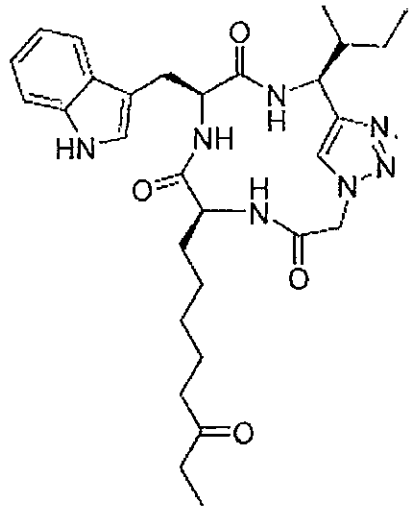
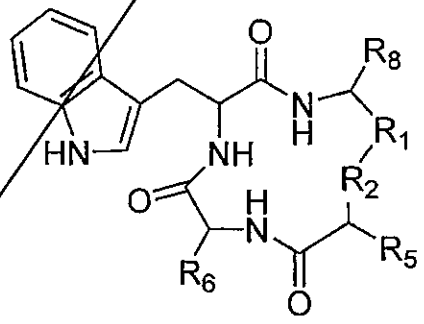
Claims

1. A therapeutically effective amount of an inhibitor of class I histone deacetylase activity for use in inhibiting covalently closed circular DNA (cccDNA) transcription of hepatitis B virus.

2. The inhibitor according to claim 1, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

3. The inhibitor according to claim 1, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Apicidin,





, and

wherein

R_1 is $-(CH_2)-$;

R_2 is $-C(Z)N(R_4)-$;

R_2 is $-C(=O)-$, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is $=O$, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

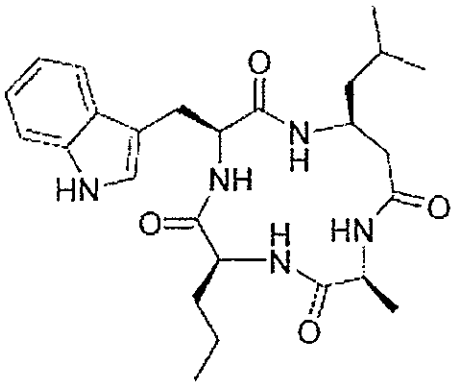
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

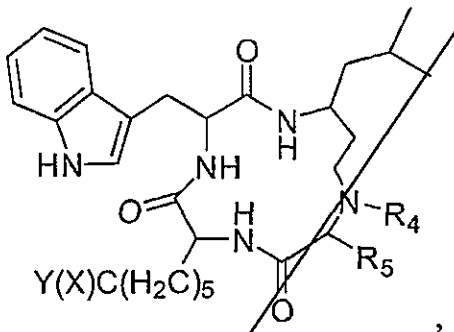
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

4. The inhibitor according to claim 3, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of:



and



,

wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

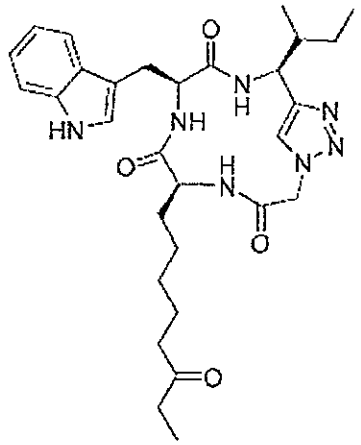
or a stereoisomer or pharmaceutically acceptable salt thereof.

5. The inhibitor according to claim 1, further comprising the administration of a therapeutically effective amount of an additional anti hepatitis B infection agent.

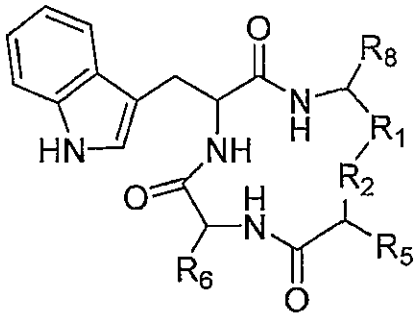
6. A therapeutically effective amount of an inhibitor of class I histone deacetylase activity for use in treating hepatitis B.

