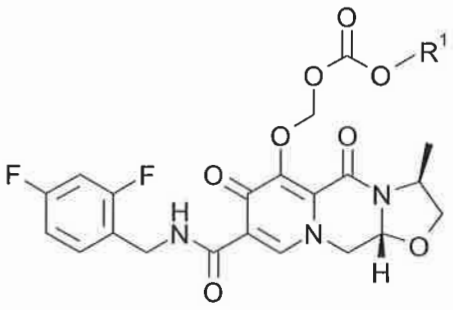
Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is C_1-C_8alkyl, C_6-C_{10}aryl or LR^2;

L is alkylene;

$R^2$is

a) hydroxy;

b) alkoxy;

c) OR^3 wherein R^3 is $P(O)(OH)_2$, alkoxy, or alkylene-alkoxy;

d) heterocyclyl optionally subsituted with oxo or C_1-C_8alkyl;

e) $C(O)OR^4$ wherein R^4 is H, C_1-C_8alkyl, or XR^5 wherein X is alkylene and R^5 is C_6-C_{10}aryl, heterocyclyl, or NR^6R^7 wherein R^6 and R^7 are independently selected from the group consisting of H and C_1-C_8alkyl;

f) NR^6R^7;

g) $C(O)NR^8R^9$ wherein R^8 and R^9 are independently selected from the group consisting of H and XR^5; or

h) $C(O)R^{10}$ wherein R^{10} is heterocyclyl optionally substituted with XR^{11} wherein R^{11} is heterocyclyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 is LR^2 wherein R^2 is OR^3 or $C(O)OR^4$.

3. A compound of formula (I) according to claim 1 wherein R^1 is LR^2 wherein R^2 is OR^3 or $C(O)OR^4$ wherein R^3 is $P(O)(OH)_2$ and R^4 is XR^5 wherein X is alkylene and R^5 is $C_{6\text{-}10}$aryl.

4. A compound selected from the group consisting of:

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl methyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(methyloxy)ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 1-methylethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-{[2-(methyloxy)ethyl]oxy}ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-hydroxyethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(phosphonooxy)ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 3-hydroxypropyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 3-(phosphonooxy)propyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-pyridinylmethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(2-oxo-1-pyrrolidinyl)ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(4-morpholinyl)ethyl carbonate;

Phenylmethyl ({[({[(3S,11aR)-8-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetate;

({[({[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetic acid;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(dimethylamino)ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-oxo-2-{4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}ethyl carbonate;

Methyl ({[({[(3S,11aR)-8-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-oxo-2-[(2-pyridinylmethyl)amino]ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(4-methyl-1-piperazinyl)ethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-{[2-(4-morpholinyl)ethyl]amino}-2-oxoethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-{[4-(dimethylamino)butyl]amino}-2-oxoethyl carbonate;

{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-{[3-(1H-imidazol-1-yl)propyl]amino}-2-oxoethyl carbonate;

2-Pyridinylmethyl ({[({[(3S,11aR)-8-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetate;

2-(4-Morpholinyl)ethyl ({[({[(3S,11aR)-8-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetate;

2-(Dimethylamino)ethyl ({[({[(3S,11aR)-8-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl)oxy]carbonyl}oxy)acetate;

{[(3*S*,11a*R*)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazin-6-yl]oxy}methyl 4-nitrophenyl carbonate; and

pharmaceutically acceptable salts thereof.

5. A pharmaceutically acceptable salt of a compound according to any of claims 1 to 4.

6. A compound according to claim 5 wherein the pharmaceutically acceptable salt is a sodium salt or hydrochloride salt.

7. A compound selected from the group consisting of:
{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(phosphonooxy)ethyl carbonate mono-sodium salt;
{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 3-(phosphonooxy)propyl carbonate mono-sodium salt; and
{[(3S,11aR)-8-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazin-6-yl]oxy}methyl 2-(4-morpholinyl)ethyl carbonate acetate.

8. A method of treatment of a viral infection in a human comprising administering to said human an antiviral effective amount of a compound according to any of claims 1 to 7.

