.28 (m, 7H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 497.

Example 26: *Cis*-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid

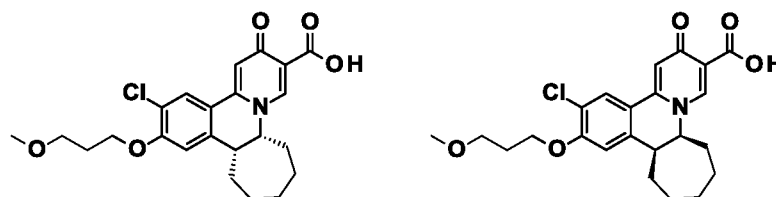


To a solution of *cis*-ethyl 11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate hydrochloride (227 mg, 0.3 mmol) and *N,N*-diisopropylethylamine (194 mg, 1.5 mmol) in CH₂Cl₂ (3 mL) was added methanesulfonic anhydride (263 mg, 1.5 mmol). The mixture was stirred at rt for 1 h, and then concentrated under reduced pressure. The residue was dissolved in methanol (3 mL) and H₂O (1 mL), then to the solution was added LiOH·H₂O (101 mg, 2.4 mmol). The resulting mixture was stirred at rt for 16 hrs, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (15 mg) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.00 (s, 1H), 6.95 (t, 1H), 4.63 (d, 1H), 4.15 - 4.01 (m, 2H), 3.89 (s, 3H), 3.76 (t, 1H), 2.93 (q, 2H), 2.88 (s, 3H), 2.37 - 2.19 (m, 2H), 1.75 (quin, 2H), 1.58 (ddd, 1H), 1.52 - 1.33 (m, 7H), 1.16 (s, 3H), 0.40 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 533.

Example 27 and 28: *Trans*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid and *cis*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid



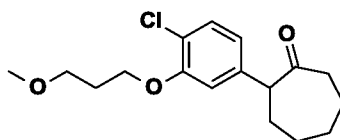
Example 27



Example 28

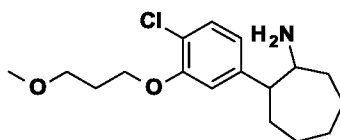
Step 1: Preparation of 2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptanone

-53-



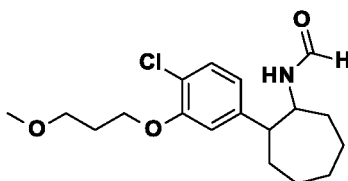
To a mixture of 4-bromo-1-chloro-2-(3-methoxypropoxy)benzene (834 mg, 3 mmol), tris(dibenzylideneacetone)dipalladium(0) (28 mg, 0.03 mmol), 2-dicyclohexylphosphino-2'-methylbiphenyl (22 mg, 0.06 mmol) and *t*-BuONa (576 mg, 6 mmol) in THF (10 mL) was added
 5 cycloheptanone (672 mg, 6 mmol). The mixture was heated at 60 °C for 30 min under microwave irradiation and argon atmosphere. Then the mixture was partitioned between 1 M hydrochloric acid and EtOAc. The aqueous layer was extracted with EtOAc for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 2-[4-chloro-3-(3-
 10 methoxypropoxy)phenyl]cycloheptanone (1.23 g) as a yellow oil which was directly used in the next step without further purification.

Step 2: Preparation of 2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptanamine



To a mixture of crude 2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptanone (1.23 g, 3
 15 mmol) and ammonium acetate (6.93 g, 90 mmol) in methanol (10 mL) was added NaBH₃CN (756 mg, 12 mmol). The mixture was stirred at rt overnight, then diluted with water and basified with 2 M NaOH aqueous solution to pH=10-12. The resulting mixture was stirred at rt for 30 min, and then extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude
 20 2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptanamine (810 mg) as a yellow oil which was directly used in the next step without further purification.

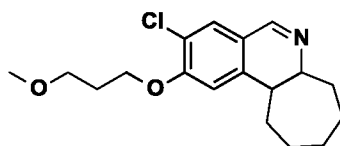
Step 3: Preparation of *N*-[2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptyl]formamide



25 A solution of crude 2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptanamine (810 mg, 2.6 mmol) and formic acid (0.15 mL) in ethyl formate (15 mL) was heated at 90 °C for 2 hrs.

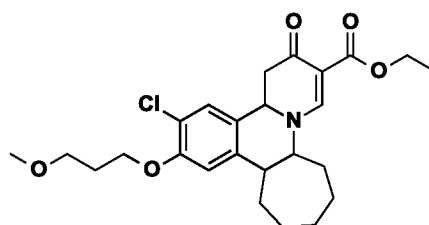
After being cooled to rt, the mixture was concentrated under reduced pressure to give crude *N*-[2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptyl]formamide (790 mg) as a yellow oil which was directly used in the next step without further purification.

Step 4: Preparation of 3-chloro-2-(3-methoxypropoxy)-7,8,9,10,11,11a-hexahydro-6a*H*-cyclohepta[*c*]isoquinoline



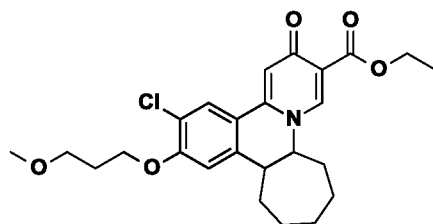
To a solution of crude *N*-[2-[4-chloro-3-(3-methoxypropoxy)phenyl]cycloheptyl]formamide (790 mg, 2.3 mmol) in CH₃CN (10 mL) was added POCl₃ (352 mg, 2.3 mmol). The mixture was heated at 80 °C with stirring for 3 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂. The resulting solution was basified with ammonia water to pH=10 at 0 °C, then allowed to warm to rt and stirred at rt for 1 hr. Then the separated aqueous layer was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 3-chloro-2-(3-methoxypropoxy)-7,8,9,10,11,11a-hexahydro-6a*H*-cyclohepta[*c*]isoquinoline (720 mg) as a yellow oil which was directly used in the next step without further purification.

Step 5: Preparation of ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-1,2,5a,6,7,8,9,10,10a,14b-decahydrocyclohepta[*c*]pyrido[2,1-*a*]isoquinoline-3-carboxylate



A mixture of crude 3-chloro-2-(3-methoxypropoxy)-7,8,9,10,11,11a-hexahydro-6a*H*-cyclohepta[*c*]isoquinoline (720 mg, 2.24 mmol) and ethyl 2-(ethoxymethylene)-3-oxo-butanoate (1.25 g, 6.72 mmol) in ethanol (10 mL) was heated at 100 °C with stirring overnight. The mixture was concentrated under reduced pressure to give crude ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-1,2,5a,6,7,8,9,10,10a,14b-decahydrocyclohepta[*c*]pyrido[2,1-*a*]isoquinoline-3-carboxylate (2.04 g) as a brown oil which was directly used in the next step without further purification.

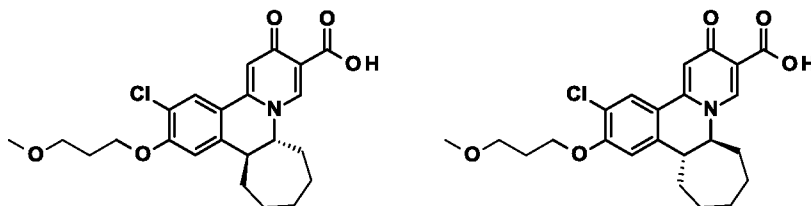
Step 6: Preparation of ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylate



A mixture of crude ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-

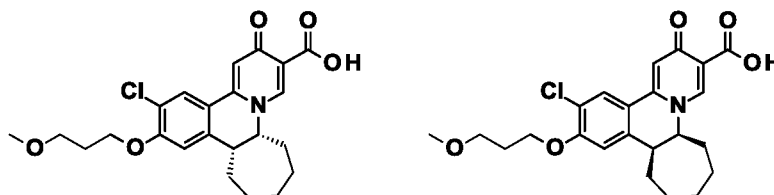
- 5 1,2,5a,6,7,8,9,10,10a,14b-decahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylate (2.04 g, 2.24 mmol) and *p*-chloranil (551 mg, 2.24 mmol) in DME (10 mL) was heated at 70 °C with stirring for 3 hrs. After being cooled to rt, the mixture was filtered. The filter cake was dried under reduced pressure to give crude ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylate (275 mg)
- 10 which was directly used in the next step without further purification.

Step 7: Preparation of *trans*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid and *cis*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid



15

Example 27



Example 28

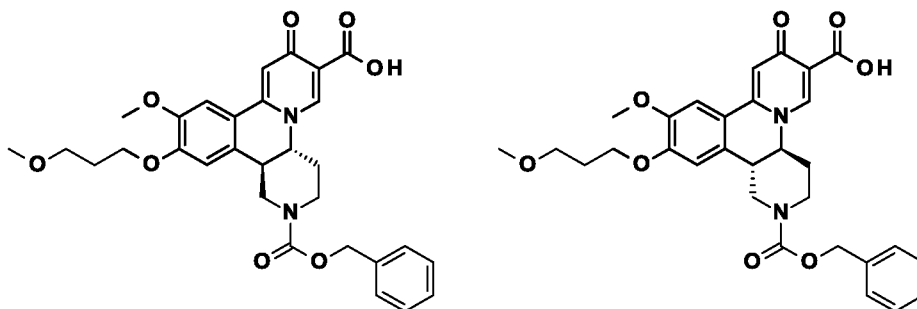
- To a solution of crude ethyl 13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-
- 20 octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylate (275 mg, 0.6 mmol) in methanol (4 mL) and H₂O (1 mL) was added LiOH·H₂O (202 mg, 4.8 mmol). The mixture was stirred at rt for 64 hrs, then diluted with water and acidified with 1 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were

washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC and precipitation from diethyl ether/methanol to afford *trans*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid (50 mg) as a yellow solid and *cis*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid (15 mg) as a yellow solid.