7. The inhibitor according to claim 6, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

8. The inhibitor according to claim 6, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Apicidin,



and



,

wherein

R_1 is $-(CH_2)-$;

R_2 is $-C(Z)N(R_4)-$;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

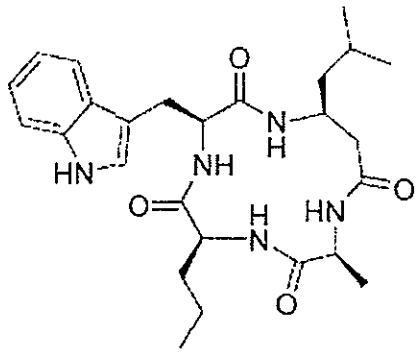
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

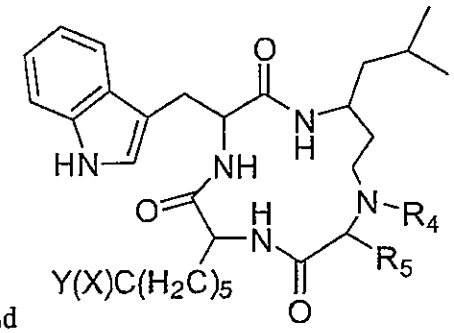
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

9. The inhibitor according to claim 8, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of:



and



,

wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

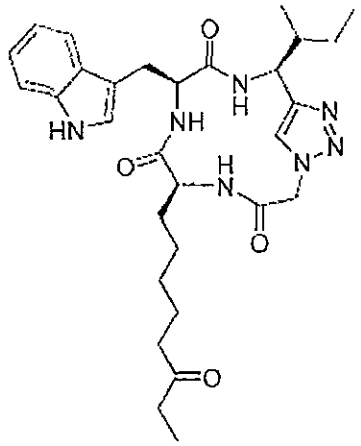
or a stereoisomer or pharmaceutically acceptable salt thereof.

10. The inhibitor according to claim 6, further comprising the administration of a therapeutically effective amount of an additional anti hepatitis B infection agent.

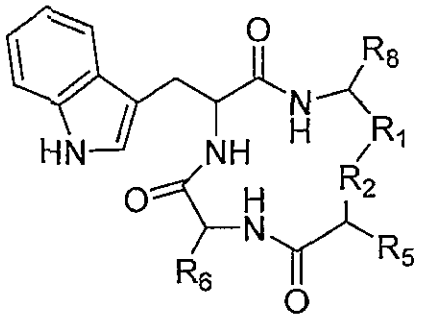
11. An inhibitor of class I histone deacetylase activity for use in repressing hepatitis B virus covalently closed circular DNA, comprising contacting the hepatitis B virus with the inhibitor.

12. The inhibitor according to claim 11, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

13. The inhibitor according to claim 11, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of Apicidin,



and



,

wherein

R_1 is $-(CH_2)-$;

R_2 is $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

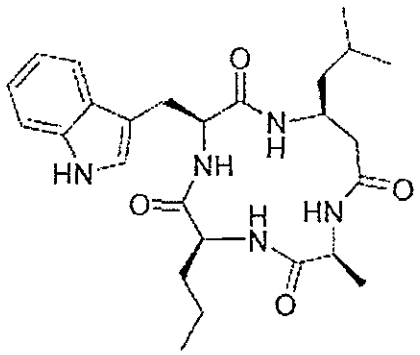
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

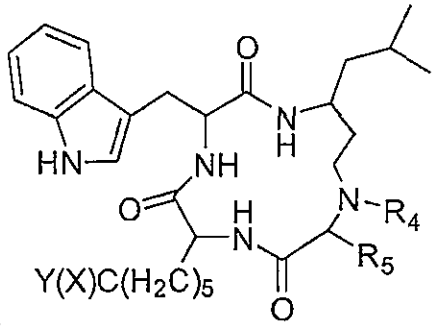
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

14. The inhibitor according to claim 13, wherein said inhibitor of histone deacetylase activity is selected from the group consisting of:



and



,

wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

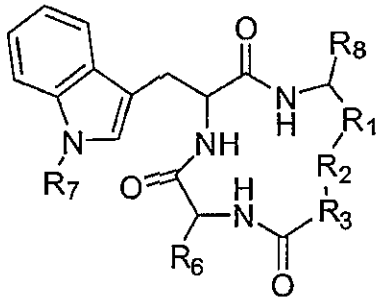
X is $=O$, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

or a stereoisomer or pharmaceutically acceptable salt thereof.

