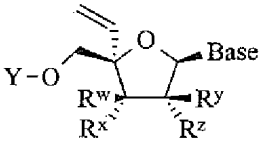
[0005] Because RSV virus continues to be the leading cause of seasonal respiratory disease throughout the world, causes risk of developing severe respiratory disease, which can result in long-lasting complications or death, there exists a need in the field for improved forms of treatment of RSV mediated diseases.

SUMMARY

[0006] The compounds of Formula I and pharmaceutical compositions comprising said compounds are useful for the treatment of diseases mediated by RSV.

[0007] The application, in one aspect, provides a compound of Formula I



I

wherein:

Y is H or P(=X)(R)(R');

R is O-R^1 or $NHC(R^{2a})(R^{2b})C(=O)OR^3$;

R' is $N(R^4)C(R^{2a})(R^{2b})C(=O)OR^3$, $-OP(=O)(OH)OP(=O)(OH)OH$, or $-OR^3$;

R^1 is H, lower alkyl, lower haloalkyl, or aryl, wherein aryl is phenyl or naphthyl, optionally substituted with one or more lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halo, lower haloalkyl, $-N(R^{1a})_2$, acylamino, $-SO_2N(R^{1a})_2$, $-C(=O)R^{1b}$, $-SO_2R^{1c}$, $-NHSO_2R^{1c}$, nitro, cyano, or $R^{1''}$;

each R^{1a} is independently H or lower alkyl;

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

each R^{1c} is lower alkyl;

each R^{2a} and R^{2b} is independently H, lower alkyl, $-(CH_2)_rN(R^{1a})_2$, lower hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH_2)_nNHC(=NH)NH_2$, (1*H*-indol-3-yl)Me, (1*H*-indol-4-yl)Me, $-(CH_2)_mC(=O)R^{1b}$, aryl or aryl lower alkyl, wherein aryl and aryl lower alkyl are optionally substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano;

m is 0, 1, or 2;

n is 1, 2, or 3;

p is 1 or 2;

r is 1 or 2;

or R^{2a} is H and R^{2b} and R^4 together form $(CH_2)_n$;

each R^3 is independently H, lower alkyl, lower haloalkyl, phenyl or phenyl lower alkyl, wherein phenyl and phenyl lower alkyl are optionally substituted with lower alkoxy;

or R^3 and $R^{1''}$ together form CH_2;

each R^4 is independently H, lower alkyl;

or R^{2b} and R^4 together form $(CH_2)_3$;

each of R^w, R^x, and R^y is independently H, OH, or F;

R^z is H or OH;

or R^3 and R^x together form a bond;

or R^1 and R^x together form a bond;

X is O or S; and

Base is uracil, cytosine, guanine, adenine, thymine, or heterocycloalkyl, each of which may optionally be substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano;

or a pharmacologically acceptable salt thereof.

[0008a] In another aspect, there is provided a compound selected from the list consisting of:

4'-Vinyluridine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(i2,2-dimethylpropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(3,3-dimethylbutoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(benzyloxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(hexoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(cyclopentoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(cyclohexoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(isopropoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(3,3-dimethylbutoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(benzyloxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(hexoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(cyclopentoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyluridine-5'-{*N,N'*-bis[(S)-1-(cyclohexoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyl-5'-*O*-(2-oxido-4-H-1,3,2-benzodioxaphosphorin-2-yl)-uridine;

4'-Vinyl-5'-*O*-[bis(4-methoxyphenoxy)phosphinyl] uridine;

4'-Vinyluridine-3',5'-cyclic phosphoric acid isopropyl ester;

4'-Vinylcytidine-5'-(*O*-phenyl-*N*-(S)-1-(ethoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-phenyl-*N*-(S)-1-(neopentoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-phenyl-*N*-(S)-1-(benzyloxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(benzyloxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(3,3-dimethybutoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(pentoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(hexoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(cyclohexoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-(isopropoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-benzyloxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-(3,3-dimethylbutoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-(hexoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinylcytidine-5'-{*N,N'*-bis[(S)-1-(cyclohexoxycarbonyl)ethyl]phosphorodiamidate};

4'-Vinyl-5'-*O*-(2-oxido-4-H-1,3,2-benzodioxaphosphorin-2-yl)-cytidine;

4'-Vinyl-5'-*O*-[bis(4-methoxyphenoxy)phosphinyl] cytidine;

4'-Vinylcytidine-3',5'-cyclic phosphoric acid isopropyl ester;