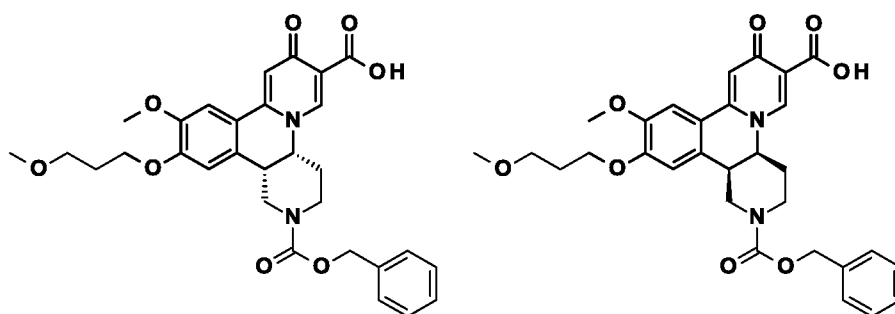
Example 27: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.85 (s, 1H), 8.22 (s, 1H), 7.37 (s, 1H), 7.14 (s, 1H), 4.89 - 4.78 (m, 1H), 4.31 - 4.17 (m, 2H), 3.65 (m, 1H), 3.52 (t, 2H), 3.27 (s, 3H), 2.34 - 2.21 (m, 1H), 2.14 - 1.96 (m, 4H), 1.76 - 1.50 (m, 7H). MS obsd. (ESI⁺) [(M+H)⁺]: 432.

Example 28: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.62 (s, 1H), 8.18 (s, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 4.27 (m, 2H), 4.00 - 3.90 (m, 1H), 3.52 (t, 2H), 3.27 (s, 3H), 3.04 (m, 1H), 2.46 - 2.30 (m, 3H), 2.08 - 1.97 (m, 2H), 1.94 - 1.50 (m, 7H). MS obsd. (ESI⁺) [(M+H)⁺]: 432.

Example 29 and 30: *Trans*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid and *cis*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid

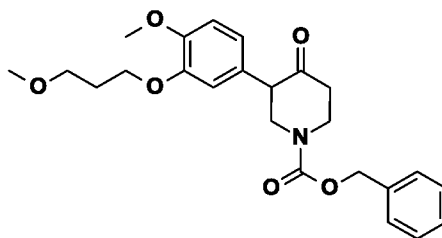


Example 29



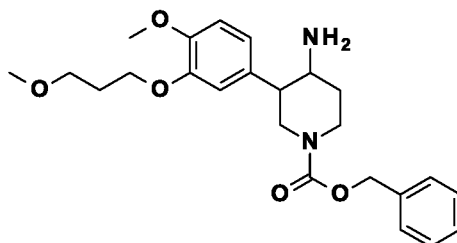
Example 30

Step 1: Preparation of benzyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxo-

piperidine-1-carboxylate

To a mixture of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (1.10 g, 4 mmol), tris(dibenzylideneacetone)dipalladium(0) (37 mg, 0.04 mmol), 2-dicyclohexylphosphino-2'-methylbiphenyl (25 mg, 0.08 mmol) and *t*-BuONa (768 mg, 8 mmol) in THF (10 mL) was added
 5 benzyl 4-oxopiperidine-1-carboxylate (1.86 g, 8 mmol). The mixture was heated at 60 °C for 15 min under microwave irradiation. After being cooled to rt, the mixture was partitioned between water and EtOAc, then the aqueous layer was extracted with EtOAc for two times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and
 10 concentrated under reduced pressure to give crude benzyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxo-piperidine-1-carboxylate (2.72 g) as a yellow oil which was directly used in the next step without further purification.

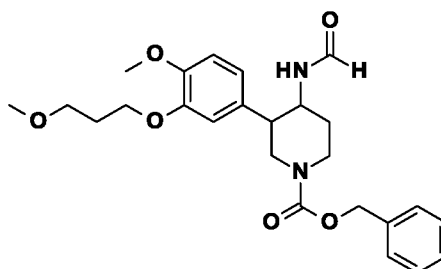
Step 2: Preparation of benzyl 4-amino-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate



15 To a mixture of crude benzyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxo-piperidine-1-carboxylate (2.72 g, 4 mmol) and ammonium acetate (4.62 g, 60 mmol) in methanol (30 mL) was added NaBH₃CN (504 mg, 8 mmol). The mixture was stirred at rt overnight, then diluted with water and basified with 2 M NaOH aqueous solution to pH=10-12. The resulting
 20 mixture was stirred at rt for 30 min, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude benzyl 4-amino-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate (1.95 g) as a yellow oil which was directly used in the next step without further purification.

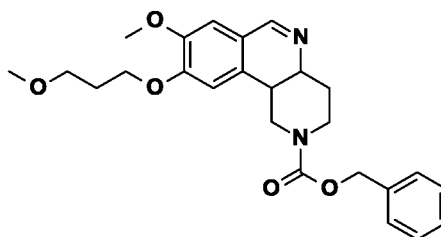
-58-

Step 3: Preparation of benzyl 4-formamido-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate



A solution of crude benzyl 4-amino-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate (1.92 g, 4 mmol) and formic acid (0.02 mL) in ethyl formate (20 mL) was heated at 90 °C with stirring overnight. After being cooled to rt, the mixture was concentrated under reduced pressure to give crude benzyl 4-formamido-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate (1.97 g) as a yellow oil which was directly used in the next step without further purification.

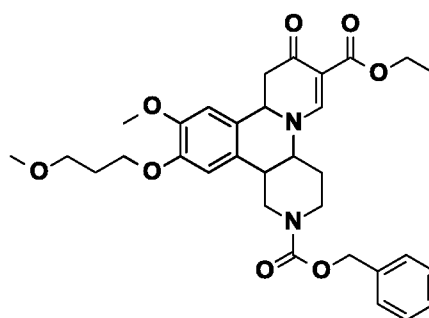
Step 4: Preparation of benzyl 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1H-benzo[c][1,6]naphthyridine-2-carboxylate



To a solution of crude benzyl 4-formamido-3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidine-1-carboxylate (1.97 g, 4 mmol) in CH₃CN (15 mL) was added POCl₃ (612 mg, 4 mmol). The mixture was heated at 70 °C with stirring for 2 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was dissolved in CH₃CN. The resulting solution was basified with ammonia water to pH=10 at 0 °C and allowed to warm to rt and stirred at rt for 1 hr. The mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude benzyl 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1H-benzo[c][1,6]naphthyridine-2-carboxylate (1.69 g) as an orange oil which was directly used in the next step without further purification.

Step 5: Preparation of 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,9,9a,13b-hexahydro-1H-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3H)-dicarboxylate

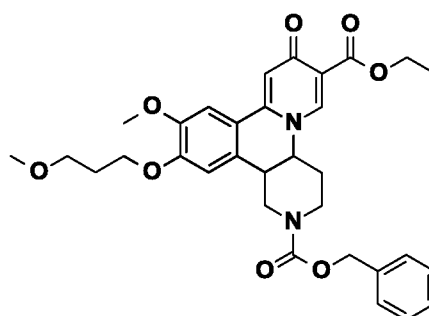
-59-



A mixture of crude benzyl 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-benzo[c][1,6]naphthyridine-2-carboxylate (1.69 g, 4 mmol) and ethyl 2-(ethoxymethylene)-3-oxo-butanoate (2.23 g, 12 mmol) in ethanol (20 mL) was heated at 100 °C with stirring overnight.

- 5 After being cooled to rt, the mixture was concentrated under reduced pressure to give crude 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,9,9a,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3*H*)-dicarboxylate (3.70 g) as a brown oil which was directly used in the next step without further purification.

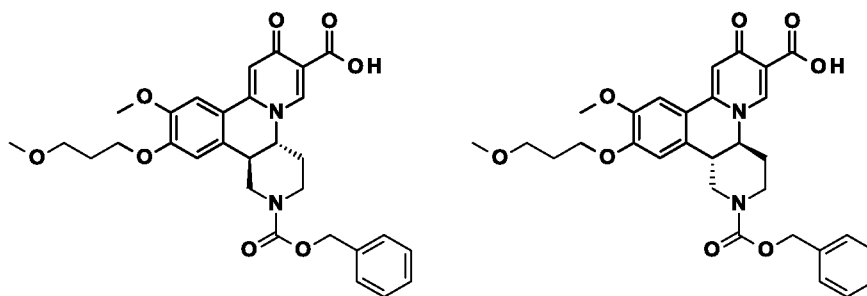
Step 6: Preparation of 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,13b-tetrahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3*H*)-dicarboxylate



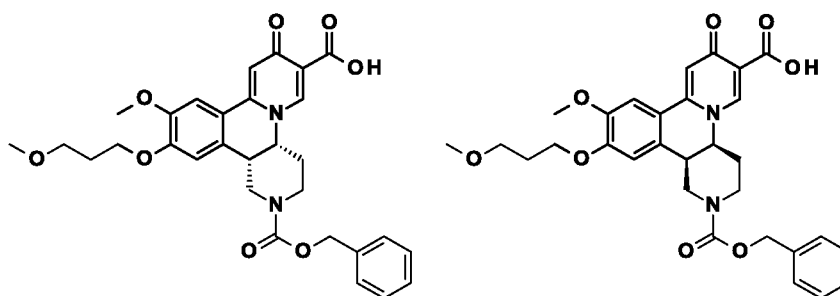
- A mixture of crude 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,9,9a,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3*H*)-dicarboxylate (3.70 g, 4 mmol) and *p*-chloranil (984 mg, 4 mmol) in DME (20 mL) was heated at 70 °C with stirring for 3 hrs under argon atmosphere. The mixture was concentrated under reduced pressure to give crude 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,13b-tetrahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3*H*)-dicarboxylate (4.91 g) as a dark brown solid which was directly used in the next step without further purification.

Step 7: Preparation of *trans*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid and *cis*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid

-60-



Example 29



Example 30

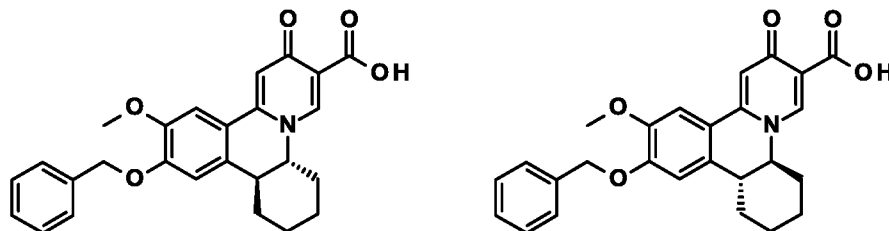
- 5 To a solution of crude 2-benzyl 7-ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-4,4a,8,13b-tetrahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-2,7(3*H*)-dicarboxylate (4.91 g, 4 mmol) in methanol (20 mL) and H₂O (4 mL) was added LiOH·H₂O (1.34 g, 32 mmol). The mixture was stirred at rt overnight, then acidified with 1 M hydrochloric acid to pH=2-3, and extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography and prep-HPLC to afford *trans*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid (5 mg) as an off-white solid and *cis*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1*H*-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid (23 mg) as a white solid.