15. The inhibitor according to claim 11, further comprising contacting the hepatitis B virus with an additional anti hepatitis B infection agent.

16. A compound according to formula II:



(II)

wherein

R_1 is $-(CH_2)_n-$ or $-C(=O)-$;

R_2 is $-C(=O)-$ or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is $-CH(R_5)-$;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is $=O$, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

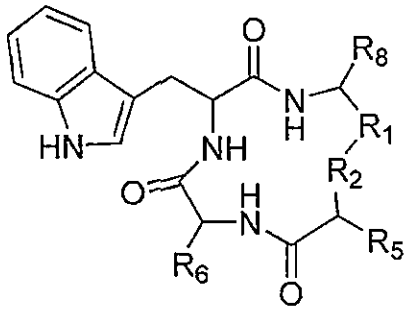
n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

17. The compound according to claim 16, wherein said compound is

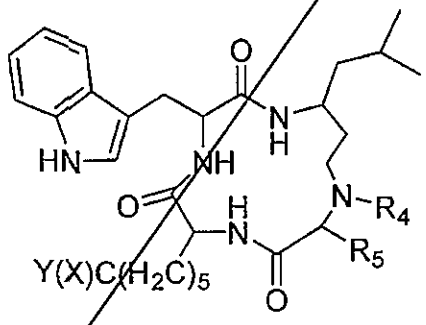


wherein

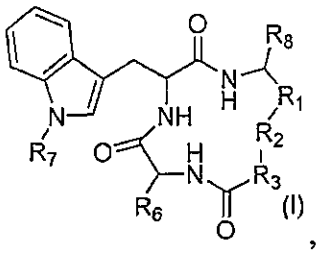
R_1 is $-(CH_2)-$, and,

R_2 is $-C(Z)N(R_4)-$.

18. The compound according to claim 16, wherein said compound is



19. The inhibitor of claim 1, wherein the inhibitor of human deacetylase activity is a compound of formula (I)



(I)

,

wherein

R_1 is $-(CH_2)_n-$ or -C(=O)-;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is $-CH(R_5)-$, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

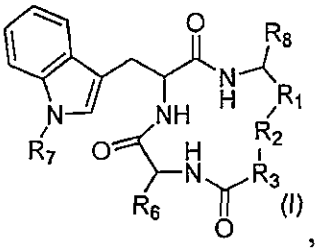
n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

20. The inhibitor of claim 6, wherein the inhibitor of human deacetylase activity is a compound of formula (I)



(I)

,

wherein

R_1 is $-(CH_2)_n-$ or -C(=O)-;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is –$CH(R_5)$-, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, -CH_3, or an alpha amino acid R group;

R_6 is -$(CH_2)_mC(X)Y$, -$(CH_2)_2CH_3$, or -$(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, =N-NH_2, or =N-NH-$C(=O)NH_2$;

Y is NHOH or -CH_2CH_3;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

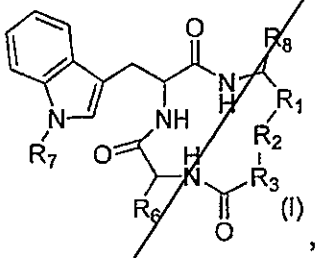
n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

21. The inhibitor of claim 11, wherein the inhibitor of human deacetylase activity is a compound of formula (I)



,

wherein

R_1 is –$(CH_2)_n$- or -C(=O)-;

R_2 is -C(=O)-, 3,5-triazolyl, or -$C(Z)N(R_4)$-;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is –$CH(R_5)$-, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, -CH_3, or an alpha amino acid R group;

R_6 is -$(CH_2)_mC(X)Y$, -$(CH_2)_2CH_3$, or -$(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, =N-NH_2, or =N-NH-$C(=O)NH_2$;