9. A method according to claim 8 wherein the viral infection is a HIV infection.

10. A compound as claimed in any of claims 1 to 7 for use in medical therapy.

11. Use of a compound as claimed in any of claims 1 to 7 in the manufacture of a medicament for the treatment or prophylaxis of a virus infection.

12. The use according to claim 11 wherein the viral infection is a HIV infection.

13. A pharmaceutical composition comprising an effective amount of a compound according to any of claims 1 to 7 together with a pharmaceutically acceptable carrier.

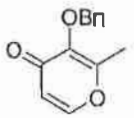
14. A pharmaceutical composition according to claim 13 in the form of a tablet, capsule, liquid or suspension.

15. A method of treatment of a HIV infection in a human comprising administering to said human a composition comprising a compound according to any of claims 1 to 7 and another therapeutic agent.

CLAIMS

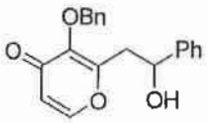
1. A process for the preparation of a synthetic intermediate compound, which process comprises

a) treating a compound of formula P-2



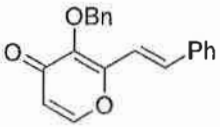
P-2

with lithium bis(trimethylsilyl)amide and benzaldehyde to form a compound of formula P-3



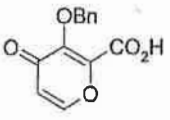
P-3 ;

treating the compound of formula P-3 with triethylamine and methanesulfonyl chloride followed by N-methyl-2-pyrrolidone and 1,8-diazabicyclo[5.4.0]undec-7-ene to form a compound of formula P-4



P-4 ; and

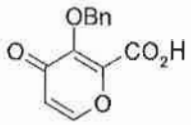
treating the compound of formula P-4 with $RuCl_3$ and $NaIO_4$ to form a compound of formula P-5



P-5

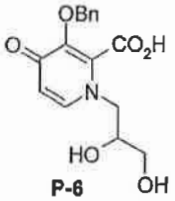
or

b) treating a compound of formula P-5



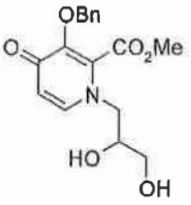
P-5

with 3-amino-propane-1,2-diol to form a compound of formula P-6



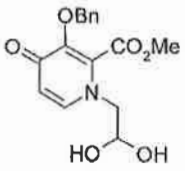
P-6 ;

treating the compound of formula P-6 with $NaHCO_3$ and either $(MeO)_2SO_2$ or MeI to form a compound of formula P-7



P-7 ; and

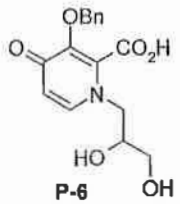
treating the compound of formula P-7 with $NaIO_4$ to form a compound of formula P-8



P-8 ;

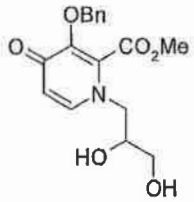
or

c) methylating a compound of formula P-6 with $NaHCo_3$ and either $(MeO)_2SO_2$ or MeI



P-6

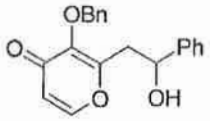
to form a compound of formula P-7



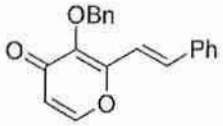
P-7 ; and

treating the compound of formula P-7 with $NaIO_4$ to form a compound of formula P-8 as defined above.

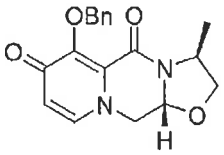
2. A synthetic intermediate compound which is of one of the following formulae



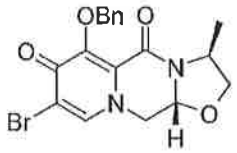
P-3



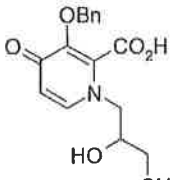
P-4



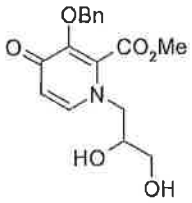
P-9



P-10



P-6



P-7



P-8