4'-Viyladenosine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyladenosine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyladenosine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinyladenosine-5'-{*N,N'*-bis[(S)-1-(isopropoxycarbonyl)ethyl]phosphorodiamidate;

4'-Vinyl-5'-*O*-(2-oxido-4-H-1,3,2-benzodioxaphosphorin-2-yl)-adenosine;

4'-Vinyl-5'-*O*-[bis(4-methoxyphenoxy)phosphinyl] adenosine;

4'-Vinyladenosine-3',5'-cyclic phosphoric acid isopropyl ester;

4'-Vinylguanosine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylguanosine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylguanosine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

4'-Vinylguanosine-5'-{*N,N'*-bis[(S)-1-(isopropoxycarbonyl)ethyl]phosphorodiamidate;

4'-Vinyl-5'-*O*-(2-oxido-4-H-1,3,2-benzodioxaphosphorin-2-yl)-guanosine;

4'-Vinyl-5'-*O*-[bis(4-methoxyphenoxy)phosphinyl] guanosine;

4'-Vinylguanosine-3',5'-cyclic phosphoric acid isopropyl ester;

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(benzyloxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-{*N,N'*-bis[(S)-1-(isopropoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinyluridine-5'-{*N,N'*-bis[(S)-1-(cyclopentoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-(*O*-1-naphthyl-*N*-(S)-1-(benzyloxycarbonyl)ethyl phosphoramidate;

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(propoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(hexoxycarbonyl)ethyl]phosphorodiamidate}; and

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(cyclopentoxycarbonyl)ethyl]phosphorodiamidate}.

[0008] The application provides the compounds of Formula I which are useful for the prevention or treatment of diseases mediated by RSV, pharmaceutical compositions comprising compounds of Formula I, compounds that result in the formation of compounds of Formula I *in vivo* during said treatment, or pharmaceutical compositions comprising compounds that result in the formation of compounds of Formula I *in vivo* during said treatment.

[0009] The application provides a method for preventing or treating RSV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a compound resulting in the formation of a compound of Formula I *in vivo*.

[0009a] In another aspect, there is provided a compound as defined herein for use in preventing or treating an RSV infection.

[0009b] In another aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for the prevention or treatment of an RSV infection.

[0010] The application provides a composition comprising a compound of Formula I, or a compound resulting in the formation of a compound of Formula I *in vivo*, and a pharmaceutically acceptable excipient. In another aspect, there is provided a composition comprising the compound as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The compounds of Formula I are efficacious as antiviral drugs for the treatment of RSV infections in human. Administration of the compounds of Formula I inhibits RSV replication in infected cells by the formation of the nucleoside 5'-triphosphate derivatives of the compounds of Formula I, as inhibitors of RSV polymerase.

Definitions

[0012] The term "alkyl" as used herein denotes a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms. Preferably, the term "alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms. Most preferred are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl or pentyl. The alkyl may be unsubstituted or substituted. The substituents are selected from one or more of cycloalkyl, nitro, amino, alkyl amino, dialkyl amino, alkyl carbonyl and cycloalkyl carbonyl.

[0013] The term "cycloalkyl" as used herein denotes an optionally substituted cycloalkyl group containing 3 to 7 carbon atoms, e. g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0014] The term "alkoxy" as used herein denotes an optionally substituted straight or branched chain alkyl-oxy group wherein the "alkyl" portion is as defined above such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, i-butyloxy, tert-butyloxy, pentyloxy, hexyloxy, heptyloxy including their isomers.

[0015] The term "alkoxyalkyl" as used herein denotes an alkoxy group as defined above which is bonded to an alkyl group as defined above. Examples are methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propyloxypropyl, methoxybutyl, ethoxybutyl, propyloxybutyl, butyloxybutyl, tert -butyloxybutyl, methoxypentyl, ethoxypentyl, propyloxypentyl including their isomers.

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropoxycarbonyl)ethyl]phosphorodiamidate};

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(hexoxycarbonyl)ethyl]phosphorodiamidate}; and

3'-Deoxy-3'-fluoro-4'-vinylcytidine-5'-{*N,N'*-bis[(S)-1-(cyclopentoxycarbonyl)ethyl]phosphorodiamidate}.

18. A compound of any one of claims 1 to 23 for use in preventing or treating an RSV infection.

19. Use of a compound of any one of claims 1 to 23 in the manufacture of a medicament for the prevention or treatment of an RSV infection.

20. A composition comprising the compound of any one of claims 1 to 17.

21. A composition comprising the compound of claim 17.