Example 29: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 7.57 (s, 1H), 7.47 (s, 1H), 7.44 - 7.30 (m, 5H), 6.93 (s, 1H), 5.16 (s, 2H), 4.91 (d, 1H), 4.36 (d, 1H), 4.18 (t, 2H), 4.08 - 3.98 (m, 1H), 3.91 (s, 3H), 3.48 (t, 2H), 3.26 (s, 3H), 3.02 (br. s., 3H), 2.66 (d, 1H), 1.99 (quin, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 549.

20 Example 30: MS obsd. (ESI⁺) [(M+H)⁺]: 549.

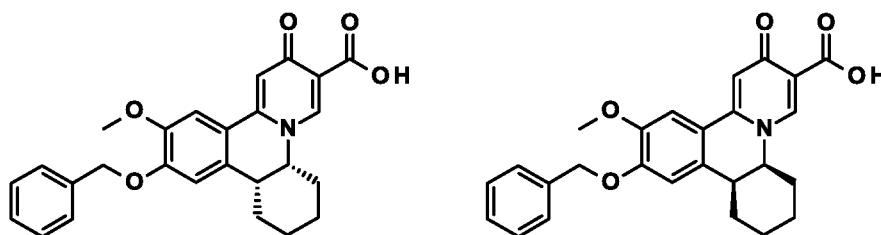
-61-

Example 31 and 32: *Trans*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid and *cis*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid



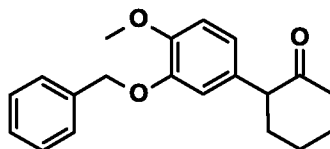
5

Example 31



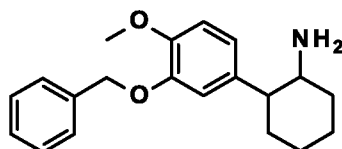
Example 32

Step 1: Preparation of 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanone



To a solution of 2-benzyloxy-4-bromo-1-methoxy-benzene (5.0 g, 17.1 mmol) in anhydrous dioxane (80 mL) was added cyclohexanone (2.0 g, 20.5 mmol), palladium acetate (38.2 mg, 0.17 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (59.2 mg, 0.20 mmol) and lithium bis(trimethylsilyl)amide (1.3 mol/L, 26.3 mL, 34.2 mmol). The reaction mixture was heated with stirring at 60°C for 3 hrs under argon atmosphere, then cooled to rt and concentrated under reduced pressure. The residue was partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to give 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanone (300 mg).

Step 2: Preparation of 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanamine



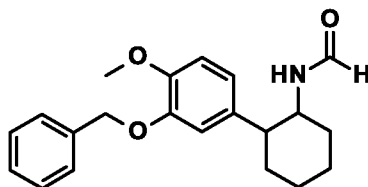
20

To a solution of 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanone (250 mg, 0.81 mmol)

-62-

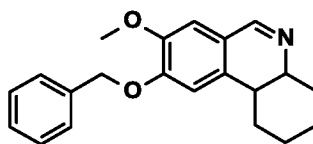
in MeOH (30 mL) was added ammonium acetate (624.5 mg, 8.1 mmol) and sodium cyanoborohydride (152.6 mg, 2.43 mmol) at rt. The reaction mixture was stirred at rt for 20 hrs, and then quenched with aqueous sodium hydroxide solution (4 mol/L). The resulting mixture was stirred at rt for 4 hrs, and then partitioned between brine DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanamine (230 mg), which was used in the next step without further purification.

Step 3: Preparation of *N*-[2-(3-benzyloxy-4-methoxy-phenyl)cyclohexyl]formamide



To a solution of 2-(3-benzyloxy-4-methoxy-phenyl)cyclohexanamine (230 mg, 0.74 mmol) in dioxane (10 mL) was added formic acid (83.7 μ L, 2.22 mmol). The reaction mixture was heated at 80 °C with stirring for 16 hrs, then cooled to rt and concentrated under reduced pressure to give crude *N*-[2-(3-benzyloxy-4-methoxy-phenyl)cyclohexyl]formamide (240 mg), which was used in the next step without further purification.

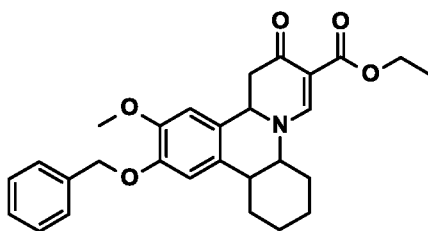
Step 4: Preparation of 9-benzyloxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridine



To a solution of *N*-[2-(3-benzyloxy-4-methoxy-phenyl)cyclohexyl]formamide (240 mg, 0.71 mmol) in MeCN (10 mL) was added phosphorus oxychloride (0.1 mL, 1.1 mmol). The resulting mixture was heated at 50 °C with stirring for 2 hrs, and then concentrated under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ solution and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give 9-benzyloxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridine (200 mg), which was used in the next step without further purification.

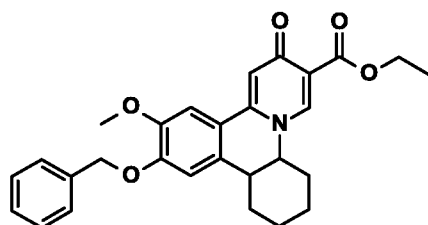
Step 5: Preparation of ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,9,9a,13b-octahydropyrido[1,2-f]phenanthridine-7-carboxylate

-63-



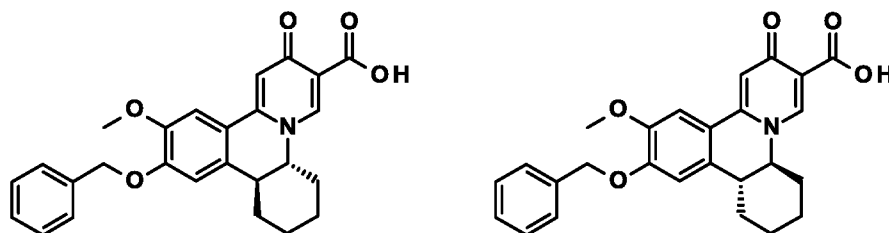
To a solution of 9-benzyloxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridine (200 mg, 0.62 mmol) in EtOH (10 mL) was added ethyl 2-(ethoxymethylene)-3-oxo-butanoate (463.6 mL, 2.49 mmol). The reaction mixture was heated at 100 °C with stirring for 16 hrs, and then concentrated under reduced pressure to give crude ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,9,9a,13b-octahydropyrido[1,2-f]phenanthridine-7-carboxylate, which was used in the next step without further purification.

Step 6: Preparation of ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylate

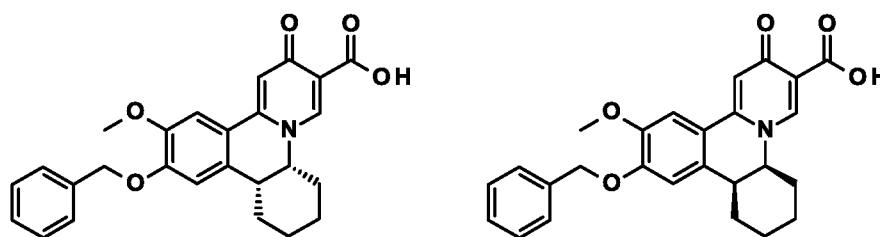


To a solution of crude ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,9,9a,13b-octahydropyrido[1,2-f]phenanthridine-7-carboxylate (all the crude product from the above step) in DME (10 mL) was added *p*-chloranil (106.7 mg, 0.43 mmol). The resulting mixture was heated at 70 °C with stirring for 2 hrs, then cooled to rt and concentrated under reduced pressure to give crude ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylate, which was used in the next step without further purification.

Step 7: Preparation of *trans*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid and *cis*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid



Example 31



Example 32

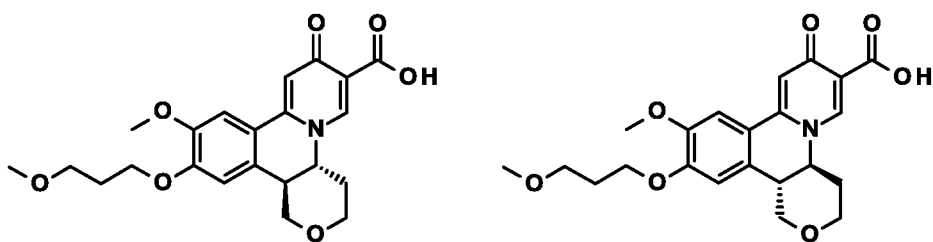
To a solution of crude ethyl 12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylate (all the crude product from the above step) in a mixture solvent of methanol (9 mL) and water (3 mL) was added LiOH·H₂O (78.1 mg, 1.86 mmol). The reaction mixture was stirred at rt for 2 hrs, and then acidified with 6 M hydrochloric acid. The resulting mixture was partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative HPLC to give *trans*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid (41 mg) and *cis*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid (5 mg).

Example 31: ¹H NMR (400MHz, DMSO-*d*₆): δ ppm 8.62 (s, 1H), 7.55 (s, 1H), 7.52 - 7.32 (m, 6H), 7.11 (s, 1H), 5.24 (s, 2H), 3.91 (s, 3H), 3.80-3.71 (m, 1H), 2.86 - 2.76 (m, 1H), 2.69 - 2.57 (m, 2H), 2.08 - 2.00 (m, 1H), 1.90 - 1.72 (m, 2H), 1.50-1.20 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 432.

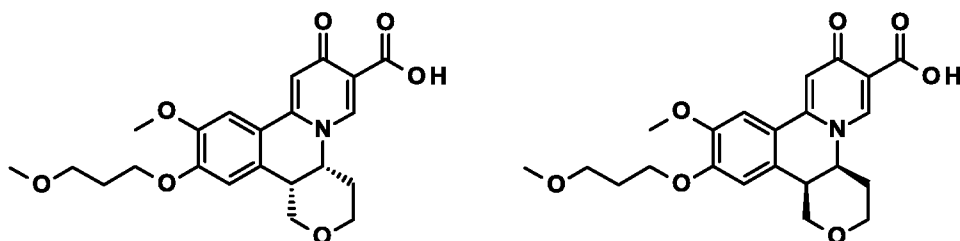
Example 32: ¹H NMR (400MHz, Acetone-*d*₆): δ ppm 8.63 (s, 1H), 7.61 (s, 1H), 7.58-7.52 (m, 2H), 7.47-7.41 (m, 2H), 7.37 - 7.34 (m, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 5.33 (s, 2H), 4.74 - 4.62 (m, 1H), 4.02 (s, 3H), 3.69 - 3.59 (m, 1H), 2.68 - 2.63 (m, 2H), 1.95 - 1.83 (m, 2H), 1.61 - 1.46 (m, 3H), 1.34 - 1.20 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 432.

