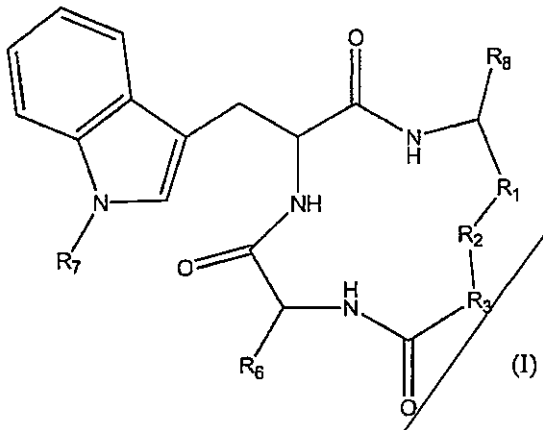
**Claims**

1. An inhibitor of histone deacetylace activity for use in modulating cccDNA transcription of hepatitis B.

2. The inhibitor according to claim 1, wherein said inhibitor of histone deacetylace activity is an inhibitor of class I histone deacetylace activity.

3. The inhibitor according to claim 1, wherein said inhibitor of histone deacetylace activity is Trichostatin A, suberoyl bis hydroxamic acid, dimethylamino hydroxy-benzamide, Apicidin or an analog thereof, or a compound according to 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;

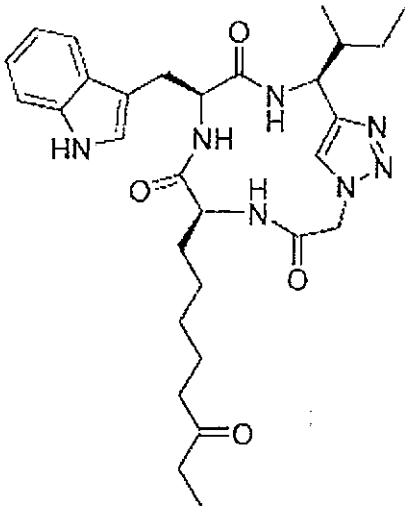
n is 0-2;

m is 0-6; and,

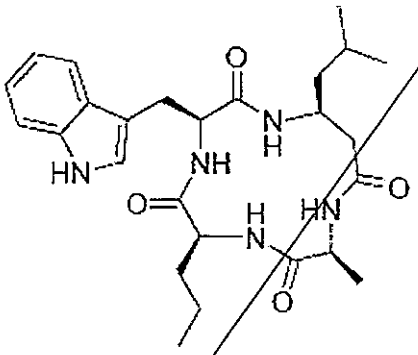
q is 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

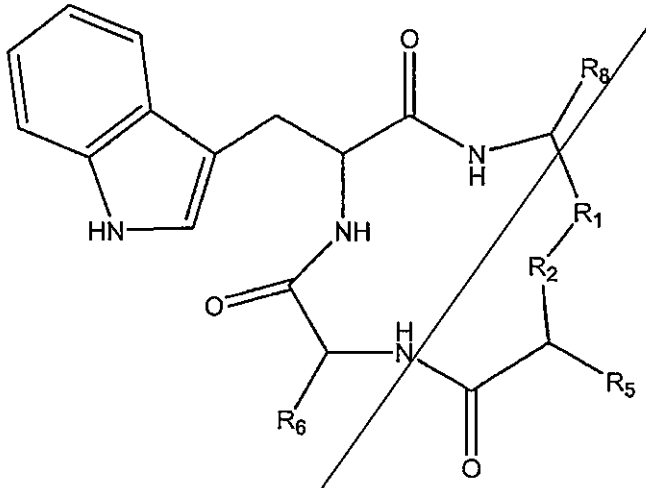
4. The inhibitor according to claim 1, wherein said inhibitor of histone deacetylace activity is Apicidin,



