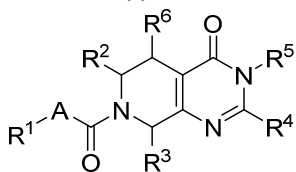


lead to significantly reduced virus burden, improved prognosis, diminished progression of the disease and enhanced seroconversion rates. Particularly, it is desired to find compounds that are capable of capsid assembly modulation.

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SUMMARY

The present application relates to compounds that are capable of capsid assembly modulation. The compounds of the present application may provide a beneficial
10 balance of properties with respect to prior art compounds. In particular, they may display favourable metabolic properties, tissue distribution, safety and pharmaceutical profile. Thus, in one aspect, provided herein is a compound of Formula (I)



(I)

15 including any of its stereoisomers or tautomeric forms thereof, wherein:

A is a bond or NH;

R¹ is a 5- to 10-membered monocyclic or bicyclic ring system, more particularly a 5- to 9-membered monocyclic or bicyclic ring, wherein the 5- to 10-membered
monocyclic or bicyclic ring system, more particularly the 5- to 9-membered
20 monocyclic or bicyclic ring system, optionally contains 1 to 3 heteroatoms, the heteroatoms each independently being selected from N, O and S;
wherein the 5- to 10-membered monocyclic or bicyclic ring, more particularly the 5- to 9-membered monocyclic or bicyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of halo, CN, CF₃,
25 CF₂H, CFH₂, CF₂CH₃, C₁₋₆alkyl, OC₁₋₆alkyl, OCF₃, OCF₂H, and C₃₋₄cycloalkyl;
or R¹ is selected from the group consisting of 1-methyl-2-oxo-1,3-dihydro-1H-benzo[d]imidazol-5-yl, 1-oxo-isindolin-5-yl, and 1,1-dioxo-benzo[b]thiophen-5-yl;

R² is selected from the group consisting of hydrogen, C₁₋₆alkyl, CF₃, CHF₂, CH₂F, phenyl and fluorophenyl;
30

R³ is hydrogen;

C₃₋₆cycloalkyl substituted with CO₂H; and
C₃₋₆cycloalkyl containing a heteroatom and being substituted with CO₂H, said heteroatom being an oxygen atom;

wherein R²⁷ is selected from the group consisting of

- 5 C₁₋₆alkyl,
 C₁₋₆alkyl substituted with C₃₋₆heterocycloalkyl, and
 C₃₋₆heterocycloalkyl;

wherein R²⁸ is C₁₋₆alkyl or C₃₋₆cycloalkyl;

- 10 wherein Cycle3 is selected from the group consisting of

 C₃₋₆cycloalkyl,

 C₃₋₆heterocycloalkyl,

 C₃₋₆heterocycloalkyl substituted with one or more substituents each independently selected from the group consisting of OH, CH₂OH, CO₂R²⁹, NHCH₃ or

- 15 NHCO₂*t*-Bu; and

 imidazolidin-4-one substituted with CH₃;

wherein R²⁹ is hydrogen or C₁₋₆alkyl;

wherein Aryl4 is selected from the group consisting of monocyclic heteroaryl and

- 20 bicyclic heteroaryl, said monocyclic or bicyclic heteroaryl being optionally substituted with one or two substituents each independently selected from the group consisting of halogens, CF₃, CH₂F, C₁₋₆alkyl, C₃₋₆cycloalkyl, OCF₃, OCH₂F, OC₁₋₆alkyl, OC₃₋₆cycloalkyl, CO₂R³⁰, SO₂CH₃, and morpholine;

wherein R³⁰ is hydrogen or C₁₋₆alkyl;

- 25

wherein R', R'' and R⁵ are not all hydrogen; and

wherein R⁶ is hydrogen, CH₃, CF₃ or CF₂H;

or a pharmaceutically acceptable salt thereof,

- 30 for use in the prevention or treatment of an HBV infection or of an HBV-induced disease.