Example 33 and 34: *Trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-*c*]pyrido[2,1-*a*]isoquinoline-7-carboxylic acid and *cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-*c*]pyrido[2,1-*a*]isoquinoline-7-carboxylic acid

-65-

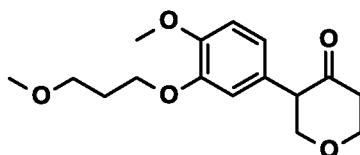


Example 33



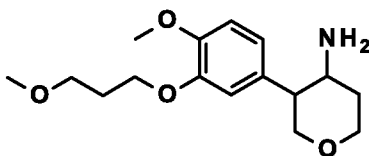
Example 34

5 **Step 1: Preparation of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-one**



To a solution of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (5.0 g, 18.2 mmol) in anhydrous toluene (80 mL) was added tetrahydropyran-4-one (7.3 g, 72.8 mmol), palladium acetate (40.9 mg, 0.18 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (210.6 mg, 0.36 mmol) and cesium carbonate (11.9 g, 36.4 mmol). The reaction mixture was heated at 100 °C with stirring for 24 hrs under argon atmosphere. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to give 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-one (200 mg).

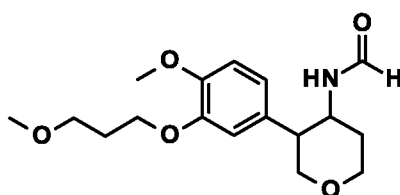
Step 2: Preparation of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-amine



20 To a solution of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-one (200

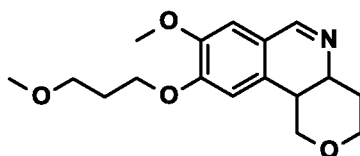
mg, 0.68 mmol) in MeOH (30 mL) was added ammonium acetate (524.3 mg, 6.8 mmol) and sodium cyanoborohydride (128.1 mg, 2.04 mmol) at rt. The reaction mixture was stirred for 16 hours at rt, and then quenched with aqueous sodium hydroxide solution. The resulting mixture was stirred at rt for 4 hrs, then partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-amine (200 mg), which was used in the next step without further purification.

Step 3: Preparation of *N*-[3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-yl]formamide



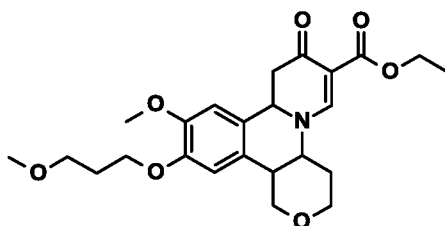
To a solution of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-amine (200 mg, 0.68 mmol) in dioxane (10 mL) was added formic acid (76.9 μ L, 2.04 mmol). The reaction mixture was heated at 100 °C with stirring for 18 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure to give crude *N*-[3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-yl]formamide (210 mg), which was used in the next step without further purification.

Step 4: Preparation of 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-pyrano[4,3-*c*]isoquinoline



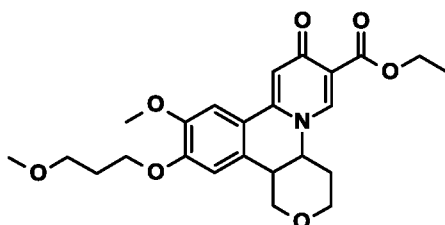
To a solution of *N*-[3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydropyran-4-yl]formamide (210 mg, 0.65 mmol) in MeCN (10 mL) was added phosphorus oxychloride (0.12 mL, 1.3 mmol). The reaction mixture was heated at 50 °C with stirring for 3 hrs, and then concentrated under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ solution and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-pyrano[4,3-*c*]isoquinoline (198 mg), which was used in the next step without further purification.

Step 5: Preparation of ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate



To a solution of 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-pyrano[4,3-c]isoquinoline (198 mg, 0.65 mmol) in EtOH (10 mL) was added ethyl 2-(ethoxymethylene)-3-oxo-butanoate (363.1 mg, 1.95 mmol). The reaction mixture was heated at 110 °C with stirring for 20 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure to give crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate, which was used in the next step without further purification.

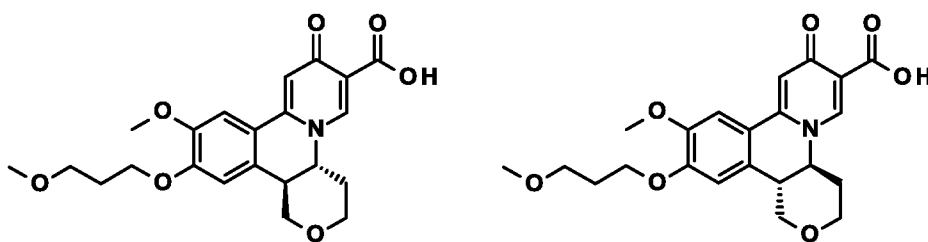
Step 6: Preparation of ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate



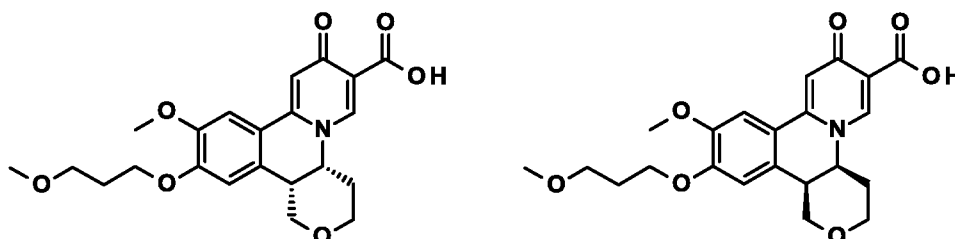
To a solution of crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate (all the crude product from the above step) in DME (10 mL) was added *p*-chloranil (113.1 mg, 0.46 mmol). The reaction mixture was heated at 70 °C with stirring for 3 hrs, and then concentrated under reduced pressure to give crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate, which was used in the next step without further purification.

Step 7: Preparation of *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid and *cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid

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Example 33



Example 34

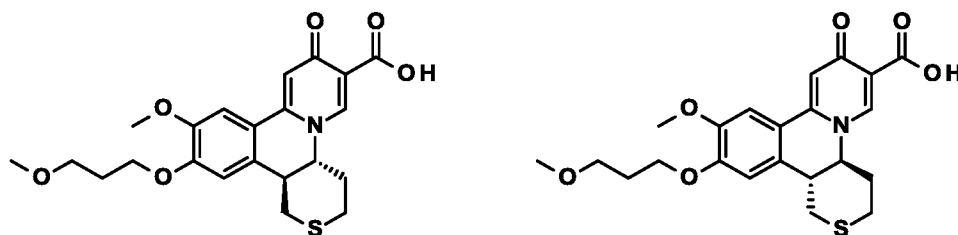
5 To a solution of crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylate (all the crude product from the above step) in a mixture solvent of methanol (9 mL) and water (3 mL) was added LiOH·H₂O (81.9 mg, 1.95 mmol). The reaction mixture was stirred at rt for 2 hrs, and then acidified with 6 M hydrochloric acid. The resulting mixture was partitioned between brine and DCM. The organic layer was separated and concentrated under reduced pressure. The residue was purified by preparative HPLC to give *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid (15 mg) and *cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid (3 mg).

15 Example 33: ¹H NMR (400MHz, CDCl₃) δ ppm 8.69 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 6.68 (s, 1H), 4.80-4.69 (m, 1H), 4.44-4.34 (m, 1H), 4.25-4.15 (m, 2H), 3.96 (s, 3H), 3.93-3.84 (m, 1H), 3.64 - 3.55 (m, 4H), 3.39 (s, 3H), 3.13 - 2.98 (m, 1H), 2.64-2.54 (m, 1H), 2.20 - 2.13 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 416.

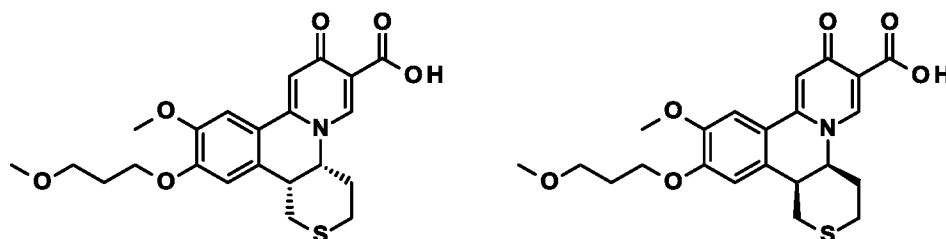
20 Example 34: ¹H NMR (400MHz, CD₃CN) δ ppm 8.61 (s, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 7.13 (s, 1H), 4.78 - 4.69 (m, 2H), 4.22-4.11 (m, 2H), 3.93 (s, 3H), 3.89 - 3.83 (m, 1H), 3.79 - 3.73 (m, 1H), 3.58 - 3.52 (m, 3H), 3.43 - 3.37 (m, 1H), 3.33 (s, 3H), 2.06-2.01 (m, 2H), 1.83 - 1.73 (m, 2H). MS obsd. (ESI⁺) [(M+H)⁺]: 416.

25 **Example 35 and 36: *Trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid and *cis*-11-**

methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid

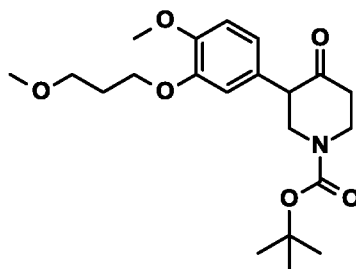


Example 35



Example 36

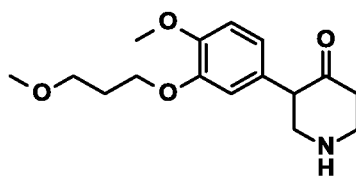
Step 1: Preparation of *tert*-butyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxopiperidine-1-carboxylate



- 10 To a solution of 4-bromo-1-methoxy-2-(3-methoxypropoxy)benzene (10.0 g, 36.4 mmol) in anhydrous THF (150 mL) was added *tert*-butyl 4-oxopiperidine-1-carboxylate (8.71 g, 43.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (329.7 mg, 0.36 mmol), 2-(dicyclohexylphosphino)-2'-methylbiphenyl (266.1 mg, 0.73 mmol) and sodium *tert*-butoxide (5.25 g, 54.6 mmol). The reaction mixture was heated at 60 °C for 6 hrs under argon atmosphere.
- 15 After being cooled to rt, the mixture was cooled to rt and concentrated under reduced pressure. The residue was partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to give *tert*-butyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxopiperidine-1-carboxylate (4.0 g).