,



, or



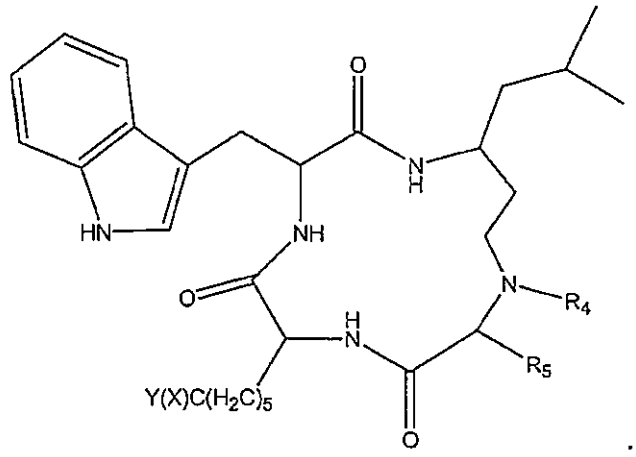
wherein

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

and,

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

5. The inhibitor according to claim 3, wherein said inhibitor of histone deacetylace activity is

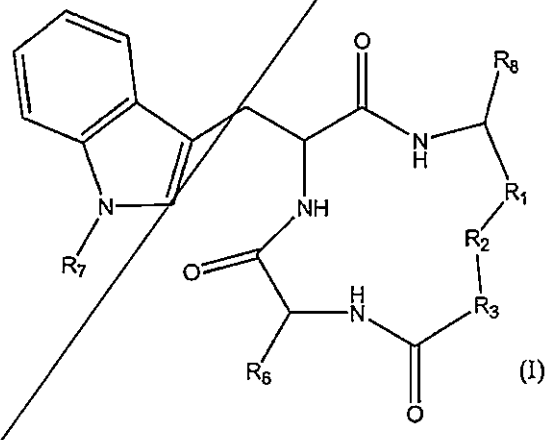


6. The inhibitor according to claim 1, further comprising the administration of a therapeutically effective amount of a further agent that modulates hepatitis B virus.

7. An inhibitor of histone deacetylace activity for use in treating hepatitis B.

8. The inhibitor according to claim 7, wherein said inhibitor of histone deacetylace activity is an inhibitor of class I histone deacetylace activity.

9. The inhibitor according to claim 7, wherein said inhibitor of histone deacetylace activity is Trichostatin A, suberoyl bis hydroxamic acid, dimethylamino hydroxy-benzamide, Apicidin or an analog thereof, or a compound according to 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;

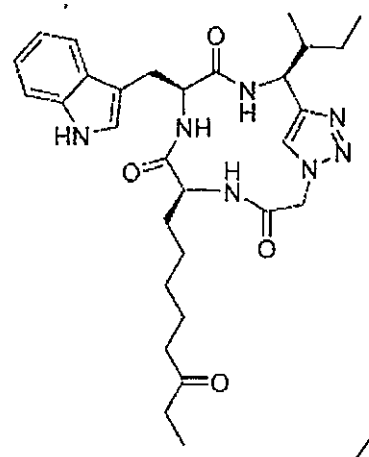
n is 0-2;

m is 0-6; and,

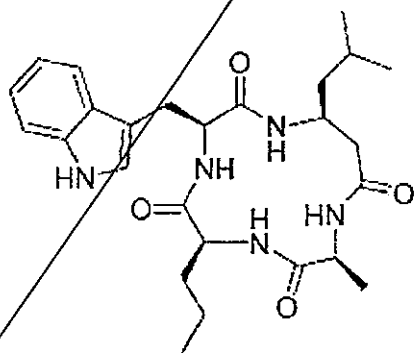
q is 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

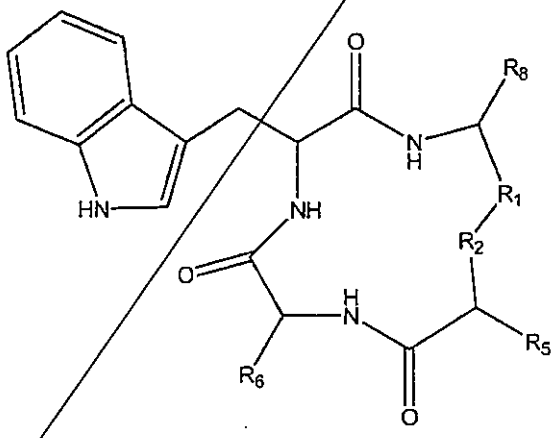
10. The inhibitor according to claim 7, wherein said inhibitor of histone deacetylace activity is Apicidin,



