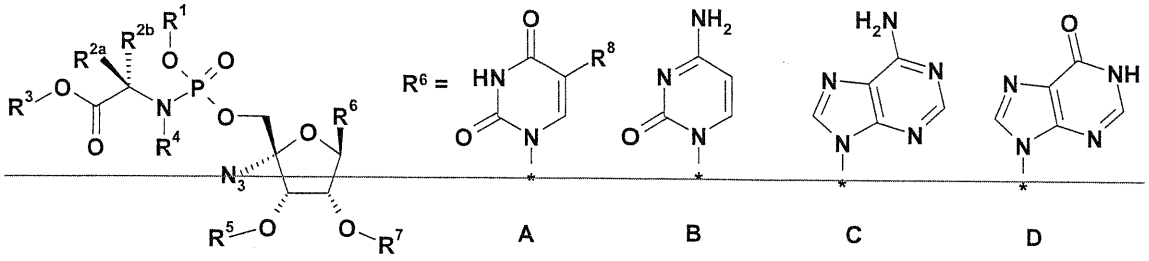
Claims

1. A method for treating dengue fever comprising administering to a patient in need thereof a compound of Formula I



I

wherein:

R^1 is hydrogen, C_{1-6}haloalkyl, or aryl wherein said aryl is phenyl or naphthyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-N(R^{1a})_2$, C_{1-6}acylamino, $-NHSO_2C_{1-6}$alkyl, $-SO_2N(R^{1a})_2$, $-SO_2C_{1-6}$alkyl, $-COR^{1b}$, nitro and cyano;

R^{1a} is independently hydrogen or C_{1-6}alkyl;

R^{1b} is $-OR^{1a}$ or $-N(R^{1a})_2$;

R^{2a} and R^{2b} are (i) independently selected from the group consisting of hydrogen, C_{1-10}alkyl, $-(CH2)_rN(R^{1a})_2$, C_{1-6}hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH2)_3NHC(=NH)NH_2$, (1*H*-indol-3-yl)methyl, (1*H*-indol-4-yl)methyl, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl C_{1-3}alkyl, said aryl groups optionally substituted with a group selected from the group consisting of hydroxyl, C_{1-10}alkyl, C_{1-6}alkoxy, halogen, nitro and cyano; (ii) R^{2a} is hydrogen and R^{2b} and R^4 together are $(CH_2)_3$; (iii) R^{2a} and R^{2b} together are $(CH_2)_n$; or, (iv) R^{2a} and R^{2b} both are C_{1-6} alkyl;

R^3 is hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, aryl or aryl C_{1-3} alkyl wherein said aryl is phenyl;

R^4 is hydrogen, C_{1-3} alkyl, or R^{2b} and R^4 together are $(CH_2)_3$;

R^6 is A, B, C or D wherein R^8 is hydrogen or C_{1-3} alkyl;

R^5 and R^7 is independently selected from hydrogen, $C(=O)C_{1-6}$alkyl, $C(=O)R^{1b}$;

m is 0 to 3;

n is 4 or 5;

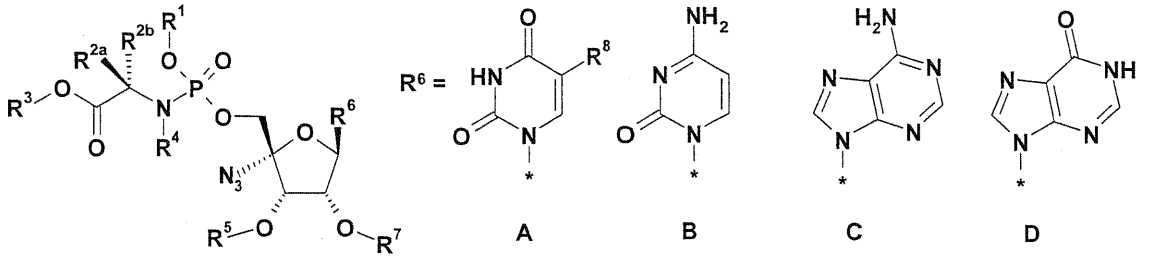
p is 0 to 2; and

r is 1 to 6;