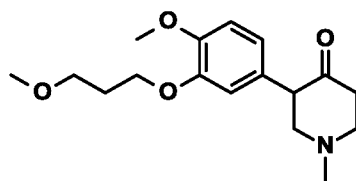
- 20 **Step 2: Preparation of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidin-4-one**

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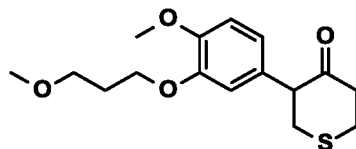
To a solution of *tert*-butyl 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-4-oxo-piperidine-1-carboxylate (4.0 g) in MeCN (50 mL) was added 6 M hydrochloric acid (10 mL). The mixture was stirred at rt for 30 minutes, then basified with aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidin-4-one (2.5 g), which was used in the next step without further purification.

Step 3: Preparation of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-1-methyl-piperidin-4-one



To a solution of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]piperidin-4-one (2.5 g, 12.9 mmol) in MeCN (40 mL) was added K₂CO₃ (3.56 g, 25.8 mmol) and iodomethane (1.2 mL, 19.4 mmol). The reaction was stirred at rt for 16 hrs, and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to give 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-1-methyl-piperidin-4-one (2.0 g).

Step 4: Preparation of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-one



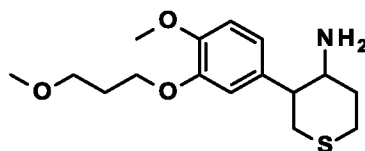
To a solution of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]-1-methyl-piperidin-4-one (2.0 g, 6.5 mmol) in isobutyl methylketone (20 mL) was added methyl trifluoromethanesulfonate (0.69 mL, 6.5 mmol) slowly at °C. The mixture was allowed to warm to rt and stirred for 30 minutes at rt. To the above mixture was added a solution of sodium hydrogen sulfide (1.82 g, 32.5 mmol) and sodium sulfide nonahydrate (1.56 g, 6.5 mmol) in water (10 mL). The resulting mixture was heated at 100 °C with stirring for 4 hrs. After being cooled to rt, the mixture was partitioned between brine and EtOAc. The organic layer was

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separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to give 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-one (600 mg).

Step 5: Preparation of 3-[4-methoxy-3-(3-

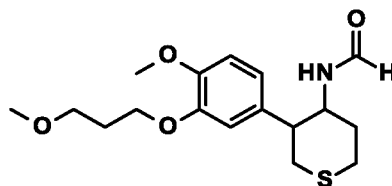
5 methoxypropoxy)phenyl]tetrahydrothiopyran-4-amine



To a solution of 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-one (0.6 g, 1.93 mmol) in MeOH (50 mL) was added ammonium acetate (2.2 g, 28.95 mmol) and sodium cyanoborohydride (0.36 g, 5.79 mmol). The reaction mixture was stirred at rt for 24 hrs, and then quenched with 4 M sodium hydroxide aqueous solution. The resulting mixture was stirred at rt for 4 hrs, and then partitioned between brine and DCM. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-amine, which was used in the next step without further purification.

Step 6: Preparation of N-[3-[4-methoxy-3-(3-

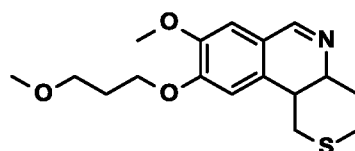
15 methoxypropoxy)phenyl]tetrahydrothiopyran-4-yl]formamide



To a solution of crude 3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-amine (all the crude product from the above step) in dioxane (10 mL) was added formic acid (0.22 mL, 5.79 mmol). The reaction mixture was heated at 100 °C with stirring for 14 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography to give N-[3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-yl]formamide (0.52 g).

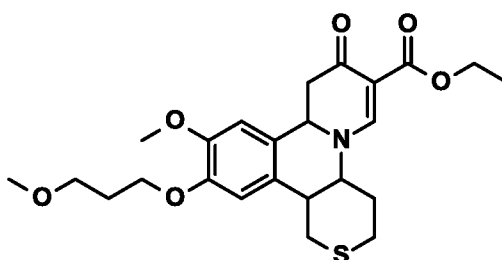
Step 7: Preparation of 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1H-

25 thiopyrano[4,3-c]isoquinoline



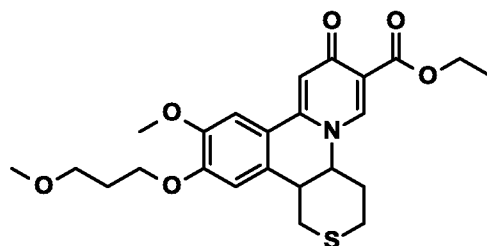
To a solution of *N*-[3-[4-methoxy-3-(3-methoxypropoxy)phenyl]tetrahydrothiopyran-4-yl]formamide (0.52 g, 1.53 mmol) in MeCN (10 mL) was added phosphorus oxychloride (0.21 mL, 2.3 mmol). The reaction mixture was heated at 50 °C for 3 hrs, and then concentrated under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ solution and DCM. The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-thiopyrano[4,3-*c*]isoquinoline, which was used in the next step without further purification.

Step 8: Preparation of ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrido[2,1-*a*]thiopyrano[4,3-*c*]isoquinoline-7-carboxylate



To a solution of crude 8-methoxy-9-(3-methoxypropoxy)-3,4,4a,10b-tetrahydro-1*H*-thiopyrano[4,3-*c*]isoquinoline (all the crude product from the above step) in EtOH (10 mL) was added ethyl 2-(ethoxymethylene)-3-oxo-butanoate (0.85 g, 4.59 mmol). The reaction mixture was heated at 100 °C for 18 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure to give crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrido[2,1-*a*]thiopyrano[4,3-*c*]isoquinoline-7-carboxylate, which was used in the next step without further purification.

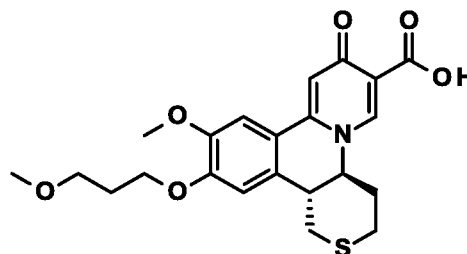
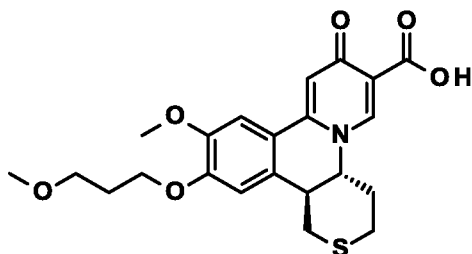
Step 9: Preparation of ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-*a*]thiopyrano[4,3-*c*]isoquinoline-7-carboxylate



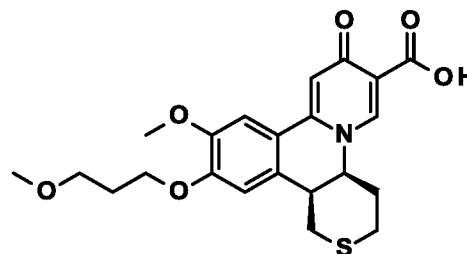
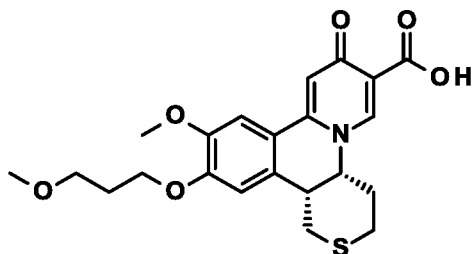
To a solution of crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,9,9a,13b-octahydropyrido[2,1-*a*]thiopyrano[4,3-*c*]isoquinoline-7-carboxylate (all the crude product from the above step) in DME (10 mL) was added *p*-chloranil (0.26 g, 1.07 mmol). The reaction mixture was heated at 70 °C for 3 hrs, then concentrated under reduced pressure to give crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-

hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylate, which was used in the next step without further purification.

Step 10: Preparation of *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid and *cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid



Example 35



Example 36

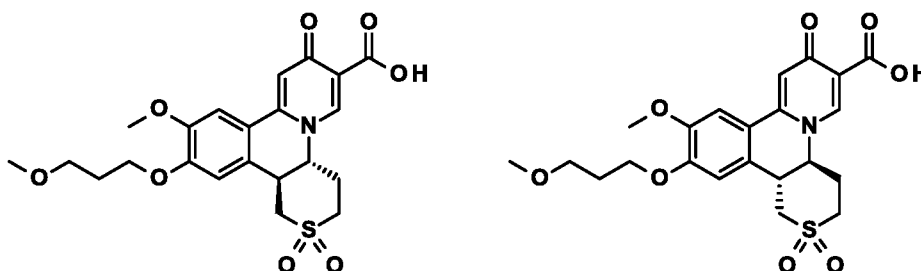
To a solution of crude ethyl 11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylate (all the crude product from the above step) in a mixture solvent of methanol (9 mL) and water (3 mL) was added LiOH·H₂O (0.19 g, 4.59 mmol). The mixture was stirred at rt for 2 hrs, and then acidified with 6 M hydrochloric acid. The mixture was partitioned between brine and DCM. The organic layer was separated and concentrated under reduced pressure. The residue was purified by preparative HPLC to give *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid (26 mg) and *cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid (4 mg).

Example 35: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.60 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.11 (s, 1H), 4.19 - 4.12 (m, 2H), 3.96 - 3.85 (m, 4H), 3.78-3.65 (m, 1H), 3.50-3.43 (m, 2H), 3.26 (s, 3H), 3.14 - 3.05 (m, 1H), 3.07 - 2.92 (m, 2H), 2.82 - 2.72 (m, 2H), 2.18 - 2.06 (m, 1H), 2.03-1.96 (m, 2H). MS obsd. (ESI⁺) [(M+H)⁺]: 432.

