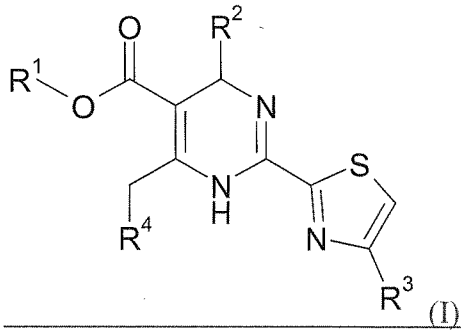
the formation of empty capsids. These very interesting results illustrate the importance of the kinetic pathway in successful virus assembly.

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

SUMMARY ~~OF THE INVENTION~~

Objects of the ~~present invention~~embodiments disclosed herein are novel compounds of formula I, 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 for the treatment or prophylaxis of HBV infection.

In one aspect, there is provided a compound of formula (I)



(I)

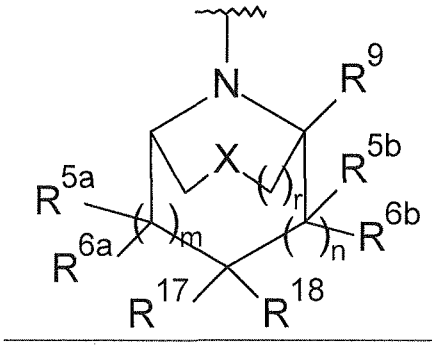
wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen or C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen, halogen or hydroxy;

one of R^{5b} and R^{6b} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, halogen, hydroxy, amino, C_{1-6}alkylsulfonylamino or trifluoromethylcarbonylamino, the other one is hydrogen, halogen, hydroxy-C_yH_{2y}-, C_{1-6}alkylcarbonyl-O-, C_{1-6}alkoxycarbonyl-C_yH_{2y}-, carboxy-C_yH_{2y}-O-, carboxy-C_yH_{2y}-, C_{1-6}alkylcarbonyl-NH-, C_{1-6}alkylsulfonyl-NH-, aminocarbonyl-NH- or aminosulfonyl-NH-;

wherein -C_yH_{2y}- is unsubstituted once or more times substituted by hydroxy;

or R^{6a} and R^{17} together with the carbon atoms, to which they are attached, form a ring of isoxazolyl, pyrazolyl or oxo-dihydropyrazolyl, which ring is unsubstituted or once or more times substituted by C_{1-6}alkyl;

or R^{17} and R^{18} together with the carbon atom, to which they are attached, form diazirinyl;

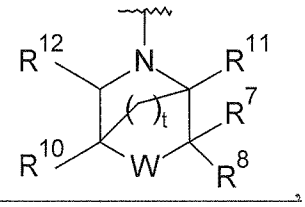
X is oxygen; sulfur; -N(carbonylC_{1-6}alkyl)-; or -C($R^{15}R^{16}$)-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy-C_yH_{2y}-;

r is 0 or 1;

m is 0 or 1;

n is 0 or 1;

y is 0-6;

or R^4 is ,

wherein R^7 is hydrogen or halogen;

R^8 is hydrogen or halogen;

R^{10} is hydrogen, halogen, hydroxy-C_yH_{2y}- or C_{1-6}alkylcarbonylamino-C_yH_{2y}-;

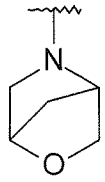
R^{11} is hydrogen or carboxy;

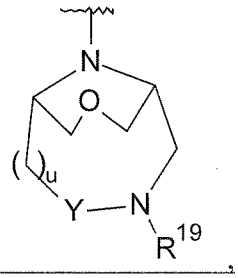
R^{12} is hydrogen or carboxy;

W is a bond, oxygen, $-CH_2-$, $-CF_2-$ or -N(carbonylC_{1-6}alkyl)-;

t is 1 or 2;

y is 0-6;

with the proviso that  is excluded;

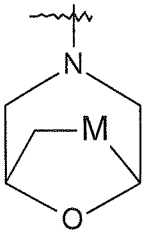
or R^4 is ,

wherein R^{19} is hydrogen; C_{1-6}alkyl, which is unsubstituted or once or more times substituted by halogen; C_{1-6}alkoxycarbonyl-C_yH_{2y}-; hydroxy-C_yH_{2y}-carbonyl; carboxy-C_yH_{2y}-carbonyl; C_{1-6}alkylaminosulfonyl; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfonyl; aminocarbonyl; or aminosulfonyl;

Y is carbonyl or $-CH_2-$;

u is 0 or 1;

y is 0-6;

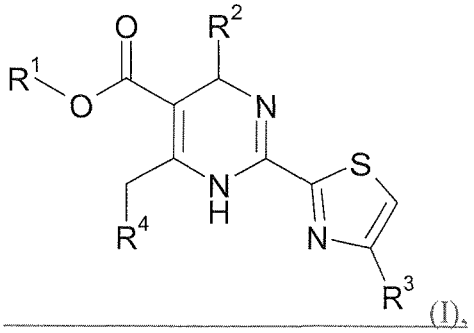
or R^4 is ,

wherein M is a bond, $-CH_2-$ or $-N(R^{14})-CH_2-$;