~~or pharmaceutically acceptable salts thereof.~~

Claims

~~21~~. The ~~use of a compound~~ compound of Formula I for use in the treatment of dengue fever,



I

wherein:

R^1 is hydrogen, C_{1-6}haloalkyl, or aryl wherein said aryl is phenyl or naphthyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-N(R^{1a})_2$, C_{1-6}acylamino, $-NHSO_2C_{1-6}$alkyl, $-SO_2N(R^{1a})_2$, $-SO_2C_{1-6}$alkyl, $-COR^{1b}$, nitro and cyano;

R^{1a} is independently hydrogen or C_{1-6}alkyl;

R^{1b} is $-OR^{1a}$ or $-N(R^{1a})_2$;

R^{2a} and R^{2b} are (i) independently selected from the group consisting of hydrogen, C_{1-10}alkyl, $-(CH2)_rN(R^{1a})_2$, C_{1-6}hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH2)_3NHC(=NH)NH_2$, (1*H*-indol-3-yl)methyl, (1*H*-indol-4-yl)methyl, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl C_{1-3}alkyl, said aryl groups optionally substituted with a group selected from the group consisting of hydroxyl, C_{1-10}alkyl, C_{1-6}alkoxy, halogen, nitro and cyano; (ii) R^{2a} is hydrogen and R^{2b} and R^4 together are $(CH_2)_3$; (iii) R^{2a} and R^{2b} together are $(CH_2)_n$; or, (iv) R^{2a} and R^{2b} both are C_{1-6} alkyl;

R^3 is hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, aryl or aryl-C_{1-3} alkyl wherein said aryl is phenyl;

R^4 is hydrogen, C_{1-3} alkyl, or R^{2b} and R^4 together are $(CH_2)_3$;

R^6 is A, B, C or D wherein R^8 is hydrogen or C_{1-3} alkyl;

R^5 and R^7 is independently selected from hydrogen, $C(=O)C_{1-6}$alkyl, $C(=O)R^{1b}$;

m is 0 to 3;

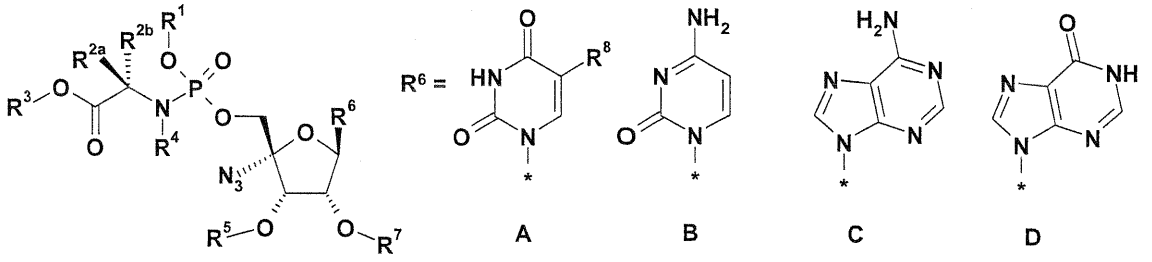
n is 4 or 5;

p is 0 to 2; and

r is 1 to 6;

or pharmaceutically acceptable salts thereof.

~~32~~. The use of a compound of Formula I for the preparation of a medicament for the treatment of dengue fever,



I

wherein:

R^1 is hydrogen, C_{1-6}haloalkyl, or aryl wherein said aryl is phenyl or naphthyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-N(R^{1a})_2$, C_{1-6}acylamino, $-NHSO_2C_{1-6}$alkyl, $-SO_2N(R^{1a})_2$, $-SO_2C_{1-6}$alkyl, $-COR^{1b}$, nitro and cyano;

R^{1a} is independently hydrogen or C_{1-6}alkyl;

R^{1b} is $-OR^{1a}$ or $-N(R^{1a})_2$;