Example 36: ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm 8.80 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.09 (s, 1H), 4.77 - 4.68 (m, 1H), 4.20 - 4.07 (m, 2H), 3.90 (s, 3H), 3.80 - 3.75 (m, 1H), 3.65 - 3.57 (m, 1H), 3.51-3.46 (m, 2H), 3.26 (s, 3H), 3.17-3.09 (m, 1H), 2.85 - 2.76 (m, 1H), 2.04 - 1.90 (m, 4H), 1.65 - 1.52 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 432.

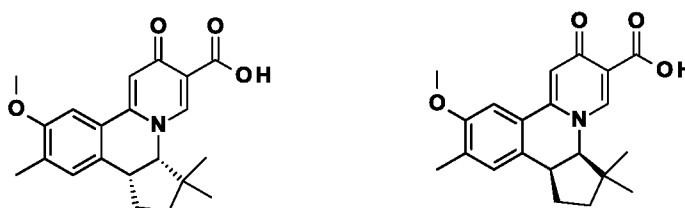
5

Example 37: *Trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid 2,2-dioxide



To a solution of *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid (20 mg, 0.05 mmol) in DCM (3 mL) was added 3-chloroperoxybenzoic acid (24.0 g, 0.1 mmol). The reaction mixture was stirred at rt for 30 hrs, and then concentrated under reduced pressure. The residue was purified by preparative HPLC to give *trans*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid 2,2-dioxide (4 mg). ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm 8.69 - 8.59 (s, 1H), 7.57 - 7.51 (s, 1H), 7.46 - 7.40 (s, 1H), 7.10 - 7.04 (s, 1H), 4.39 - 4.31 (m, 1H), 4.20-4.08 (m, 3H), 3.91 (s, 3H), 3.72 - 3.61 (m, 1H), 3.54 - 3.43 (m, 3H), 3.26 (s, 3H), 3.19-3.16 (m, 4H), 2.05-1.92 (m, 2H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 464.

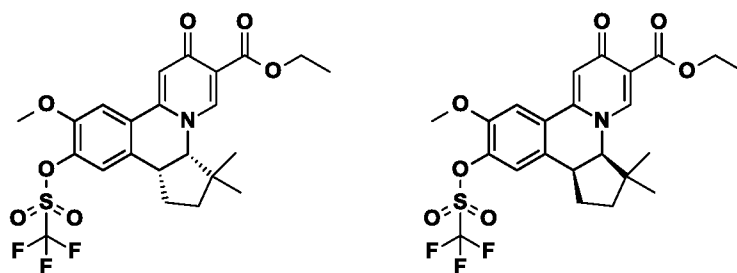
Example 38: *Cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



Step 1: Preparation of *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate

25

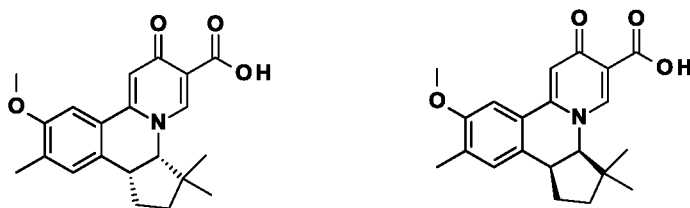
-75-



To a solution of *cis*-ethyl 11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (1.53 g, 4 mmol) and triethylamine (1.21 g, 12 mmol) in CH₂Cl₂ (15 mL) was added *N*-phenyl-

- 5 bis(trifluoromethanesulfonimide) (2.14 g, 6 mmol) at 0 °C dropwise. The mixture was stirred at 0 °C to rt overnight, and then diluted with CH₂Cl₂. The resulting mixture was washed with 1 M hydrochloric acid and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to afford *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-(((trifluoromethyl)sulfonyl)oxy)-
- 10 1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (1.21 g) as a yellow solid.

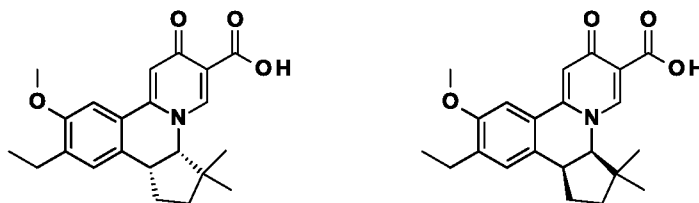
Step 2: Preparation of *cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



- 15 A mixture of *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (103 mg, 0.2 mmol), methylboronic acid (24 mg, 0.4 mmol), K₂CO₃ (83 mg, 0.6 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (15 mg, 0.02 mmol) in THF (2.4 mL) and water (0.6 mL) was heated at 60 °C with stirring overnight under argon. After being cooled to rt,
- 20 to the mixture was added 4 M sodium hydroxide solution (0.5 mL, 2 mmol). The resulting mixture was stirred at rt for 1 h, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3,11-trimethyl-7-oxo-
- 25 1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (17 mg) as a

yellow solid. ^1H NMR (400MHz, CDCl_3) δ ppm 8.47 (s, 1H), 7.39 (s, 1H), 7.19 (s, 1H), 7.17 (s, 1H), 4.18 (d, 1H), 3.93 (s, 3H), 3.84 - 3.76 (m, 1H), 2.37 - 2.26 (m, 2H), 2.31 (s, 3H), 1.68 (ddd, 1H), 1.50 (td, 1H), 1.28 (s, 3H), 0.53 (s, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 354.

5 **Example 39: *Cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**

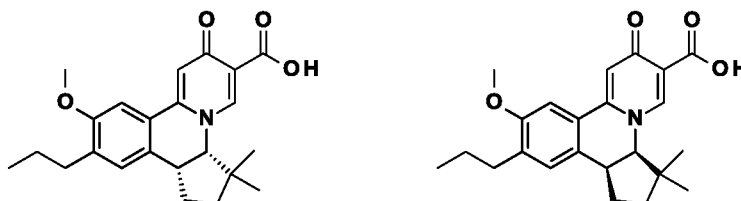


A mixture of *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (155 mg, 0.3 mmol), ethylboronic acid (89 mg, 1.2 mmol), K_2CO_3 (249 mg, 1.8mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (44 mg, 0.06 mmol) in THF (3.6 mL) and water (0.9 mL) was heated at 65 °C with stirring overnight under argon. After being cooled to rt, to the mixture was added 4 M sodium hydroxide solution (1.5 mL, 6 mmol). The resulting mixture was stirred at rt for 1 h, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3.

15 The mixture was extracted with CH_2Cl_2 for three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (9 mg) as a yellow solid. ^1H NMR (400MHz, CDCl_3) δ ppm 8.47 (s, 1H), 7.42 (s, 1H), 7.19 (s, 1H), 7.18 (s, 1H), 4.18 (d, 1H), 3.93 (s, 3H), 3.85 - 3.78(m, 1H), 2.81 - 2.63 (m, 2H), 2.39 - 2.26 (m, 2H), 1.68 (ddd, 1H), 1.50 (td, $J=8.4, 12.9$ Hz, 1H), 1.28 (s, 3H), 1.24 (t, 3H), 0.53 (s, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 368.

20

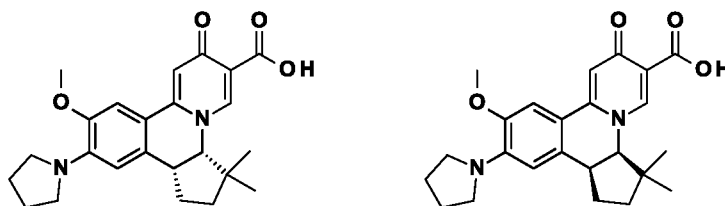
25 **Example 40: *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-propyl-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid**



A mixture of *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-

(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (155 mg, 0.3 mmol), propylboronic acid (105 mg, 1.2 mmol), K₂CO₃ (249 mg, 1.8 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (44 mg, 0.06 mmol) in THF (3.6 mL) and water (0.9 mL) was heated at 65 °C overnight under argon. After being cooled to rt, to the mixture was added 4 M sodium hydroxide solution (1.5 mL, 6 mmol). The mixture was stirred at rt for 1 h, then diluted with water and acidified with 2 M hydrochloric acid to pH=2-3. The resulting mixture was extracted with CH₂Cl₂ for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-7-oxo-11-propyl-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (12 mg) as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ ppm 8.46 (s, 1H), 7.37 (s, 1H), 7.18 (s, 1H), 7.17 (s, 1H), 4.17 (d, 1H), 3.92 (s, 3H), 3.85 - 3.77 (m, 1H), 2.74 - 2.59 (m, 2H), 2.38 - 2.28 (m, 2H), 1.65 (m, 2H), 1.54 - 1.44 (m, 1H), 1.28 (s, 3H), 1.25 (s, 1H), 0.98 (t, 3H), 0.53 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 382.

Example 41: *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid



To a solution of *cis*-ethyl 10-methoxy-3,3-dimethyl-7-oxo-11-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylate (155 mg, 0.3 mmol) in NMP (2 mL) was added pyrrolidine (107 mg, 1.5 mmol). The reaction vessel was sealed and heated to 150 °C under microwave irradiation for 3 hrs. After being cooled to rt, to the resulting mixture was added 4 M sodium hydroxide aqueous solution (1.5 mL, 6 mmol). The resulting mixture was stirred at rt for 1 h, and then purified by prep-HPLC to afford *cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid (18 mg) as a yellow powder. ¹H NMR (400MHz, CDCl₃) δ ppm 8.37 (s, 1H), 7.08 (s, 1H), 7.07 (s, 1H), 6.46 (s, 1H), 4.10 (d, 1H), 3.87 (s, 3H), 3.78 - 3.70 (m, 1H), 3.63 - 3.49 (m, 4H), 2.34 - 2.25 (m, 2H), 2.02 - 1.94 (m, 4H), 1.69 - 1.49 (m, 2H), 1.26 (s, 3H), 0.56 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 409.

BIOLOGICAL EXAMPLES

Example 42 materials and methods

HBV cell line

- 5 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), supplemented with 10% fetal bovine serum (Invitrogen) and G418 (Invitrogen) at a final concentration of 200 mg/L and maintained in 5% CO₂ at 37°C.

10 HBsAg Assay

HepG2.2.15 cells were seeded in duplicate into white, 96-well plates at 1.5×10^4 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 IC₅₀ value was extrapolated by using the E-WorkBook Suite (ID Business Solutions Ltd., Guildford, UK). The IC₅₀ 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.