R^{14} is C_{1-6}alkoxycarbonyl;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

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



(I),

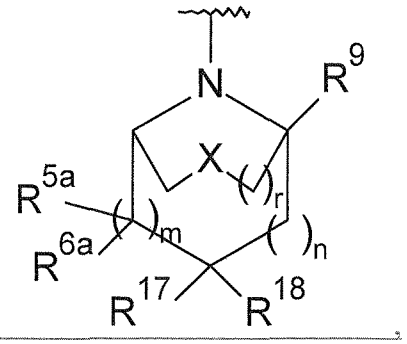
wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

R^4 is



wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, the other one is hydrogen or carboxy-C_yH_{2y}-;

X is oxygen; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy-C_yH_{2y}-;

r is 0 or 1;

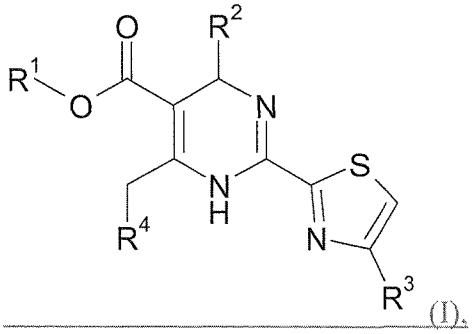
m is 1;

n is 0 or 1;

y is 0-6;

or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof.

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



(I),

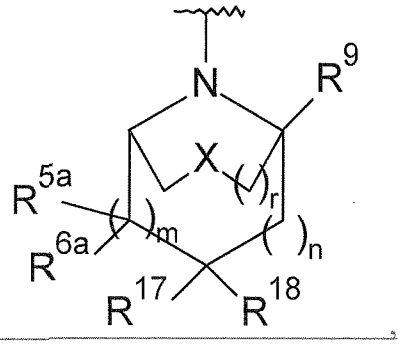
wherein

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R^3 is hydrogen;

R^4 is



,

wherein one of R^{5a} and R^{6a} is hydrogen or fluoro, and the other one is hydrogen or fluoro;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, the other one is hydrogen or carboxymethyl;

X is oxygen; or $-C(R^{15}R^{16})-$, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxymethyl;

r is 0 or 1;

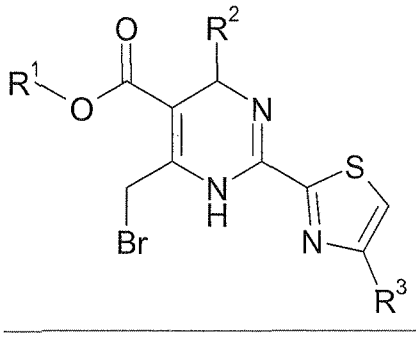
m is 1;

n is 0 or 1;

or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof.

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

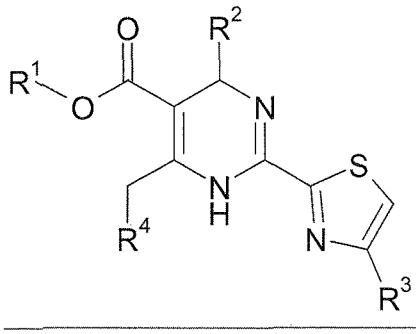
(a) a compound of formula (A)



(A)

with bridged amine in the presence of a base;

(b) a compound of formula (B)



(B)

under chiral separation condition;

wherein R^1 to R^4 are defined herein.

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 hepatitis B virus infection.

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

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

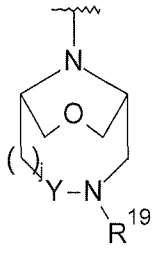
As used herein, the term "C_{1-6}alkyl" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups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

The term "cycloalkyl", 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 "cycloalkyl" groups are cyclopropyl, cyclopentyl and cyclohexyl.

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

R^4 is



,

wherein R^{19} is hydrogen, aminocarbonyl, aminosulfonyl or hydroxy-C_yH_{2y}-carbonyl;

Y is $-CH_2-$ or carbonyl;

j is 0 or 1;

y is 0-6;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

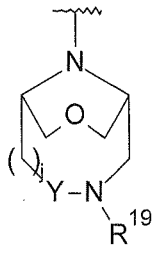
10. A compound according to claim 1 or 9, wherein

R^1 is methyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R^3 is hydrogen;

R^4 is



,

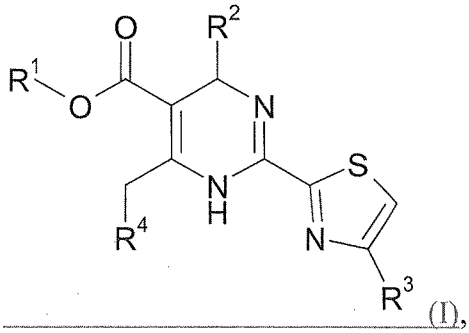
wherein R^{19} is hydrogen, aminocarbonyl, aminosulfonyl or hydroxymethylcarbonyl;

Y is $-CH_2-$ or carbonyl;

j is 0 or 1;

or pharmaceutically acceptable salts, or tautomerism isomers, or enantiomers, or diastereomers thereof.

