

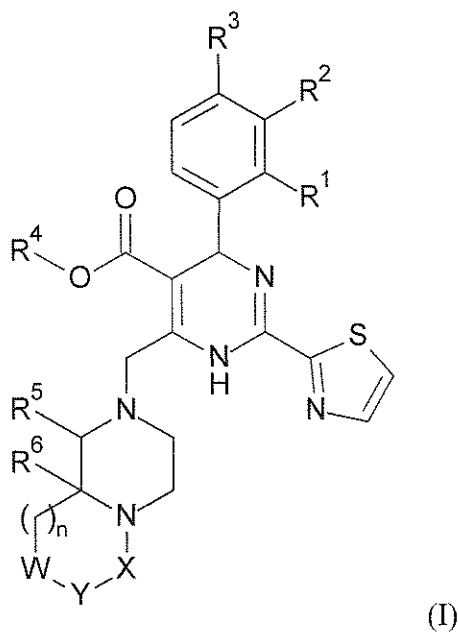
replication. The HBV capsid spontaneously self-assembles from many copies of core dimers present in the cytoplasm. It has been shown that the formation of a trimeric nucleus and the subsequent elongation reactions occur by adding one dimeric subunit at a time until it is complete. Besides this function, capsid protein regulates viral DNA synthesis through different phosphorylation status of its C-terminal phosphorylation sites. When a near full-length relaxed circular DNA is formed through reverse-transcription of viral pregenomic RNA, an immature capsid becomes a mature capsid. On one hand, capsid protein might facilitate the nuclear translocation of viral relaxed circular genome by means of the nuclear localization signals located in the Arginine-rich domain of the C-terminal region of capsid protein. In nucleus, as a component of viral cccDNA minichromosome, capsid protein could play a structural and regulatory role in the functionality of cccDNA minichromosomes. Capsid protein also interacts with viral large envelope protein in endoplasmic reticulum and triggers the release of intact viral particles from hepatocytes.

There has been a couple of capsid related anti-HBV inhibitors reported. For example, phenylpropenamide derivatives, including compounds named AT-61 and AT-130 (Feld J. et al. *Antiviral Research* **2007**, 168-177), and a class of thiazolidin-4-ones from Valeant R&D (WO2006/033995), have been shown to inhibit pgRNA packaging. A recent study suggested that phenylpropenamides are, in fact, accelerators of HBV capsid assembly, and their actions result in the formation of empty capsids. These very interesting results illustrate the importance of the kinetic pathway in successful virus assembly.

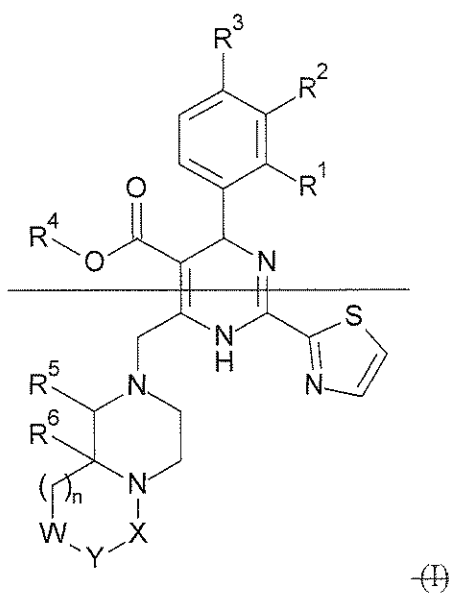
Heteroaryldihydropyrimidines or HAP, including compounds named Bay 41-4109, Bay 38-7690 and Bay 39-5493, were discovered in a tissue culture-based screening (Deres K. et al. *Science* **2003**, 893). These HAP analogs act as synthetic allosteric activators and are able to induce aberrant capsid formation 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

The present ~~invention~~ disclosure, in one aspect, relates to novel compounds of formula (I)



wherein



wherein

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

R^2 is hydrogen or halogen;

R^3 is hydrogen or halogen;

R^4 is C_{1-6} alkyl;

R^5 is hydrogen, hydroxy C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkoxycarbonyl or carboxy;

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

X is carbonyl or sulfonyl;

Y is $-\text{CH}_2-$, $-\text{O}-$ or $-\text{N}(\text{R}^7)-$,

wherein R^7 is hydrogen, C_{1-6} alkyl, halo C_{1-6} alkyl, C_{3-7} cycloalkyl- C_mH_{2m-} , C_{1-6} alkoxycarbonyl- C_mH_{2m-} , $-\text{C}_t\text{H}_{2t}-\text{COOH}$, $-\text{haloC}_{1-6}$ alkyl- COOH , $-(\text{C}_{1-6}\text{alkoxy})\text{C}_{1-6}$ alkyl- COOH , $-\text{C}_{1-6}$ alkyl- $\text{O}-\text{C}_{1-6}$ alkyl- COOH , $-\text{C}_{3-7}$ cycloalkyl- $\text{C}_m\text{H}_{2m}-\text{COOH}$, $-\text{C}_m\text{H}_{2m}-\text{C}_{3-7}$ cycloalkyl- COOH , hydroxy- $\text{C}_t\text{H}_{2t}-$, carboxyspiro[3.3]heptyl or carboxyphenyl- C_mH_{2m-} , carboxypyridinyl- C_mH_{2m-} ;