- The compounds of the present invention were tested for their activity to inhibit HBsAg as described herein. The Examples were tested in the above assay and found to have IC₅₀ below 25.0 µM. Particular compounds of formula I were found to have IC₅₀ below 0.100 µM. More Particular compounds of formula I were found to have IC₅₀ below 0.010 µM. Results of HBsAg assay are given in Table 1.

Table 1: Activity data in HBsAg assay

Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)
1	0.01	12	0.004	23	0.002	34	0.186
2	0.001	13	0.005	24	0.02	35	0.11
3	0.003	14	0.003	25	0.006	36	0.028
4	0.003	15	0.006	26	0.002	37	2.202
5	0.308	16	0.128	27	0.02	38	0.036
6	0.084	17	0.025	28	0.003	39	0.02
7	0.005	18	0.01	29	0.152	40	0.019
8	0.003	19	0.505	30	0.564	41	<0.0016
9	0.001	20	0.002	31	0.12		
10	0.001	21	0.017	32	0.044		
11	0.004	22	0.001	33	0.265		

HBV DNA assay

The assay employs real-time qPCR (TaqMan) to directly measure extracellular HBV DNA copy number. HepG2.2.15 cells were plated in 96-well microtiter plates. Only the interior wells were utilized to reduce “edge effects” observed during cell culture, the exterior wells were filled with complete medium to help minimize sample evaporation. On the following day, the HepG2.2.15 cells were washed and the medium was replaced with complete medium containing various concentrations of a test compound in triplicate. 3TC was used as the positive control, while media alone was added to cells as a negative control (virus control, VC). Three days later, the culture medium was replaced with fresh medium containing the appropriately diluted drug. Six days following the initial administration of the test compound, the cell culture supernatant was collected, treated with pronase and then used in a real-time qPCR/TaqMan assay to determine HBV DNA copy numbers. Antiviral activity was calculated from the reduction in HBV DNA levels (IC₅₀).

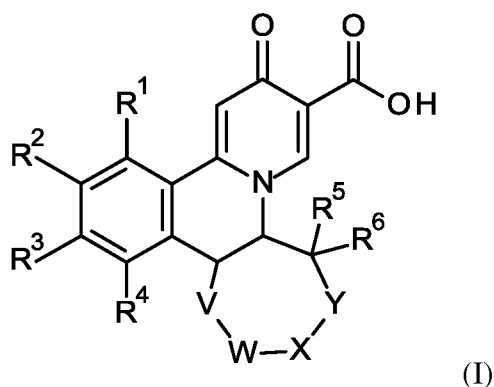
The compounds of the present invention were tested for their activity to anti HBV DNA production as described herein. The Examples were tested in the above assay and found to have IC₅₀ below 25.0 μ M. Particular compounds of formula I were found to have IC₅₀ below 0.10 μ M. Results of HBV DNA assay are given in Table 2.

5 Table 2: Anti HBV DNA production activity in HepG2.2.15 cells

Example No.	IC ₅₀ (μ M)
3	0.04
28	<0.032

Claims

1. A compound of formula I,



5 wherein

R^1 , R^2 , R^3 and R^4 are independently selected from hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, halogen, cyano, amino, C_{1-6} alkylamino, di C_{1-6} alkylamino, pyrrolidinyl and OR^7 ;

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

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

10 R^7 is hydrogen; C_{1-6} alkyl; halo C_{1-6} alkyl; C_{3-7} cycloalkyl C_{1-6} alkyl; phenyl C_{1-6} alkyl; cyano C_{1-6} alkyl; hydroxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; carboxy C_{1-6} alkyl; C_{1-6} alkoxycarbonyl C_{1-6} alkyl; C_{1-6} alkylsulfanyl C_{1-6} alkyl; C_{1-6} alkylsulfonyl C_{1-6} alkyl; amino C_{1-6} alkyl; C_{1-6} alkylamino C_{1-6} alkyl; di C_{1-6} alkylamino C_{1-6} alkyl; C_{1-6} alkylcarbonylamino C_{1-6} alkyl; C_{1-6} alkylsulfonylamino C_{1-6} alkyl; C_{1-6} alkoxycarbonylamino C_{1-6} alkyl; or heterocycloalkyl C_{1-6} alkyl, wherein heterocycloalkyl is *N*-
15 containing monocyclic heterocycloalkyl;

One of V, W, X and Y is selected from CR^8R^9 , O, S, SO_2 and NR^{10} , the others of V, W, X and Y are independently selected from a bond and CR^8R^9 , wherein

R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

20 R^{10} is phenyl C_{1-6} alkoxycarbonyl, phenyl C_{1-6} alkylcarbonyl, phenyl C_{1-6} alkylsulfonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl, or C_{1-6} alkylsulfonyl;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

2. A compound of formula I according to claim 1, wherein

25 R^1 is hydrogen;

R^2 is halogen or C_{1-6} alkoxy;

R^3 is selected from C_{1-6} alkyl, pyrrolidinyl or OR^7 , wherein

R⁷ is hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, phenylC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxyC₁₋₆alkyl, C₁₋₆alkoxycarbonylC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl, morpholinylC₁₋₆alkyl, pyrrolidinylC₁₋₆alkyl or (2-oxo-pyrrolidinyl)C₁₋₆alkyl;

R⁴ is hydrogen;

R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen or C₁₋₆alkyl;

10 V and Y are CH₂;

X is selected from a bond, CH₂, O, S, SO₂ and phenylC₁₋₆alkoxycarbonylamino when W is a bond; or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

15

3. A compound of formula I according to claim 1 or 2, wherein

R¹ is hydrogen;

R² is chloro or methoxy;

R³ is selected from methyl, ethyl, propyl, pyrrolidinyl, hydroxy, methoxy, difluoroethoxy,

20 trifluoroethoxy, cyclopropylmethoxy, benzyloxy, cyanopropoxy, hydroxypropoxy,

hydroxyhexyloxy, hydroxydimethylpropoxy, methoxyethoxy, methoxypropoxy,

carboxypropoxy, ethoxycarbonylpropoxy, methylsulfanylpropoxy, methylsulfonylpropoxy,

aminohexyloxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy, *tert*-

butoxycarbonylaminohexyloxy, morpholinylpropoxy, pyrrolidinylpropoxy and (2-oxo-

25 pyrrolidinyl)propoxy;

R⁴ is hydrogen;

R⁵ is hydrogen or methyl;

R⁶ is hydrogen or methyl;

V and Y are CH₂;

30 X is selected from a bond, CH₂, O, S, SO₂ and phenylmethoxycarbonylamino when W is a bond; or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

4. A compound of formula I according to any one of claims 1 to 3, wherein
R¹ is hydrogen;
R² is C₁₋₆alkoxy;
- 5 R³ is selected from C₁₋₆alkyl, pyrrolidinyl or OR⁷, wherein R⁷ is hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, phenylC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxyC₁₋₆alkyl, C₁₋₆alkoxycarbonylC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl, morpholinylC₁₋₆alkyl,
10 pyrrolidinylC₁₋₆alkyl or (2-oxo-pyrrolidinyl)C₁₋₆alkyl;
R⁴ is hydrogen;
R⁵ is C₁₋₆alkyl;
R⁶ is C₁₋₆alkyl;
V and Y are CH₂;
- 15 W is a bond;
X is a bond;
or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.
5. A compound of formula I according to any one of claim 1 to 4, or pharmaceutically
20 acceptable salts, or enantiomers, or diastereomer thereof, wherein R² is methoxy.
6. A compound of formula I according to any one of claim 1 to 5, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R³ is OR⁷, wherein R⁷ is C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₇cycloalkylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfanylC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl, C₁₋₆alkoxycarbonylaminoC₁₋₆alkyl or morpholinylC₁₋₆alkyl.
25
7. A compound of formula I according to any one of claim 1 to 6, or pharmaceutically
30 acceptable salts, or enantiomers, or diastereomer thereof, wherein R³ is selected from methoxy, difluoroethoxy, trifluoroethoxy, cyclopropylmethoxy, hydroxypropoxy, hydroxyhexyloxy, hydroxydimethylpropoxy, methoxyethoxy, methoxypropoxy, methylsulfanylpropoxy,

methylsulfonylpropoxy, aminohexyloxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy, *tert*-butoxycarbonylaminohexyloxy or morpholinylpropoxy.

8. A compound of formula I according to any one of claim 1 to 7, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R⁵ is methyl; R⁶ is methyl.
9. A compound of formula I according to any one of claims 1 to 3, wherein
R¹ is hydrogen;
R² is halogen or C₁₋₆alkoxy;
- 10 R³ is OR⁷; wherein R⁷ is phenylC₁₋₆alkyl or C₁₋₆alkoxyC₁₋₆alkyl;
R⁴ is hydrogen;
R⁵ is hydrogen;
R⁶ is hydrogen;
V and Y are CH₂;
- 15 X is selected from CH₂, O, S, SO₂ and phenylC₁₋₆alkoxycarbonylamino when W is a bond; or
X is CH₂ when W is CH₂;
or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.
10. A compound according to any one of claims 1 to 3 and 9, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R² is chloro or methoxy.
- 20 11. A compound according to any one of claims 1 to 3, 9 and 10, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein R³ is benzyloxy or methoxypropoxy.
- 25 12. A compound according to any one of claims 1 to 3 and 9 to 11, or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof, wherein X is CH₂ or S when W is a bond, or X is CH₂ when W is CH₂.
- 30 13. A compound according to claim 1 or 2, wherein
R¹ is hydrogen;
R² is halogen or C₁₋₆alkoxy;

R³ is selected from C₁₋₆alkyl, pyrrolidinyl or OR⁷, wherein R⁷ is haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfonylC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, C₁₋₆alkylsulfonylaminoC₁₋₆alkyl or morpholinylC₁₋₆alkyl;

R⁴ is hydrogen;

5 R⁵ is hydrogen or C₁₋₆alkyl;

R⁶ is hydrogen or C₁₋₆alkyl;

V and Y are CH₂;

X is a bond or S when W is a bond, or

X is CH₂ when W is CH₂;

10 or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

14. A compound according to claim 1, 2 or 13, wherein

R¹ is hydrogen;

R² is chloro or methoxy;

15 R³ is selected from ethyl, pyrrolidinyl, difluoroethoxy, trifluoroethoxy, hydroxydimethylpropoxy, methoxypropoxy, methylsulfonylpropoxy, methylcarbonylaminohexyloxy, methylsulfonylaminohexyloxy and morpholinylpropoxy;