There is also provided a method of treating or preventing HBV infection or an HBV-induced disease in a subject in need thereof, said method comprising administering

- 35 to said subject a therapeutically effective amount of a compound of Formula (I)

C₃₋₆heterocycloalkyl substituted with one or more substituents each independently selected from the group consisting of OH, CH₂OH, CO₂R²⁹, NHCH₃ or NHCO₂*t*-Bu; and

imidazolidin-4-one substituted with CH₃;

5 wherein R²⁹ is hydrogen or C₁₋₆alkyl;

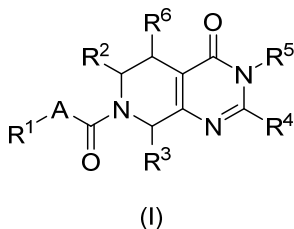
wherein Aryl₄ is selected from the group consisting of monocyclic heteroaryl and bicyclic heteroaryl, said monocyclic or bicyclic heteroaryl being optionally substituted with one or two substituents each independently selected from the group consisting of halogens, CF₃, CH₂F, C₁₋₆alkyl, C₃₋₆cycloalkyl, OCF₃, OCH₂F, OC₁₋₆alkyl, 10 OC₃₋₆cycloalkyl, CO₂R³⁰, SO₂CH₃, and morpholine; wherein R³⁰ is hydrogen or C₁₋₆alkyl;

wherein R', R'' and R⁵ are not all hydrogen; and

15

wherein R⁶ is hydrogen, CH₃, CF₃ or CF₂H;
or a pharmaceutically acceptable salt thereof.

20 Also provided herein, in another aspect, is a compound of Formula (I)



including any of its stereoisomers or tautomeric forms thereof, wherein:

A is a bond or NH;

R¹ is a 5- to 10-membered monocyclic or bicyclic ring system, more particularly a

25 5- to 9-membered monocyclic or bicyclic ring system, wherein the 5- to 10-membered monocyclic or bicyclic ring system, more particularly the 5- to 9-membered monocyclic or bicyclic ring system, optionally contains 1 to 3 heteroatoms, the heteroatoms each independently being selected from N, O and S;

wherein the 5- to 10-membered monocyclic or bicyclic ring, more particularly the 5- to

30 9-membered monocyclic or bicyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of halo, CN, CF₃, CF₂H, CFH₂, CF₂CH₃, C₁₋₆alkyl, OC₁₋₆alkyl, OCF₃, OCF₂H, and C₃₋₄cycloalkyl;

CH₂F, C₁₋₆alkyl, C₃₋₆cycloalkyl, OCF₃, OCH₂F, OC₁₋₆alkyl, OC₃₋₆cycloalkyl, CO₂R³⁰, SO₂CH₃, and morpholine;

wherein R³⁰ is hydrogen or C₁₋₆alkyl;

wherein R', R'' and R⁵ are not all hydrogen; and R⁵ is not CH(Ph)₂ when R⁴ is NH₂;

5 and

wherein R⁶ is hydrogen, CH₃, CF₃ or CF₂H.

The application, in another aspect, relates to a pharmaceutical composition, which comprises at least one compound or a pharmaceutically acceptable salt thereof as defined herein, and which further comprises at least one pharmaceutically acceptable carrier.

In yet another aspect, the application pertains to a process for the preparation of the pharmaceutical composition as defined herein, characterized in that at least one pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I) as defined herein.

The application pertains to the compound or pharmaceutically acceptable salt thereof as defined herein or the pharmaceutical composition as defined herein, for use as a medicament. In another aspect, the application pertains to the compound as defined herein, or the pharmaceutical composition as defined herein, for use as a medicament.

The application pertains to the compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof.

The application pertains to the compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for use in the prevention or treatment of chronic Hepatitis B.