W is $-\text{CH}_2-$, $-\text{C}(\text{C}_{1-6}\text{alkyl})_2-$, $-\text{O}-$ or carbonyl;

n is 0 or 1;

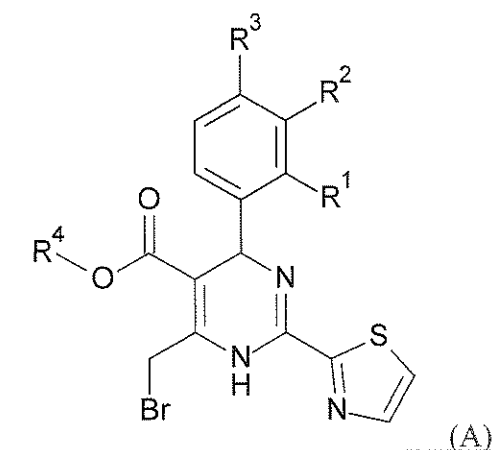
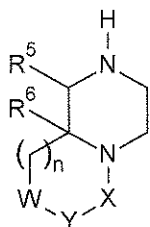
m is 0-7;

t is 1-7;

or pharmaceutically acceptable salts, or enantiomers or diastereomers thereof.

The ~~invention-disclosure~~ is also relates to their manufacture, medicaments based on a compound in accordance with the ~~disclosure invention~~ and their production as well as the use of compounds of formula (I) or other compounds of the present ~~disclosure invention~~ for the treatment or prophylaxis of HBV infection.

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



with $-(\text{CH}_2)_n-\text{W}-\text{Y}-\text{X}$ in the presence of a base;

wherein R^1 to R^6 , X, Y, W and n are as 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 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.

In another aspect, there is provided a compound as defined herein as HBV capsid inhibitor.

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

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” 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 “-C_mH_{2m}-” alone or in combination signifies a saturated, linear or branched chain alkyl group containing m (m≠0) carbon atoms or a bond (m=0). In particular, “-C_mH_{2m}-” alone or in combination signifies a saturated, linear or branched chain alkyl group containing 1 to 4 carbon atoms.

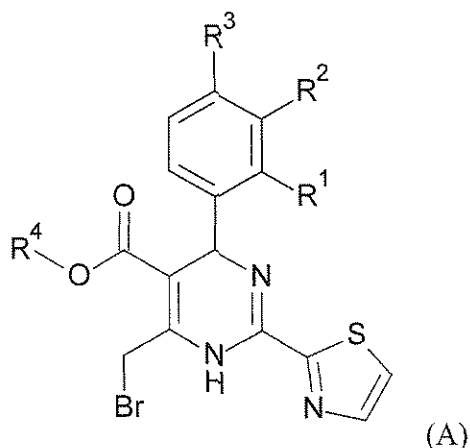
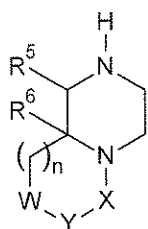
The term “-C_tH_{2t}-” alone or in combination signifies a chemical link or a saturated, linear or branched chain alkyl group containing t (t≠0) carbon atoms or a bond (t=0). In particular, “-C_tH_{2t}-” alone or in combination signifies a saturated, linear or branched chain alkyl group containing 1 to 4 carbon atoms.

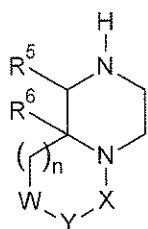
The term “C₁₋₆alkoxy” alone or in combination signifies a group C₁₋₆alkyl-O-, wherein the “C₁₋₆alkyl” is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy,

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

or pharmaceutically acceptable salts, or enantiomers or diastereomers thereof.

19. A process for the preparation of a compound according to any one of claims 1 to 18 comprising the reaction of a compound of formula (A)



with  in the presence of a base;

wherein R¹ to R⁶, X, Y, W and n are defined as in any one of claims 1 to 16.

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

21. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 18 and a therapeutically inert carrier.

~~22. The use of a compound according to any one of claims 1 to 18 for the treatment or prophylaxis of hepatitis B virus infection.~~

- ~~23~~22. The use of a compound according to any one of claims 1 to 18 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

~~24~~23. A compound according to any one of claims 1 to 18 for the treatment or prophylaxis of hepatitis B virus infection.

~~25~~24. A compound according to any one of claims 1 to 18 as HBV capsid inhibitor.

~~26~~25. A compound according to any one of claims 1 to 18, when manufactured according to a process of claim 19.

~~27.~~ 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 18.