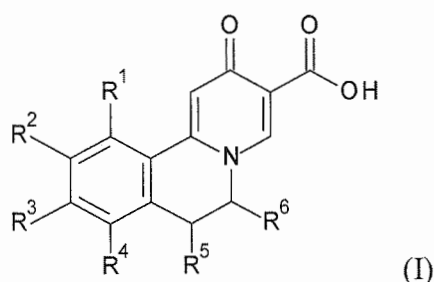


et al. *J Virol*, (2011), 85, 987-95; Woltman et al. *PLoS One*, (2011), 6, e15324; Op den Brouw et al. *Immunology*, (2009b), 126, 280-9).

SUMMARY OF THE INVENTION

In an aspect, there is provided the ~~The present invention relates to novel compounds of~~ formula I



wherein

- 10 R^1 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylamino or C_{1-6} alkoxy;
 R^2 is hydrogen; halogen; C_{1-6} alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C_{1-6} alkoxy, which is unsubstituted or once, twice or three times substituted by fluoro; cyano; C_{3-7} cycloalkyl; hydroxy or phenyl- C_xH_{2x} -O-;
 R^3 is hydrogen;
 15 halogen;
 C_{1-6} alkyl, which is unsubstituted or once, twice or three times substituted by fluoro;
 cyano;
 pyrrolidinyl;
 amino;
 20 phenyl- C_xH_{2x} -N(C_{1-6} alkyl)-;
 C_{1-6} alkoxycarbonylpiperazinyl;
 or R^7 -O-, wherein R^7 is hydrogen; C_{1-6} alkyl, which is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy and C_{2-6} alkenyl; C_{1-6} alkoxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkoxy C_{1-6} alkyl; amino C_{1-8} alkyl; C_{1-6} alkylcarbonylamino C_{1-8} alkyl; C_{1-6} alkylsulfonylamino C_{1-8} alkyl; C_{1-6} alkylsulfanyl C_{1-6} alkyl; C_{1-6} alkylsulfonyl C_{1-6} alkyl; cyano C_{1-6} alkyl; C_{3-7} cycloalkyl C_{1-6} alkyl; cyano C_{3-7} cycloalkyl C_{1-6} alkyl; phenyl C_{1-6} alkyl;
 25 pyrrolidinylcarbonyl C_{1-6} alkyl; C_{2-6} alkynyl; hydroxy C_{1-6} alkyl C_{2-6} alkynyl; amino C_{1-6} alkoxy C_{1-6} alkyl; C_{1-6} alkylamino C_{1-6} alkoxy C_{1-6} alkyl; di C_{1-6} alkylamino C_{1-6} alkoxy C_{1-6} alkyl; carboxy C_{1-6} alkyl; or C_{1-6} alkoxycarbonylamino C_{1-8} alkyl; heteroaryl C_{1-6} alkyl, wherein heteroaryl is *N*-

containing monocyclic heteroaryl; or heterocycloalkylC₁₋₆alkyl, wherein heterocycloalkyl is monocyclic heterocycloalkyl;

R⁴ is hydrogen, halogen, C₁₋₆alkyl, cyano or C₁₋₆alkoxy;

provided that R¹, R², R³ and R⁴ are not hydrogen simultaneously;

5 R⁵ is hydrogen or C₁₋₆alkyl;

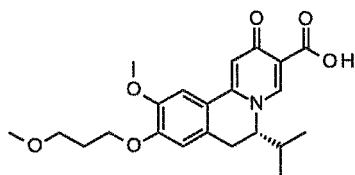
R⁶ is hydrogen; C₁₋₆alkyl, which is unsubstituted or once, twice or three times substituted by fluoro; C₃₋₇cycloalkyl, which is unsubstituted or once, twice or three times substituted by fluoro or C₁₋₆alkyl; or phenyl-C_xH_{2x-};

x is 1-6;

10 with the proviso that 6-methyl-2-oxo-9-pyrrolidin-1-yl-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; 9-fluoro-6-methyl-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid; and 9,10-difluoro-6-methyl-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid are excluded; or pharmaceutically acceptable salts, or enantiomers thereof.