,



, or



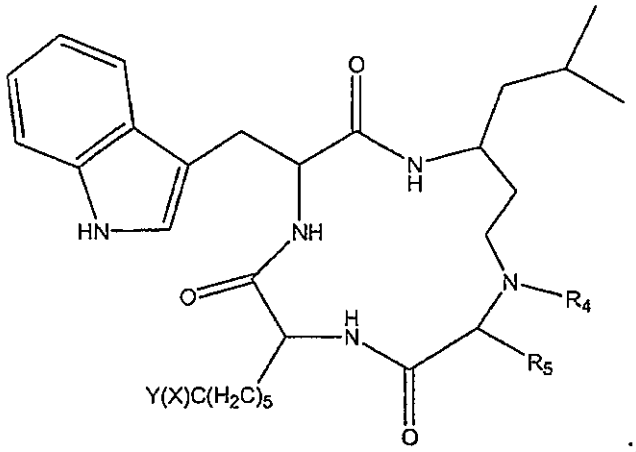
wherein

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

and,

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

11. The inhibitor according to claim 10, wherein said inhibitor of histone deacetylace activity is

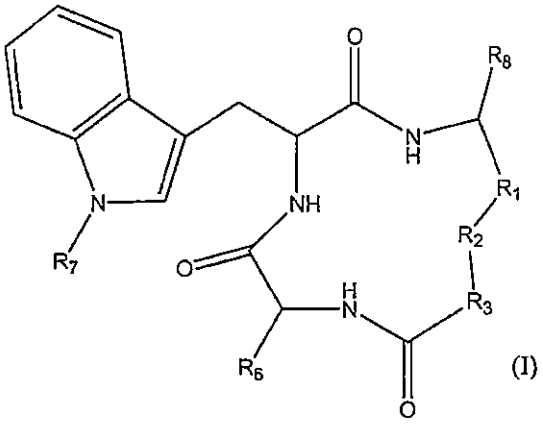



12. The inhibitor according to claim 7, further comprising the administration of a therapeutically effective amount of a further agent that modulates hepatitis B virus.

13. An inhibitor of histone deacetylace activity for use in modulating hepatitis B virus covalently closed circular DNA comprising contacting the hepatitis B virus with the inhibitor.

14. The inhibitor according to claim 13, wherein said inhibitor of histone deacetylace activity is an inhibitor of class I histone deacetylace activity.

15. The inhibitor according to claim 13, wherein said inhibitor of histone deacetylace activity is Trichostatin A, suberoyl bis hydroxamic acid, dimethylamino hydroxy-benzamide, Apicidin or an analog thereof, or a compound according to 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;

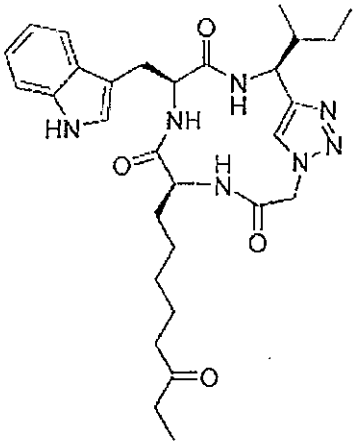
n is 0-2;

m is 0-6; and,

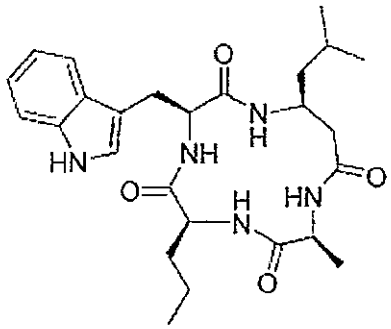
q is 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