HBV-induced disease or condition includes progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Additionally, HBV acts as a helper virus to hepatitis delta virus (HDV), and it is estimated that more than 15 million people may be HBV/HDV co-infected worldwide, with an increased risk of rapid progression to cirrhosis and increased

hepatic decompensation, than patients suffering from HBV alone (Hughes, S.A. et al. Lancet 2011, 378, 73-85). HDV, infects therefore subjects suffering from HBV infection. In a particular example, the compounds of the application may be used in the treatment and/or prophylaxis of HBV/HDV co-infection, or diseases associated
5 with HBV/HDV co infection. Therefore, in a particular example, the HBV infection is in particular HBV/HDV co-infection, and the mammal, in particular the human, may be HBV/HDV co-infected, or be at risk of HBV/HDV co infection.

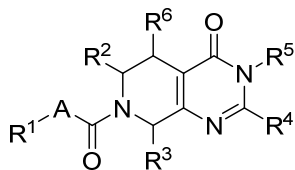
The application pertains to the compound or pharmaceutically acceptable salt thereof as defined herein, or the pharmaceutical composition as defined herein, for use in the prevention or treatment of liver fibrosis, liver inflammation, liver necrosis, cirrhosis, end-stage liver disease or hepatocellular carcinoma.

5

In yet another aspect, the application pertains to a product comprising a first compound and a second compound as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof, wherein said first compound is different from said second compound, wherein said first compound is the compound or pharmaceutically acceptable salt thereof as defined herein or the pharmaceutical composition as defined herein, and wherein said second compound is another HBV inhibitor which is selected from the group consisting of: therapeutic agents selected from HBV combination drugs, HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators, toll-like receptor (TLR) modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HBsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ip4) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA) and ddRNAi endonuclease modulators, ribonucleotide reductase inhibitors, HBV E antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, farnesoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 simulators, NOD2 stimulators, phosphatidylinositol 3-kinase (PI3K) inhibitors, indoleamine-2, 3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and other HBV drugs.

25

In yet another aspect, the application pertains to use of a compound of Formula (I)



30

(I)

including any of its stereoisomers or tautomeric forms thereof, wherein:

A is a bond or NH;

R¹ is a 5- to 10-membered monocyclic or bicyclic ring system, more particularly a 5- to 9-membered monocyclic or bicyclic ring, wherein the 5- to 10-membered monocyclic or bicyclic ring system, more particularly the 5- to 9-membered monocyclic or bicyclic ring system, optionally contains 1 to 3 heteroatoms, the
5 heteroatoms each independently being selected from N, O and S;
wherein the 5- to 10-membered monocyclic or bicyclic ring, more particularly the 5- to 9-membered monocyclic or bicyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of halo, CN, CF₃, CF₂H, CFH₂, CF₂CH₃, C₁₋₆alkyl, OC₁₋₆alkyl, OCF₃, OCF₂H, and C₃₋₄cycloalkyl;
10 or R¹ is selected from the group consisting of 1-methyl-2-oxo-1,3-dihydro-1H-benzo[d]imidazol-5-yl, 1-oxo-isoindolin-5-yl, and 1,1-dioxo-benzo[b]thiophen-5-yl;

R² is selected from the group consisting of hydrogen, C₁₋₆alkyl, CF₃, CHF₂, CH₂F, phenyl and fluorophenyl;
15

R³ is hydrogen;

R⁴ is X-R';
wherein X is NR'', S or O;
20 wherein R' is hydrogen, C₁₋₄alkyl, C₁₋₆alkyl substituted with OH, or C₂₋₃alkenyl, when X is NR'';
wherein R' is C₁₋₆alkyl, when X is S;
wherein R' is C₁₋₆alkyl, when X is O;
wherein R'' is selected from the group consisting of hydrogen, Cycle1, Aryl1, C₂₋₄alkynyl, C₁₋₆alkyl and C₁₋₆alkyl substituted with one or more substituents each
25 independently selected from the group consisting of