In another aspect, there is provided the compound of formula (I)

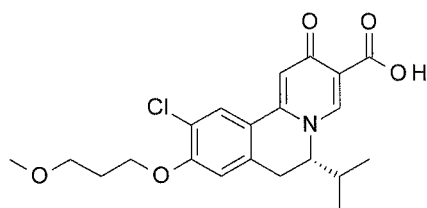
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Example 124

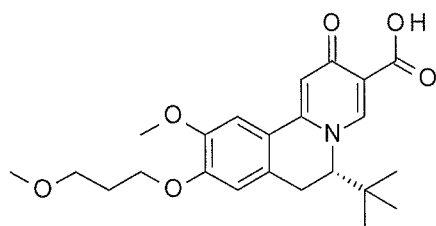
or pharmaceutically acceptable salts, or enantiomers thereof.

In another aspect, there is provided the compound of formula (I)



or pharmaceutically acceptable salts, or enantiomers thereof.

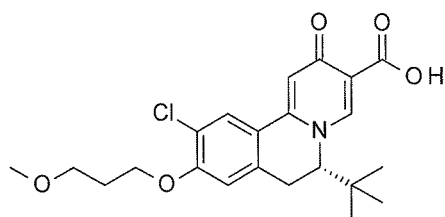
In another aspect, there is provided the compound of formula (I)



20

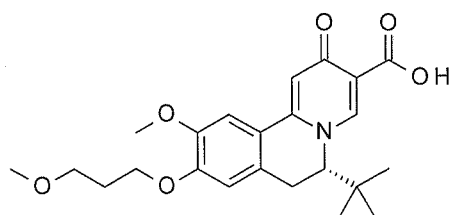
or pharmaceutically acceptable salts, or enantiomers thereof.

In another aspect, there is provided the compound of formula (I)



or pharmaceutically acceptable salts, or enantiomers thereof.

In another aspect, there is provided the compound of formula (I)

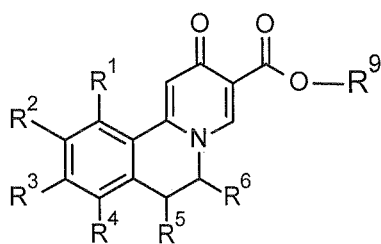


or pharmaceutically acceptable salts, or enantiomers

thereof.

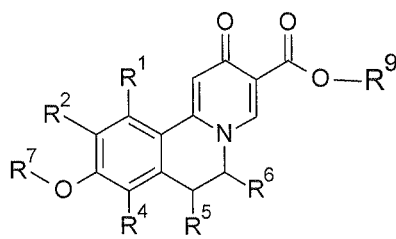
In another aspect, there is provided a process for the preparation of a compound as defined herein comprising

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



(A); or

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



(B);

wherein R¹ to R⁷ are defined herein, R⁹ is C₁₋₆alkyl.

In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the inhibition of HBsAg production or secretion.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the inhibition of HBV DNA production.

5 In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of HBV infection.

In another aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.

10 The ~~invention-disclosure~~ is also relates to their manufacture, medicaments based on a compound in accordance with the ~~invention-disclosure~~ and their production as well as the use of compounds of formula I as HBsAg inhibitors and HBV DNA production inhibitors. Accordingly, the compounds of formula I are useful for the treatment or prophylaxis of HBV infection.

DETAILED DESCRIPTION OF THE INVENTION

15

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.

20 The term “C₂₋₆alkenyl” denotes an unsaturated, linear or branched chain alkenyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example vinyl, propenyl, allyl, butenyl and the like. Particular “C₂₋₆alkenyl” group is allyl and vinyl.

25 The term “C₂₋₆alkynyl” denotes an unsaturated, linear or branched chain alkynyl group containing 2 to 6, particularly 2 to 4 carbon atoms, for example ethynyl, 1-propynyl, propargyl, butynyl and the like. Particular “C₂₋₆alkynyl” groups are ethynyl and 1-propynyl.