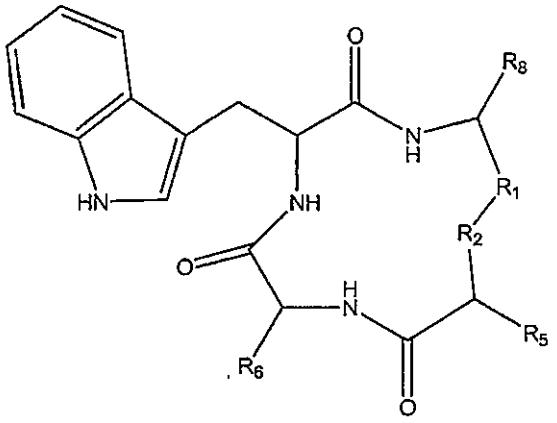
16. The inhibitor according to claim 13, wherein said inhibitor of histone deacetylace activity is Apicidin,



,



, or



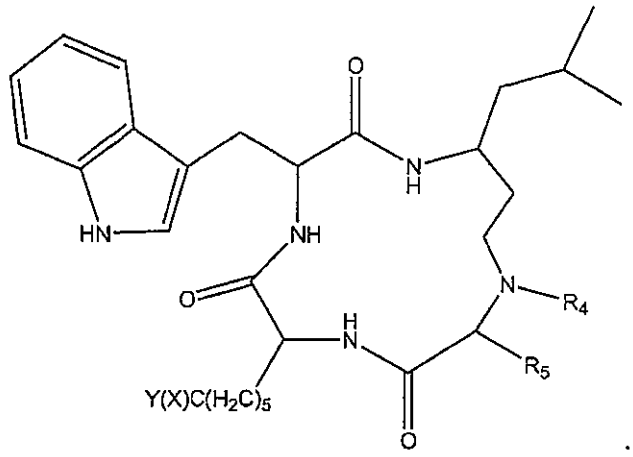
wherein

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

and,

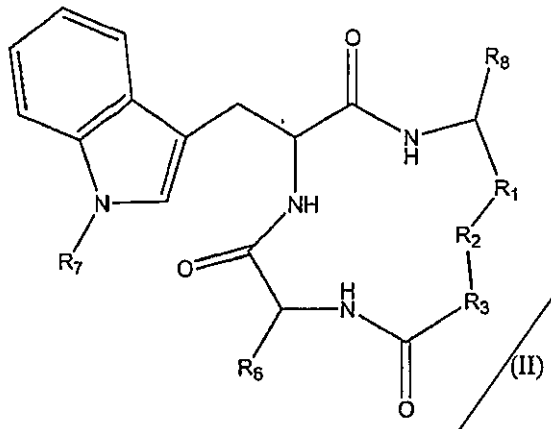
$R_2$ is $-C(Z)N(R_4)-$.

17. The inhibitor according to claim 13, wherein said inhibitor of histone deacetylace activity is



18. The inhibitor according to claim 13, further comprising contacting the hepatitis B virus with a further agent that modulates hepatitis B virus.

19. A compound according to formula II:



(II)

wherein

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

$R_2$ is -C(=O)- or $-C(\mathbb{Z})N(R_4)-$;

$R_4$ 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 $-CH_2CH_3$;

$\mathbb{Z}$ is $H_2$ or O;

$R_7$ is hydrogen or alkoxy;

$R_8$ is alkyl or carboxyalkyl;

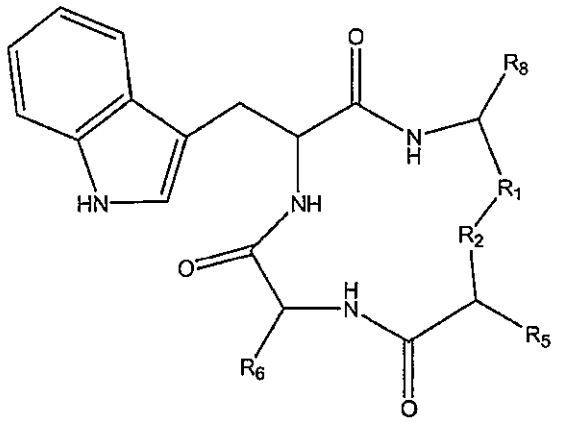
n is 0-2;