fluoro,
OH,
CO₂R¹⁶,
30 OCONHR¹⁷,
C₃₋₆cycloalkyl,
C₃₋₆cycloalkyl substituted with one or more from among C₁₋₆alkyl,
N-acetyl piperidine,
cubanyl,
35 benzo[d][1,3]dioxole, and
Aryl2;

wherein R¹⁶ is hydrogen or C₁₋₆alkyl;

wherein R¹⁷ is C₁₋₆alkyl;

wherein Cycle1 is selected from the group consisting of

C₃₋₈cycloalkyl,

5 C₃₋₈cycloalkyl containing a heteroatom, said heteroatom being an oxygen atom,

C₃₋₈cycloalkyl substituted with one or more substituents each independently selected from CH₃ and Aryl2,

10 C₃₋₈cycloalkyl containing a heteroatom and being substituted with one or more substituents each independently selected from the group consisting of CH₃, cyclopropyl, and Aryl2, said heteroatom being an oxygen atom,

a 5- to 9- membered fused bicyclic unsaturated or saturated ring system, in particular a saturated heterocycle fused with an aromatic ring, which may be optionally substituted with OCH₃,

15 a 5- to 9- membered bridged bicyclic unsaturated or saturated ring system optionally substituted with 1, 2 or 3 CH₃ substituents,

a C₅₋₁₂spirocycloalkyl, and

cubanyl;

20 wherein Aryl1 is selected from the group consisting of phenyl, monocyclic heteroaryl, and bicyclic heteroaryl which is in particular an aromatic ring fused to a saturated ring or an aromatic ring fused to another aromatic ring, said Aryl1 being optionally substituted with CH₃;

25 wherein Aryl2 is selected from the group consisting of phenyl, monocyclic heteroaryl, and bicyclic heteroaryl, said Aryl2 being optionally substituted with one or more substituents each independently selected from the group consisting of halogens, CF₃, CF₂H, CH₂F, C₁₋₄alkyl, C₃₋₆cycloalkyl, CN, CONR¹⁸R¹⁹, OH, OCF₃, OCF₂H, OCH₂F, OC₁₋₄alkyl, OC₃₋₆cycloalkyl, SO₂CH₃, imidazolyl optionally substituted with CH₃,
30 phenyl optionally substituted with fluoro, and triazolyl;

wherein R¹⁸ and R¹⁹ are independently selected from the group consisting of hydrogen, C₁₋₆alkyl and C₃₋₆cycloalkyl;

or wherein N, R' and R'' together form a cycle selected from the group consisting of

35 a C₃₋₈cycloalkyl ring,

a C₃₋₈cycloalkyl ring containing a heteroatom, said heteroatom being an oxygen atom, and optionally being substituted with CH₃,

a C₃₋₈cycloalkyl ring substituted with one or more substituents each independently selected from the group consisting of C₁₋₆alkyl, phenyl, C₂₋₆alkynyl and C₃₋₆cycloalkyl,

5 a C₃₋₈cycloalkyl ring containing a heteroatom and being substituted with one or more substituents each independently selected from C₁₋₆alkyl, CN, phenyl, C₂₋₆alkynyl and C₃₋₆cycloalkyl, said heteroatom being an oxygen atom,

a C₅₋₁₂-spirocycloalkyl optionally substituted with CH₃, and

a C₅₋₆ bridged bicyclic saturated ring system;

10 R⁵ is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₃alkenyl, Cycle2 and Aryl3;

wherein C₁₋₆alkyl is optionally substituted with one or more substituents each independently selected from the group consisting of phenyl, methoxyphenyl, OC₁₋₆alkyl, NHSO₂CH₃, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl containing a heteroatom, said

15 heteroatom being an oxygen atom;

wherein Cycle2 is selected from the group consisting of

C₃₋₆cycloalkyl,

20 C₃₋₆cycloalkyl containing SO₂ or a heteroatom, the heteroatom being selected from the group consisting of oxygen and nitrogen,