Y is NHOH or -CH_2CH_3;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

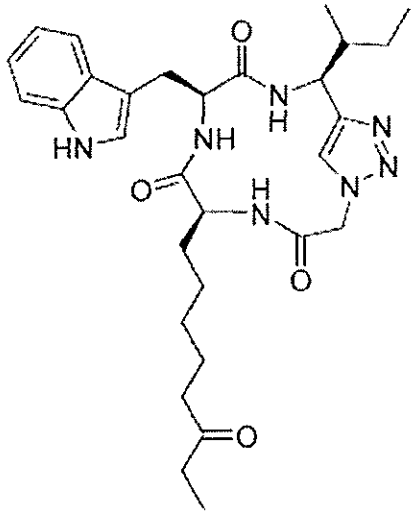
or a stereoisomer or pharmaceutically acceptable salt thereof.

CLAIMS

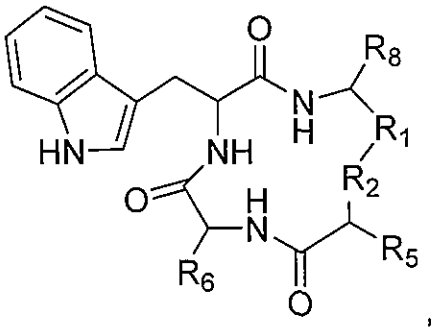
1. The use of a class I histone deacetylase activity inhibitor in the manufacture of a medicament for inhibiting covalently closed circular DNA (cccDNA) transcription of hepatitis B virus.

2. The use according to claim 1, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

3. The use according to claim 1, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Apicidin,



, and



, wherein

R_1 is $-(CH_2)-$;

R_2 is $-C(Z)N(R_4)-$;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

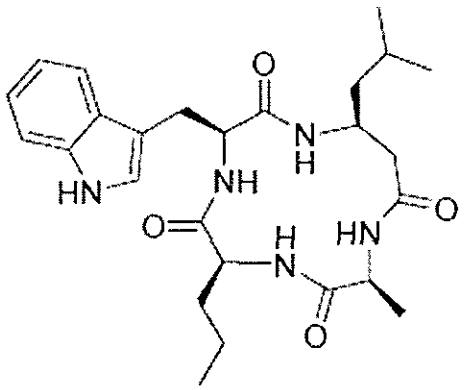
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

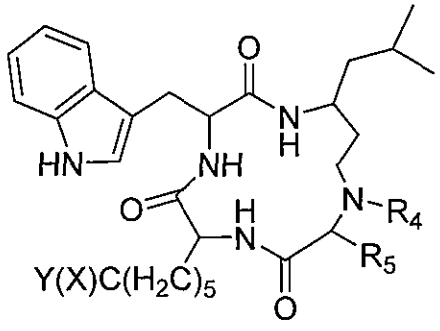
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

4. The use according to claim 3, wherein said histone deacetylase activity inhibitor is selected from the group consisting of:



and



, wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

or a stereoisomer or pharmaceutically acceptable salt thereof.

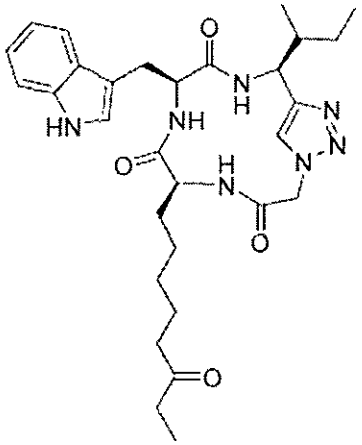
5. The use according to claim 1, further wherein the medicament further comprises a therapeutically effective amount of an additional anti hepatitis B infection agent.

6. The use of a class I histone deacetylase activity inhibitor in the manufacture of a medicament for treating hepatitis B.