The term “C_xH_{2x}” alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

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

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

5 6-Cyclobutyl-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

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

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

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

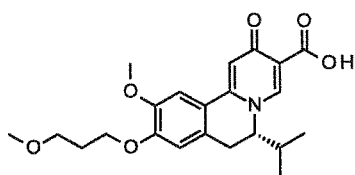
10-Methoxy-9-(3-methoxypropoxy)-6-(1-methylcyclopropyl)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

15 (6*R**, 7*S**)-10-Chloro-6-ethyl-9-(2-methoxyethoxy)-7-methyl-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

10,11-Difluoro-6-isopropyl-9-(3-methoxypropoxy)-2-oxo-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

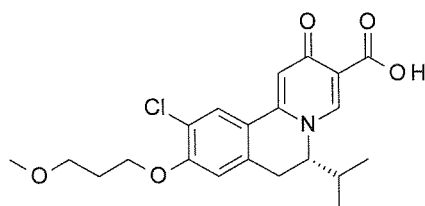
20 23. The compound of formula (I)



Example 124

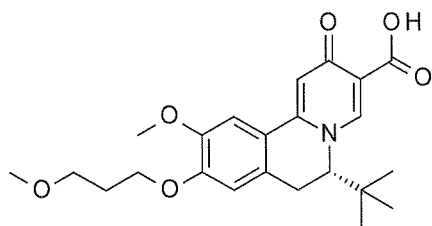
or pharmaceutically acceptable salts, or enantiomers thereof.

24. The compound of formula (I)



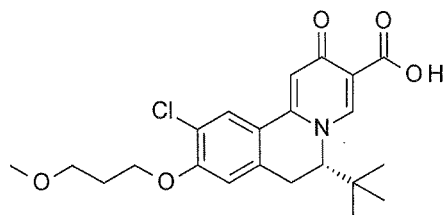
or pharmaceutically acceptable salts, or enantiomers thereof.

25. The compound of formula (I)



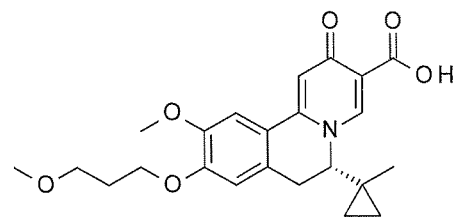
or pharmaceutically acceptable salts, or enantiomers thereof.

26. The compound of formula (I)



or pharmaceutically acceptable salts, or enantiomers thereof.

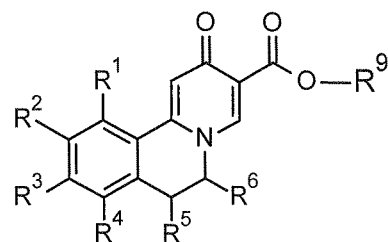
5 27. The compound of formula (I)



or pharmaceutically acceptable salts, or enantiomers thereof.

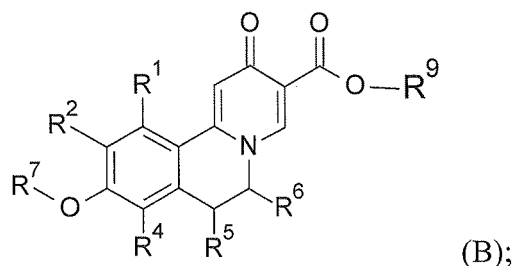
23.28. A process for the preparation of a compound according to any one of claims 1 to 22 comprising

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



(A); or

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



wherein R¹ to R⁷ are defined as in any one of claims 1 to 20, R⁹ is C₁₋₆alkyl.

5 | ~~24.29.~~ A compound according to any one of claims 1 to ~~22.27~~ for use as therapeutically active substance.

~~25.30.~~ A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to ~~22.27~~ and a therapeutically inert carrier.

10

~~26.~~ The use of a compound according to any one of claims 1 to ~~22~~ for the treatment or prophylaxis of HBV infection.

15

~~27.31.~~ The use of a compound according to any one of claims 1 to ~~22.27~~ for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

~~28.32.~~ The use of a compound according to any one of claims 1 to ~~22.27~~ for the preparation of a medicament for the inhibition of HBsAg production or secretion.

20

~~29.33.~~ The use of a compound according to any one of claims 1 to ~~22.27~~ for the preparation of a medicament for the inhibition of HBV DNA production.

~~30.34.~~ A compound according to any one of claims 1 to ~~22.27~~ for the treatment or prophylaxis of HBV infection.

25

~~31.35.~~ A compound according to any one of claims 1 to ~~22.27~~, when manufactured according to a process of claim ~~23.28~~.

30

~~32.~~ 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 ~~22~~.