m is 0-6; and,

q is 0-3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

20. The compound according to claim 19, wherein said compound is



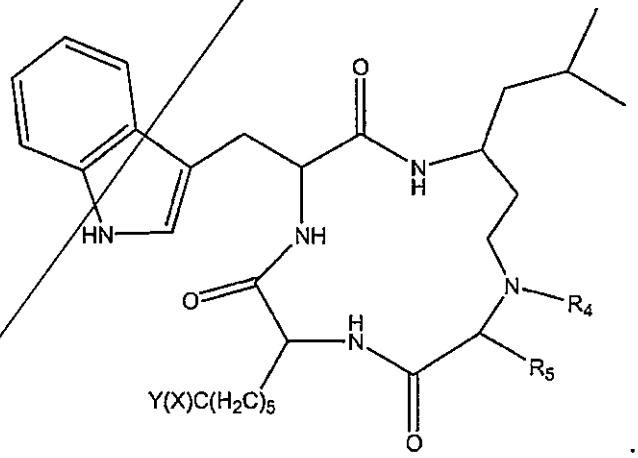
wherein

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

and,

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

21. The compound according to claim 19, wherein said compound is

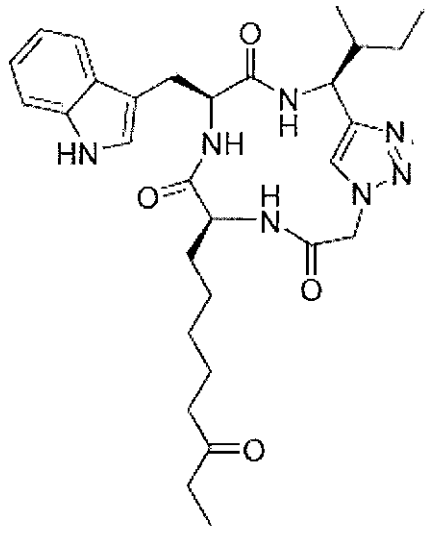


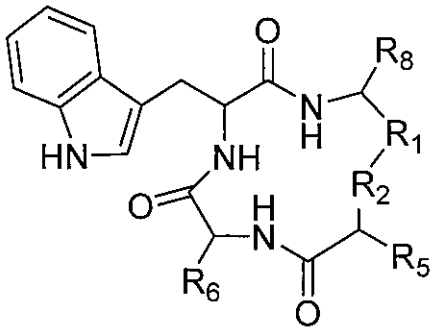
**Claims**

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;

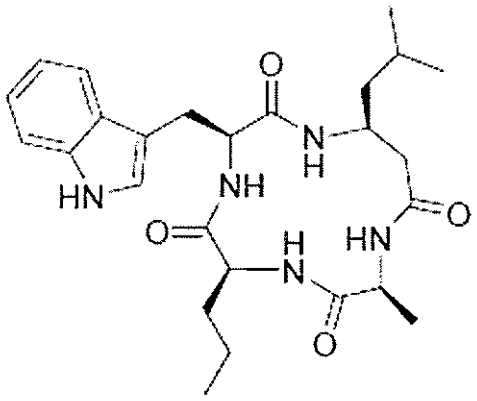
$R_8$ is alkyl or carboxyalkyl;

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

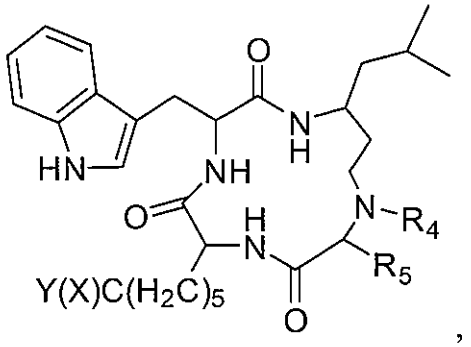
q is an integer selected from the group consisting of 0-3;