R^{2a} and R^{2b} are (i) independently selected from the group consisting of hydrogen, C_{1-10}alkyl, $-(CH2)_rN(R^{1a})_2$, C_{1-6}hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH2)_3NHC(=NH)NH_2$, (1*H*-indol-3-yl)methyl, (1*H*-indol-4-yl)methyl, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl C_{1-3}alkyl, said aryl groups optionally substituted with a group selected from the group consisting of hydroxyl, C_{1-10}alkyl, C_{1-6}alkoxy, halogen, nitro and cyano; (ii) R^{2a} is hydrogen and R^{2b} and R^4 together are $(CH_2)_3$; (iii) R^{2a} and R^{2b} together are $(CH_2)_n$; or, (iv) R^{2a} and R^{2b} both are C_{1-6} alkyl;

R^3 is hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, aryl or aryl-C_{1-3} alkyl wherein said aryl is phenyl;

R^4 is hydrogen, C_{1-3} alkyl, or R^{2b} and R^4 together are $(CH_2)_3$;

R^6 is A, B, C or D wherein R^8 is hydrogen or C_{1-3} alkyl;

R^5 and R^7 is independently selected from hydrogen, $C(=O)C_{1-6}$alkyl, $C(=O)R^{1b}$;

m is 0 to 3;

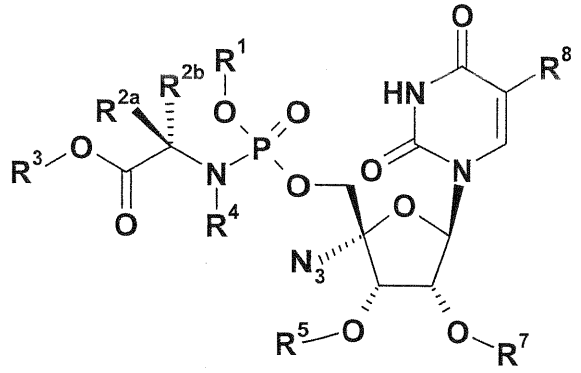
n is 4 or 5;

p is 0 to 2; and

r is 1 to 6;

or pharmaceutically acceptable salts thereof.

43. A ~~method~~ compound and use according to claim 1 or 2 ~~or 3~~; comprising ~~administering to a patient in need thereof~~ a compound of Formula Ia



Ia

wherein:

R^1 is hydrogen, C_{1-6}haloalkyl, or aryl wherein said aryl is phenyl or naphthyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, halogen, C_{1-6}haloalkyl, $-N(R^{1a})_2$, C_{1-6}acylamino, $-NHSO_2C_{1-6}$alkyl, $-SO_2N(R^{1a})_2$, $-SO_2C_{1-6}$alkyl, $-COR^{1b}$, nitro and cyano;

R^{1a} is independently hydrogen or C_{1-6}alkyl;

R^{1b} is $-OR^{1a}$ or $-N(R^{1a})_2$;

R^{2a} and R^{2b} are (i) independently selected from the group consisting of hydrogen, C_{1-10}alkyl, $-(CH2)_rN(R^{1a})_2$, C_{1-6}hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH2)_3NHC(=NH)NH_2$, (1*H*-indol-3-yl)methyl, (1*H*-indol-4-yl)methyl, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl C_{1-3}alkyl, said aryl groups optionally substituted with a group selected from the group consisting of hydroxyl, C_{1-10}alkyl, C_{1-6}alkoxy, halogen, nitro and cyano; (ii) R^{2a} is hydrogen and R^{2b} and R^4 together are $(CH_2)_3$; (iii) R^{2a} and R^{2b} together are $(CH_2)_n$; or, (iv) R^{2a} and R^{2b} both are C_{1-6} alkyl;

R^3 is hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, aryl or aryl-C_{1-3} alkyl wherein said aryl is phenyl;

R^4 is hydrogen, C_{1-3} alkyl, or R^{2b} and R^4 together are $(CH_2)_3$;

R^5 and R^7 is independently selected from hydrogen, $C(=O)C_{1-6}$alkyl, $C(=O)R^{1b}$;

R^8 is hydrogen or C_{1-3} alkyl;

m is 0 to 3;

n is 4 or 5;

p is 0 to 2; and

r is 1 to 6;

or pharmaceutically acceptable salts thereof.