C₃₋₆cycloalkyl substituted with CO₂R^{20a}, CONHR^{20b} or SO₂C₁₋₆alkyl,

C₃₋₆cycloalkyl containing SO₂ or a heteroatom and being substituted with CO₂R^{20a}, CONHR^{20b} or SO₂C₁₋₆alkyl, the heteroatom being selected from the group consisting of oxygen and nitrogen,

25 a 5-membered bridged bicyclic saturated ring substituted with CO₂C₁₋₆alkyl or CONHR^{20b},

cubanyl optionally substituted with CO₂C₁₋₆alkyl or CONHR^{20b},

isoindoline-1-one, and

indoline-2-one;

30 wherein R^{20a} is hydrogen or C₁₋₆alkyl;

wherein R^{20b} is C₁₋₆alkyl or C₃₋₆cycloalkyl;

wherein Aryl3 is selected from the group consisting of phenyl, monocyclic heteroaryl, and bicyclic heteroaryl, said Aryl3 being optionally substituted with one or more

35 substituents each independently selected from the group consisting of halogen, C₁₋₆alkyl, CF₃, CF₂H, CH₂F, CN, OC₁₋₆alkyl, OCF₃, OCF₂H, OCH₂F, OC₃₋₆cycloalkyl,

SO₂R²¹, SO₂NHR²², CO₂R²³, COR²⁴, CONR²⁵R²⁶, NHR²⁷, NHCOR²⁸, Cycle3 and Aryl4;

wherein R²¹ is C₁₋₆alkyl or C₃₋₆cycloalkyl;

wherein R²² is C₁₋₆alkyl or pyridine;

5 wherein R²³ is hydrogen or C₁₋₆alkyl;

wherein R²⁴ is selected from the group consisting of C₁₋₆alkyl, C₅₋₆heterocycle and C₅₋₆heterocycle substituted with CH₃;

wherein R²⁵ is hydrogen or CH₃;

wherein R²⁶ is selected from the group consisting of

10 hydrogen,

C₁₋₆alkyl,

C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from the group consisting of OH, OCH₃, NH₂, CO₂H, C₃₋₆heterocycloalkyl and C₃₋₆heterocycloalkyl substituted with CH₃,

15 C₃₋₆cycloalkyl;

C₃₋₆cycloalkyl containing a heteroatom, said heteroatom being an oxygen atom;

C₃₋₆cycloalkyl substituted with CO₂H; and

20 C₃₋₆cycloalkyl containing a heteroatom and being substituted with CO₂H, said heteroatom being an oxygen atom;

wherein R²⁷ is selected from the group consisting of

C₁₋₆alkyl,

C₁₋₆alkyl substituted with C₃₋₆heterocycloalkyl, and

C₃₋₆heterocycloalkyl;

25 wherein R²⁸ is C₁₋₆alkyl or C₃₋₆cycloalkyl;

wherein Cycle3 is selected from the group consisting of

C₃₋₆cycloalkyl,

C₃₋₆heterocycloalkyl,

30 C₃₋₆heterocycloalkyl substituted with one or more substituents each independently selected from the group consisting of OH, CH₂OH, CO₂R²⁹, NHCH₃ or NHCO₂*t*-Bu; and

imidazolidin-4-one substituted with CH₃;

wherein R²⁹ is hydrogen or C₁₋₆alkyl;

35

wherein Aryl4 is selected from the group consisting of monocyclic heteroaryl and bicyclic heteroaryl, said monocyclic or bicyclic heteroaryl being optionally substituted

with one or two substituents each independently selected from the group consisting of halogens, CF₃, CH₂F, C₁₋₆alkyl, C₃₋₆cycloalkyl, OCF₃, OCH₂F, OC₁₋₆alkyl, OC₃₋₆cycloalkyl, CO₂R³⁰, SO₂CH₃, and morpholine;

wherein R³⁰ is hydrogen or C₁₋₆alkyl;

5

wherein R', R'' and R⁵ are not all hydrogen; and

wherein R⁶ is hydrogen, CH₃, CF₃ or CF₂H;

or a pharmaceutically acceptable salt thereof,

10

in the manufacture of a medicament for the prevention or treatment of an HBV infection or of an HBV-induced disease.