R⁴ is hydrogen;

R⁵ is hydrogen or methyl;

20 R⁶ is hydrogen or methyl;

V and Y are CH₂;

X is a bond or S when W is a bond, or

X is CH₂ when W is CH₂;

or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

25

15. A compound according to claim 1, selected from

Trans-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

30 *Cis*-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

(3*aS*,12*bR*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

(3*aR*,12*bS*)-11-(benzyloxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

5 *Cis*-11-hydroxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-10,11-dimethoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

10 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-11-(cyclopropylmethoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

15 *Cis*-10-methoxy-11-(2-methoxyethoxy)-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-11-(3-cyanopropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

20 *Cis*-11-(3-hydroxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

25 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(pyrrolidin-1-yl)propoxy)-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(3-(2-oxopyrrolidin-1-yl)propoxy)-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

30 *Cis*-11-(4-ethoxy-4-oxobutoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-11-(3-carboxypropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3*a*,7,12*b*-hexahydrocyclopenta[*c*]pyrido[2,1-*a*]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-(methylthio)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

5 *Cis*-11-((6-hydroxyhexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-((tert-butoxycarbonyl)amino)hexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

10 *Cis*-11-((6-aminohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

15 *Trans*-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

Cis-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

20 *Trans*-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1H-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid;

Cis-2-((benzyloxy)carbonyl)-11-methoxy-12-(3-methoxypropoxy)-8-oxo-2,3,4,4a,8,13b-hexahydro-1H-benzo[c]pyrido[1,2-a][1,6]naphthyridine-7-carboxylic acid;

Trans-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid;

25 *Cis*-12-benzyloxy-11-methoxy-8-oxo-1,2,3,4,4a,13b-hexahydropyrido[1,2-f]phenanthridine-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid;

30 *Cis*-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrano[4,3-c]pyrido[2,1-a]isoquinoline-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

Cis-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

Trans-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid 2,2-dioxide;

5 *Cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

10 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-propyl-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;
or pharmaceutically acceptable salts, or enantiomers, or diastereomer thereof.

15 16. A compound according to claim 1, selected from

Trans-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-11-(3-methoxypropoxy)-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

20 *Cis*-10-methoxy-3,3-dimethyl-7-oxo-11-(2,2,2-trifluoroethoxy)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-11-isobutoxy-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

25 *Cis*-11-(3-hydroxy-2,2-dimethylpropoxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-morpholinopropoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-(3-(methylsulfonyl)propoxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

30 *Cis*-11-((6-acetamidohexyl)oxy)-10-methoxy-3,3-dimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-11-((6-(methylsulfonamido)hexyl)oxy)-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-13-chloro-12-(3-methoxypropoxy)-2-oxo-2,5a,6,7,8,9,10,10a-octahydrocyclohepta[c]pyrido[2,1-a]isoquinoline-3-carboxylic acid;

Cis-11-methoxy-12-(3-methoxypropoxy)-8-oxo-1,3,4,4a,8,13b-hexahydropyrido[2,1-a]thiopyrano[4,3-c]isoquinoline-7-carboxylic acid;

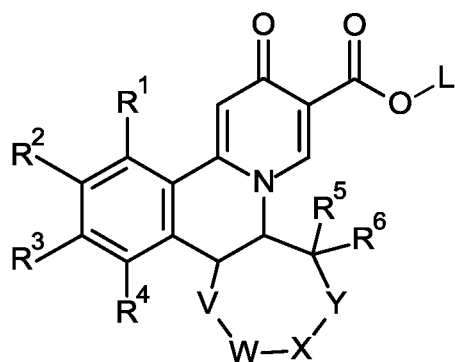
5 *Cis*-10-methoxy-3,3,11-trimethyl-7-oxo-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;

Cis-10-methoxy-3,3-dimethyl-7-oxo-11-(pyrrolidin-1-yl)-1,2,3,3a,7,12b-hexahydrocyclopenta[c]pyrido[2,1-a]isoquinoline-6-carboxylic acid;
or pharmaceutically acceptable salts, or enantiomers, or diastereomers thereof.

10

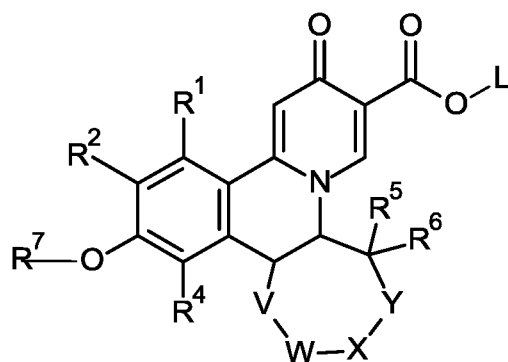
17. A process for the preparation of a compound according to any one of claims 1 to 16 comprising

(a) hydrolysis of a compound of formula (A)



(A); or

15 (b) hydrolysis of a compound of formula (B)



(B);

wherein R¹ to R⁷, V, W, X and Y are defined as in any one of claims 1 to 16, L is C₁₋₆alkyl.

18. A compound according to any one of claims 1 to 16 for use as therapeutically active
20 substance.

19. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 16 and a therapeutically inert carrier.

5 20. The use of a compound according to any one of claims 1 to 16 for the treatment or prophylaxis of HBV infection.

21. The use of a compound according to any one of claims 1 to 16 for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

10

22. The use of a compound according to any one of claims 1 to 16 for the inhibition of HBsAg production or secretion, or for the the inhibition of HBsAg production or secretion.

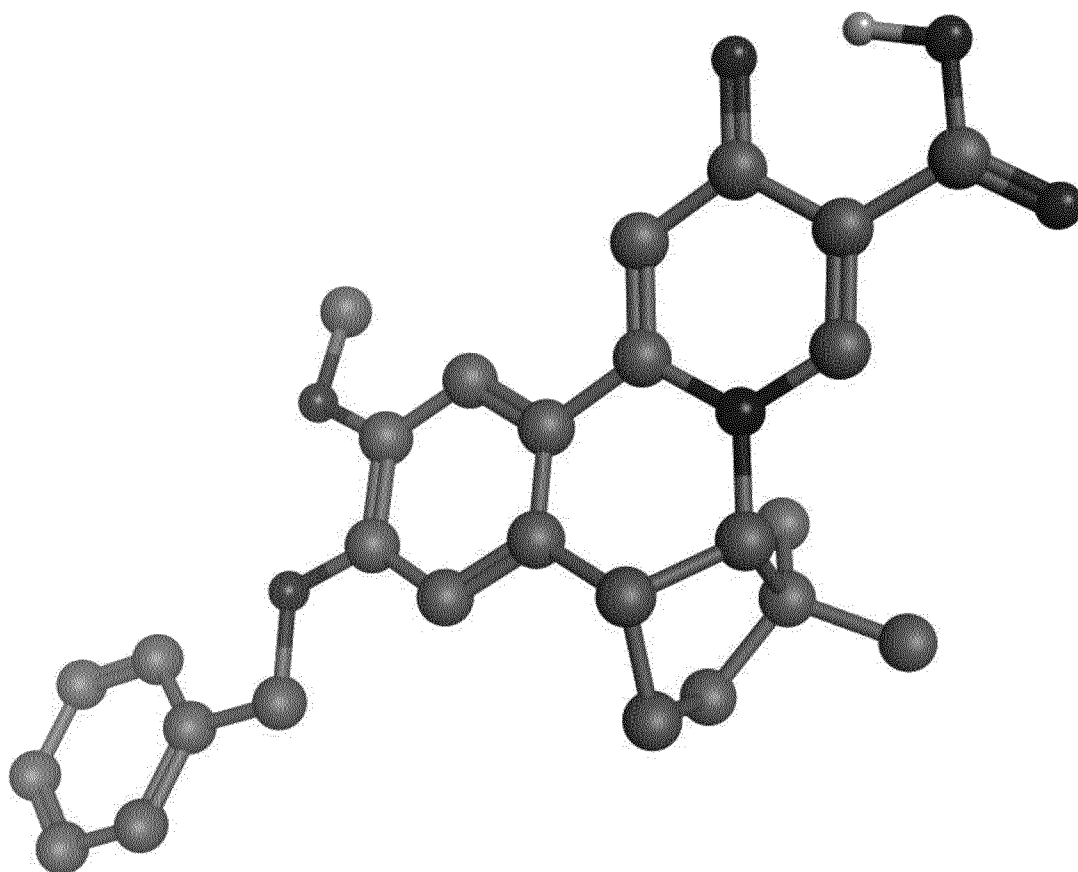
15 23. A compound according to any one of claims 1 to 16 for the treatment or prophylaxis of HBV infection.

24. A compound according to any one of claims 1 to 16, when manufactured according to a process of claim 17.

20 25. A method for the treatment or prophylaxis of HBV infection, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 16.

26. The invention as hereinbefore described.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/067607

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D455/06 C07D471/14 C07D491/147 C07D495/14 A61K31/4745
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)

C07D

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHANG-AN GENG ET AL: "Small-molecule inhibitors for the treatment of hepatitis B virus documented in patents", MINI REVIEWS IN MEDICINAL CHEMISTRY, vol. 13, no. 5, 2013, pages 749-776, XP009176654, ISSN: 1389-5575 the whole document figures; tables ----- -/--	1-26



Further documents are listed in the continuation of Box C.



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

"E" earlier application or patent but published on or after the international filing date

"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

29 August 2016

Date of mailing of the international search report

12/09/2016

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Authorized officer

Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/067607

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBERT A FECIK ET AL: "Chiral DNA chirase inhibitors.3. Probing the chiral preference of the active site of DNA Gyrase. Synthesis of 10-fluoro-6-methyl-6,7-dihydro-9-piperazinyl-2H-benzo[a]quinolizin-20-one-3-carboxylic acid analogues", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 4, 2005, pages 1229-1236, XP002736276, ISSN: 0022-2623, DOI: 10.1021/JM0401356 [retrieved on 2005-01-26] the whole document schemes 1-2; compounds 12, 22, 34-36 -----	1-26
A,P	WO 2015/113990 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 6 August 2015 (2015-08-06) the whole document -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/067607

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015113990 A1	06-08-2015	AU 2015212903 A1	19-05-2016
		CA 2931329 A1	06-08-2015
		TW 201540715 A	01-11-2015
		US 2015210682 A1	30-07-2015
		WO 2015113990 A1	06-08-2015