11. A compound of formula (I)



(I),

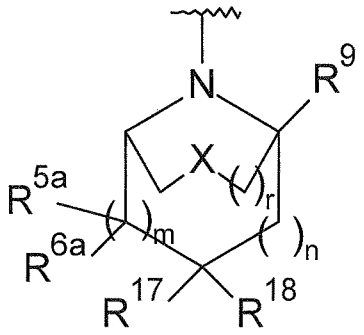
wherein

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

R^2 is phenyl, which is once or twice or three times substituted by halogen;

R^3 is hydrogen;

R^4 is



,

wherein one of R^{5a} and R^{6a} is hydrogen or halogen, and the other one is hydrogen or halogen;

R^9 is hydrogen or carboxy;

one of R^{17} and R^{18} is hydrogen, the other one is hydrogen or carboxy-C_yH_{2y}-;

X is oxygen; or -$C(R^{15}R^{16})$-, wherein one of R^{15} and R^{16} is hydrogen or hydroxy, and the other one is hydrogen or carboxy-C_yH_{2y}-;

r is 0 or 1;

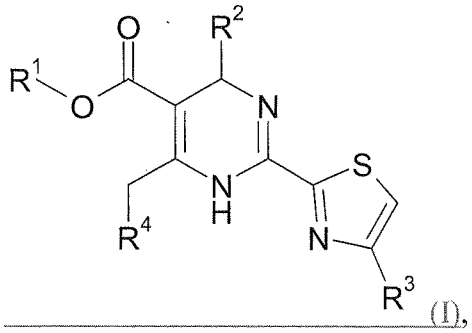
m is 1;

n is 0 or 1;

y is 0-6;

or a pharmaceutically acceptable salt or tautomerism isomers or enantiomers or diastereomers thereof.

12. A compound of formula (I)



(I),

wherein

R^1 is methyl or ethyl;

R^2 is phenyl, which is once or twice or three times substituted by fluoro or chloro;

R^3 is hydrogen;

R^4 is

(*R*)-4-(2-Chloro-4-fluoro-phenyl)-6-(7-methanesulfonylamino-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

~~(*R*)-4-(2-Chloro-4-fluoro-phenyl)-6-(2-methoxymethyl-azetidin-1-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;~~

(*R*)-4-(2-Chloro-4-fluoro-phenyl)-6-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(*S*)-3-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-3,6-diaza-bicyclo[3.2.1]octane-7-carboxylic acid;

2-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-4-fluoro-2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid;

(R)-6-(5-Acetyl-2,5-diaza-bicyclo[2.2.1]hept-2-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

6-(7-Carboxymethyl-3-thia-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(*R*)-6-(7-Diazirine-3-oxa-9-aza-bicyclo[3.3.1]non-9-ylmethyl)-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(*R*)-4-(2-Chloro-4-fluoro-phenyl)-6-((1*R*,3*R*,5*S*)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

(R)-4-(2-Chloro-4-fluoro-phenyl)-6-(9-oxa-3,4,11-triaza-tricyclo[5.3.1.0*2,6*]undeca-2(6),4-dien-11-ylmethyl)-2-thiazol-2-yl-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester;

2-[[(1R,5S)-9-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

2-[[(1R,5S)-9-[[(4S)-4-(3,4-difluorophenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl]oxy]acetic acid;

Methyl (4R)-6-[(6-acetamido-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-4-(2-chloro-4-fluoro-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

2-[[8-[[(4R)-4-(2-bromo-4-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxa-8-azabicyclo[3.2.1]octan-6-yl]oxy]acetic acid;

Methyl (4R)-4-(2-chloro-4-fluoro-phenyl)-6-[(6-fluoro-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl]-2-thiazol-2-yl-1,4-dihydropyrimidine-5-carboxylate;

23. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 20 and a therapeutically inert carrier.

~~24. The use of a compound according to any one of claims 1 to 20 for the treatment or prophylaxis of hepatitis B virus infection.~~

~~25~~24. The use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

~~26~~25. A compound according to any one of claims 1 to 20 for the treatment or prophylaxis of hepatitis B virus infection.

~~27. A compound according to any one of claims 1 to 20, when manufactured according to a process of claim 21.~~

~~28. A method for the treatment or prophylaxis of hepatitis B virus infection, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 20.~~