In yet another aspect, the application pertains to use of compound as defined herein, or the pharmaceutical composition as defined herein, in the manufacture of a

15

medicament for the prevention or treatment of an HBV infection or of an HBV-induced disease.

In yet another aspect, the application pertains to use of a product comprising a first compound and a second compound in the manufacture of a combined preparation

20

for simultaneous, separate or sequential use in the prevention or treatment of an HBV infection or of an HBV-induced disease in mammal in need thereof, wherein said first compound is different from said second compound, wherein said first compound is the compound or pharmaceutically acceptable salt as defined herein or the pharmaceutical composition as defined herein, and wherein said second

25

compound is another HBV inhibitor which is selected from the group consisting of: therapeutic agents selected from HBV combination drugs, HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators, toll-like receptor (TLR) modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HBsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ip4) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA) and ddRNAi endonuclease modulators, ribonucleotide reductase inhibitors, HBV E antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, farnesoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein

30

modulators, retinoic acid-inducible gene 1 simulators, NOD2 stimulators, phosphatidylinositol 3-kinase (PI3K) inhibitors, indoleamine-2, 3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1,

35

bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV replication inhibitors, arginase inhibitors, and other HBV drugs.

5 The application pertains to a method for the preparation of a compound as defined herein, said method comprising the step of providing a compound according to Formula (XI):

wherein when M^7 is sulfhydryl the method comprises steps e), f) and h); or steps g) and h);

wherein when M^7 is $-SCH_3$, the method comprises steps f) and h);

wherein when M^7 is $-Cl$ or $-S(O)CH_3$, the method comprises step h);

- 5 wherein when the method comprises steps e) and/or f), the method does not comprise step g);

wherein when the method comprises step c), the method does not comprise step d);
and wherein:

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , A, X, R' , R'' , Cycle2, and Aryl3 are as defined herein;

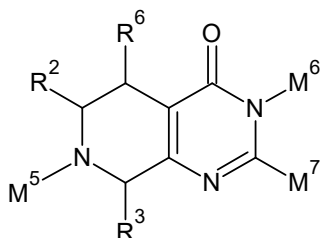
- 10 G is selected from the group consisting of OH and Cl;

when G is OH, step b) comprises contacting the compound according to Formula (XI) with $R^1-A-C(O)-G$ in the presence of a coupling reagent; and

wherein the coupling reagent more particularly is 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU).

15

The application relates to a method for the preparation of a compound as defined herein, wherein R^5 is other than hydrogen, said method comprising the step of providing a compound according to Formula (XI):



- 20 Formula (XI) or a tautomer thereof; wherein

M^5 is $R^1-A-C(O)-$;

M^6 is hydrogen; and

M^7 is R^4 ;

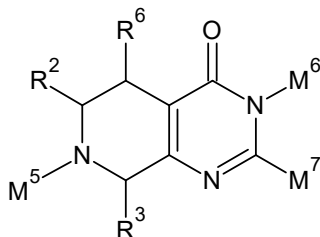
wherein the method further comprises at most one of steps a) and b):

- 25 a) contacting the compound according to Formula (XI) with $M^{10}-H^A$, more particularly in the presence of Cs_2CO_3 , wherein M^{10} is selected from the group consisting of C_{1-6} alkyl, C_{2-3} alkenyl, and Cycle2; wherein C_{1-6} alkyl is optionally substituted with phenyl, methoxyphenyl, OC_{1-6} alkyl, $NHSO_2CH_3$, and C_{3-6} cycloalkyl optionally containing an oxygen atom;
- 30 and wherein H^A is a halogen, more particularly Br;
- b) contacting the compound according to Formula (XII) with Aryl3- $B(OH)_2$, more particularly in the presence of copper(II) acetate;

and wherein:

R¹, R², R³, R⁴, R⁵, R⁶, A, Cycle2, and Aryl3 are as defined herein, with the proviso that R⁵ is not hydrogen.