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 $-CH_2CH_3$;

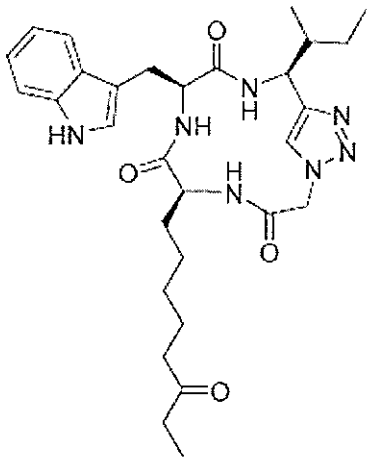
or a stereoisomer or pharmaceutically acceptable salt thereof.

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

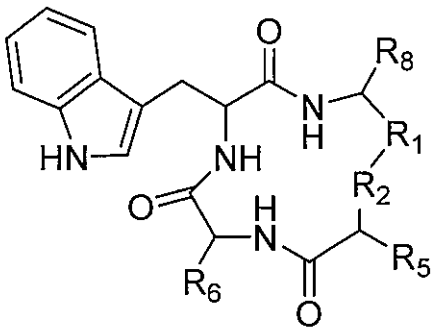
6. A therapeutically effective amount of an inhibitor of class I histone deacetylase activity for use in treating hepatitis B.

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;

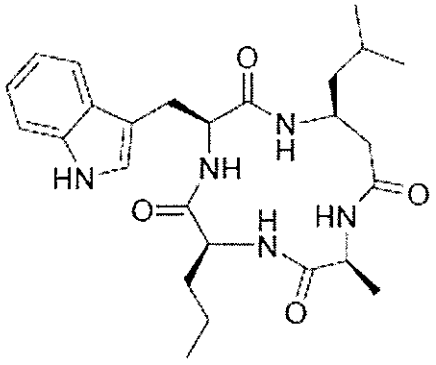
$R_8$ is alkyl or carboxyalkyl;

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

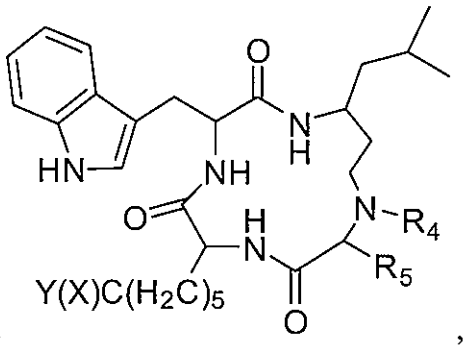
q is an integer selected from the group consisting of 0-3;

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 $-CH_2CH_3$;

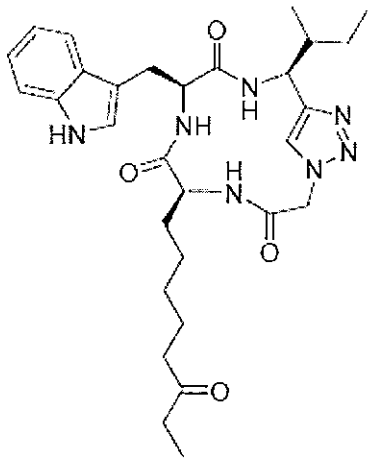
or a stereoisomer or pharmaceutically acceptable salt thereof.

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

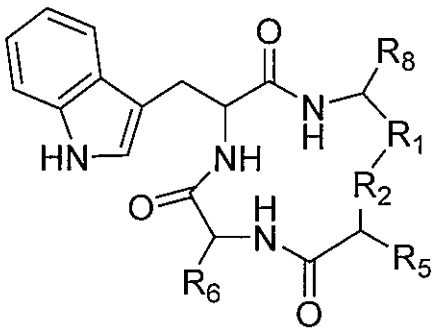
11. An inhibitor of class I histone deacetylase activity for use in repressing hepatitis B virus covalently closed circular DNA, comprising contacting the hepatitis B virus with the inhibitor.