~~5~~4. The ~~method~~ compound and the use of claim ~~4~~ 3 wherein:

R^1 is phenyl, naphthyl, or o-methoxyphenyl;

R^{2a} and R^{2b} are independently hydrogen, methyl, or benzyl;

R^3 is methyl, ethyl, or benzyl;

R^4 is H;

R^5 and R^7 are both H, –C(=O)Et, or –C(=O)Bu; and

R^8 is H.

~~6~~5. The ~~method~~ compound and the use of claim ~~5~~ 4 wherein:

R^1 is phenyl or naphthyl;

R^{2a} is hydrogen and R^{2b} is methyl;

R^3 is ethyl or benzyl; and

R^5 and R^7 are both H or –C(=O)Et.

~~7~~6. The ~~method~~ compound and the use of claim ~~6~~ 5 wherein:

R^1 is naphthyl;

R^{2a} is hydrogen and R^{2b} is methyl;

R^3 is benzyl; and

R^5 and R^7 are both H.

~~8~~7. The ~~method~~ compound and the use of claim ~~5~~ 4 wherein:

R^1 is naphthyl;

R^{2a} is H and R^{2b} is benzyl;

R^3 is ethyl; and

R^5 and R^7 are both H.

~~9~~8. The ~~method~~ compound of claim ~~5~~ 4 wherein:

R^1 is naphthyl;

R^{2a} is H and R^{2b} is benzyl;

R^3 is benzyl; and

R^5 and R^7 are both H.

~~10~~9. The ~~method~~ compound and use of claim 1 or 2 ~~or 3~~ wherein:

R^1 is phenyl;

R^{2a} is H and R^{2b} is methyl;

R^3 is benzyl;

R^5 is H;

R^6 is C; and

R^7 is H.

~~11~~10. A ~~method~~ compound and use of any one of claims 1 to ~~10~~ 9 for treating dengue fever comprising ~~administering to a patient in need thereof~~ a compound selected from the group consisting of:

(S)-2-[[(2R,3S,4R,5R)-5-(6-Amino-purin-9-yl)-2-azido-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid ethyl ester;

(S)-2-{[(2R,3S,4R,5R)-5-(6-Amino-purin-9-yl)-2-azido-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid benzyl ester;

(S)-2-{[(2R,3S,4R,5R)-5-(4-Amino-2-oxo-2H-pyrimidin-1-yl)-2-azido-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid methyl ester;

Pentanoic acid (2R,3S,4R,5R)-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-2-azido-2-[((S)-1-benzyloxycarbonyl-ethylamino)-(2-methoxy-phenoxy)-phosphoryloxymethyl]-4-pentanoyloxy-tetrahydro-furan-3-yl ester;

(S)-2-[[(2R,3S,4R,5R)-5-(4-Amino-2-oxo-2H-pyrimidin-1-yl)-2-azido-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-propionic acid benzyl ester;

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-pentanedioic acid diethyl ester;

(S)-2-{[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-bis-propionyloxy-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid ethyl ester;

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-3-phenyl-propionic acid benzyl ester; and

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-3-phenyl-propionic acid ethyl ester.

~~12~~11. The ~~method~~ compound and use of claim 1 or 2 ~~or 3~~ further comprising ~~administering~~ at least one other antiviral agent.

~~13~~12. A compound selected from the group consisting of:

Pentanoic acid (2R,3S,4R,5R)-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-2-azido-2-[((S)-1-benzyloxycarbonyl-ethylamino)-(2-methoxy-phenoxy)-phosphoryloxymethyl]-4-pentanoyloxy-tetrahydro-furan-3-yl ester;

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-pentanedioic acid diethyl ester;

(S)-2-{[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-bis-propionyloxy-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid ethyl ester;

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-3-phenyl-propionic acid benzyl ester; and

(S)-2-[[(2R,3S,4R,5R)-2-Azido-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]-(naphthalen-1-yloxy)-phosphorylamino]-3-phenyl-propionic acid ethyl ester.