- 5 The application relates to a method for the preparation of a compound as defined herein, wherein R⁵ is other than hydrogen, said method comprising the step of providing a compound according to Formula (XI):



Formula (XI) or a tautomer thereof; wherein

- 10 M⁵ is selected from the group consisting of *tert*-butoxycarbonyl, hydrogen, and R¹-A-C(O);
M⁶ is R⁵ and is other than hydrogen; and
M⁷ is selected from the group consisting of sulfhydryl, -SCH₃, -Cl, -S(O)CH₃, and R⁴;
wherein when M⁵ is R¹-A-C(O)-, then M⁷ is not R⁴;
- 15 wherein the method further comprises at least one of steps a) to f):
- a) contacting the compound according to Formula (XIII) with a strong acid, more particularly hydrochloric acid or trifluoroacetic acid;
 - b) contacting the compound according to Formula (XIII) with R¹-A-C(O)-G, more particularly in the presence of a non-nucleophilic base;
 - 20 c) contacting the compound according to Formula (XIII) with a methylating agent, more particularly methyl iodide;
 - d) contacting the compound according to Formula (XIII) with an oxidizing agent, more particularly meta-chloroperoxybenzoic acid;
 - e) contacting the compound according to Formula (XIII) with a chlorinating agent, more particularly thiophosgene;
 - 25 f) contacting the compound according to Formula (XIII) with one of the reagents consisting of R'-S-H, R'-O-H and R'R''N-H, more particularly in the absence or in the presence of a non-nucleophilic base;
- wherein when M⁵ is *tert*-butoxycarbonyl, the method comprises the steps a) and b);
- 30 wherein when M⁵ is hydrogen, the method comprises step b);

wherein when M⁷ is sulfhydryl the method comprises steps c), d) and f); or steps e) and f);

wherein when M⁷ is -SCH₃, the method comprises steps d) and f);

wherein when M⁷ is -Cl or -S(O)CH₃, the method comprises step f);

- 5 wherein when the method comprises steps c) and/or d), the method does not comprise step e); and wherein:

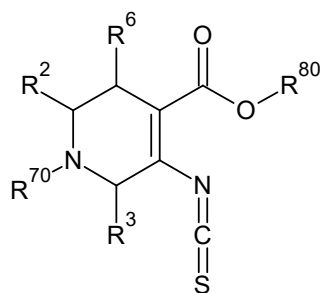
R¹, R², R³, R⁴, R⁵, R⁶, A, X, R', R'', Cycle2, and Aryl3 are as defined herein, with the proviso that R⁵ is other than hydrogen;

G is selected from the group consisting of OH and Cl;

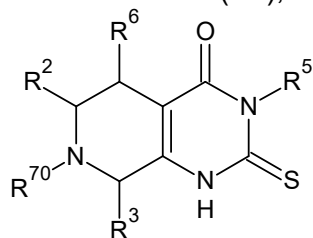
- 10 when G is OH, step b) comprises contacting the compound according to Formula (XIII) with R¹-A-C(O)-G in the presence of a coupling reagent; and wherein the coupling reagent more particularly is 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU).

- 15 The application pertains to a process for the preparation of a compound as defined herein, comprising the steps of:

a) contacting a compound of Formula (XII) with R⁵-NH₂, wherein Formula (XII) is



- 20 Formula (XII), to provide the compound of Formula (XIII):



Formula (XIII);

b) contacting the compound of Formula (XIII) with a methylating agent, more particularly methyl iodide, to form a compound according to Formula (XIV):