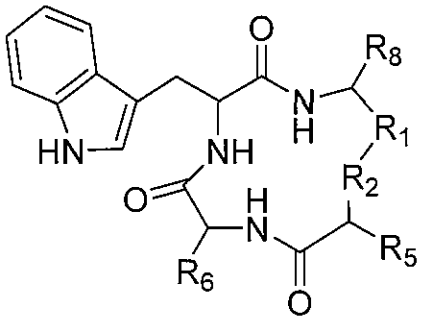
7. The use according to claim 6, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-

(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

8. The use according to claim 6, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Apicidin,



and



, wherein

R_1 is $-(CH_2)-$;

R_2 is $-C(Z)N(R_4)-$;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

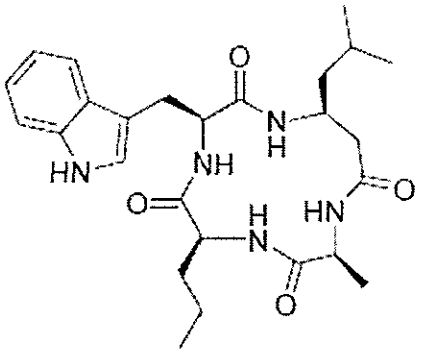
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

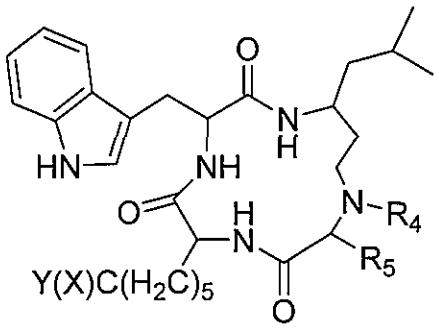
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

9. The use according to claim 8, wherein said histone deacetylase activity inhibitor is selected from the group consisting of:



and



, wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

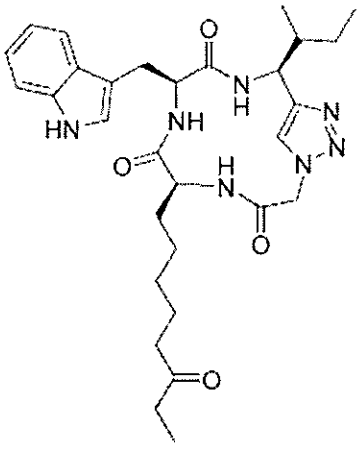
or a stereoisomer or pharmaceutically acceptable salt thereof.

10. The use according to claim 6, further wherein the medicament further comprises a therapeutically effective amount of an additional anti hepatitis B infection agent.

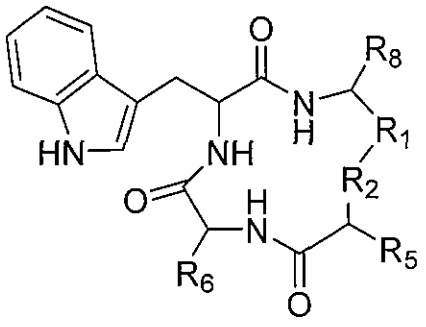
11. The use of a class I histone deacetylase activity inhibitor in the manufacture of a medicament for repressing hepatitis B virus covalently closed circular DNA.

12. The use according to claim 11, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Trichostatin A, suberoyl bis hydroxamic acid, 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide, and Apicidin or an analog thereof, or a stereoisomer or pharmaceutically acceptable salt thereof.

13. The use according to claim 11, wherein said histone deacetylase activity inhibitor is selected from the group consisting of Apicidin,



and



,

wherein

R_1 is -(CH_2)-;

R_2 is -$C(Z)N(R_4)$-;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, -CH_3, or an alpha amino acid R group;

R_6 is -$(CH_2)_mC(X)Y$, -$(CH_2)_2CH_3$, or -$(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, =N-NH_2, or =N-NH-$C(=O)NH_2$;

Y is NHOH or -CH_2CH_3;

Z is H_2 or O;