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;

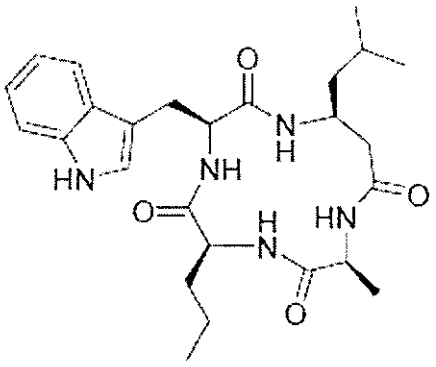
$R_8$ is alkyl or carboxyalkyl;

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

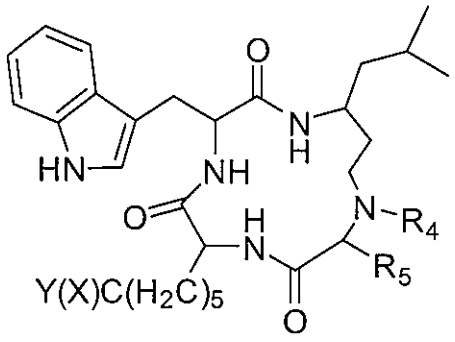
q is an integer selected from the group consisting of 0-3;

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;

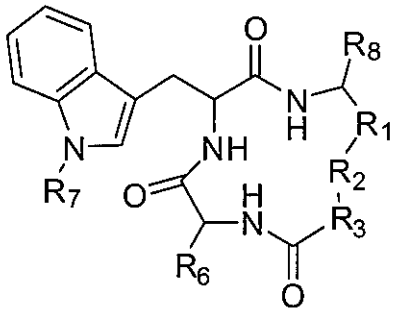
X is =O, $H_2$, $=N-NH_2$, or $=N-NH-C(=O)NH_2$;

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;

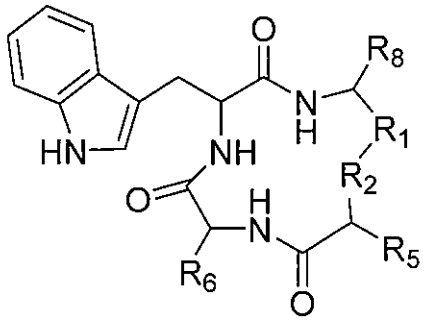
n is an integer selected from the group consisting of 0-2;

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

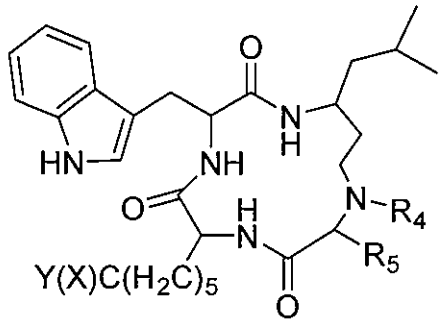



wherein

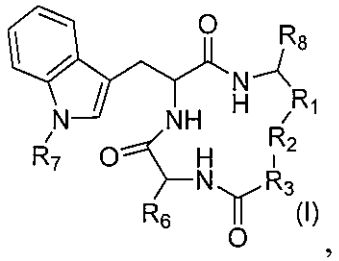
$R_1$ is $-(CH_2)-$, and,

$R_2$ 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;

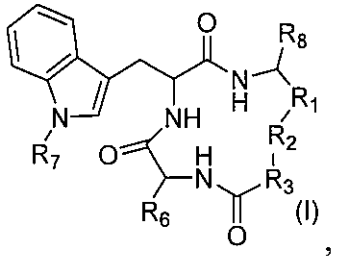
n is an integer selected from the group consisting of 0-2;

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;

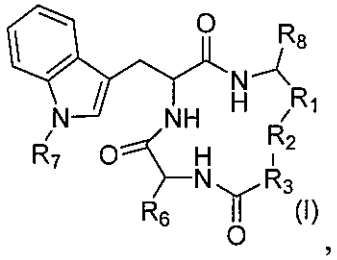
n is an integer selected from the group consisting of 0-2;

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.