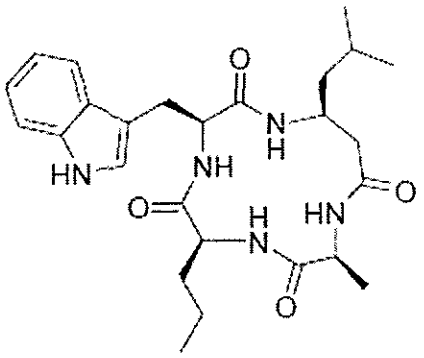
R_8 is alkyl or carboxyalkyl;

m is an integer selected from the group consisting of 0-6; and,

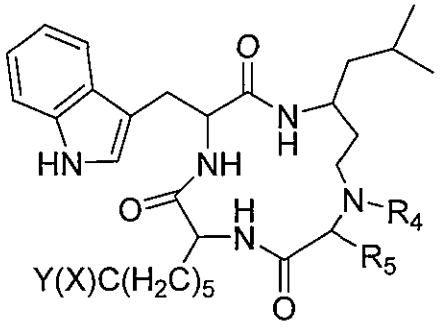
q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

14. The use according to claim 13, wherein said histone deacetylase activity inhibitor is selected from the group consisting of:



and



, wherein

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

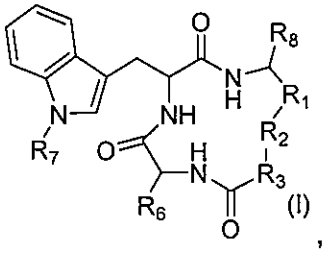
X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

or a stereoisomer or pharmaceutically acceptable salt thereof.

15. The use according to claim 11, further wherein the medicament further comprises a therapeutically effective amount of an additional anti hepatitis B infection agent.

16. The use of claim 1, wherein the human deacetylase activity inhibitor is a compound of formula (I)



, wherein

R_1 is $-(CH_2)_n-$ or $-C(=O)-$;

R_2 is $-C(=O)-$, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is $-CH(R_5)-$, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, =N-NH_2, or =N-NH-C(=O)NH_2;

Y is NHOH or -CH_2CH_3;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

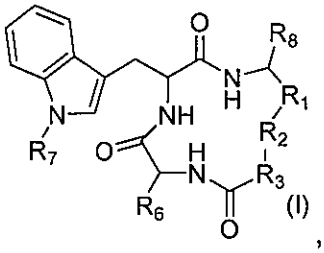
n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

17. The use of claim 6, wherein the human deacetylase activity inhibitor is a compound of formula (I)



, wherein

R_1 is –$(CH_2)_n$- or -C(=O)-;

R_2 is -C(=O)-, 3,5-triazolyl, or -C(Z)N(R_4)-;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is –CH(R_5)-, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, -CH_3, or an alpha amino acid R group;

R_6 is -$(CH_2)_m$C(X)Y, -$(CH_2)_2CH_3$, or -$(CH_2)_q$-phenyl-$(CH_2)_m$C(=O)NHOH;

X is =O, H_2, =N-NH_2, or =N-NH-C(=O)NH_2;

Y is NHOH or -CH_2CH_3;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

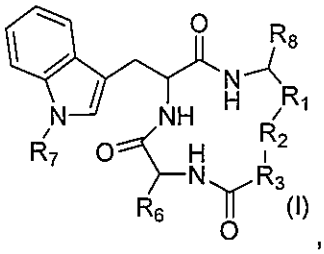
n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

18. The use of claim 11, wherein the human deacetylase activity inhibitor is a compound of formula (I)



(I), wherein

R_1 is $-(CH_2)_n-$ or -C(=O)-;

R_2 is -C(=O)-, 3,5-triazolyl, or $-C(Z)N(R_4)-$;

R_4 is hydrogen, alkyl, aryl, aralkyl, dialkylaminoalkyl, or carboxyalkyl;

R_3 is $-CH(R_5)-$, or R_2 is nitrogen and R_3 is -CH- and R_2 and R_3 together form piperidinyl;

R_5 is hydrogen, $-CH_3$, or an alpha amino acid R group;

R_6 is $-(CH_2)_mC(X)Y$, $-(CH_2)_2CH_3$, or $-(CH_2)_q$-phenyl-$(CH_2)_mC(=O)NHOH$;

X is =O, H_2, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

Y is NHOH or $-CH_2CH_3$;

Z is H_2 or O;

R_7 is hydrogen or alkoxy;

R_8 is alkyl or carboxyalkyl;

n is an integer selected from the group consisting of 0-2;

m is an integer selected from the group consisting of 0-6; and,

q is an integer selected from the group consisting of 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.