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(54) Benævnelse: **NUKLEOSID-PHOSPHORAMIDAT-PRODRUGS**

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DESCRIPTION

Description

Field of Invention

[0001] The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals. The invention provides novel chemical compounds, and the use of these compounds alone or in combination with other antiviral agents for treating HCV infection.

Background

[0002] Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

[0003] The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-

stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex (K. Ishi, et al, Heptology, 1999, 29: 1227-1235; V. Lohmann, et al., Virology, 1998, 249: 108-118). Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

[0004] HCV belongs to a much larger family of viruses that share many common features.

Flaviviridae Viruses

[0005] The Flaviviridae family of viruses comprises at least three distinct genera: *pestiviruses,* which cause disease in cattle and pigs; *flavivruses,* which are the primary cause of diseases such as dengue fever and yellow fever; and *hepaciviruses,* whose sole member is HCV. The flavivirus genus includes more than 68 members separated into groups on the basis of serological relatedness (Calisher et al., J. Gen. Virol, 1993,70,37-43). Clinical symptoms vary and include fever, encephalitis and hemorrhagic fever (Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, 1996, Chapter 31, 931-959). Flaviviruses of global concern that are associated with human disease include the Dengue Hemorrhagic Fever viruses (DHF), yellow fever virus, shock syndrome and Japanese encephalitis virus (Halstead, S. B., Rev. Infect. Dis., 1984, 6, 251-264; Halstead, S. B., Science, 239:476-481, 1988; Monath, T. P., New Eng. J. Med, 1988, 319, 64 1-643).

[0006] The pestivirus genus includes bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, also called hog cholera virus) and border disease virus (BDV) of sheep (Moennig, V. et al. Adv. Vir. Res. 1992, 41, 53-98). Pestivirus infections of domesticated livestock (cattle, pigs and sheep) cause significant economic losses worldwide. BVDV causes mucosal disease in cattle and is of significant economic importance to the livestock industry (Meyers, G. and Thiel, H.J., Advances in Virus Research, 1996, 47, 53-118; Moennig V., et al, Adv. Vir. Res. 1992, 41, 53-98). Human pestiviruses have not been as extensively characterized as the animal pestiviruses. However, serological surveys indicate considerable pestivirus exposure in humans.

[0007] Pestiviruses and hepaciviruses are closely related virus groups within the Flaviviridae family. Other closely related viruses in this family include the GB virus A, GB virus A-like agents, GB virus-B and GB virus-C (also called hepatitis G virus, HGV). The hepacivirus group (hepatitis C virus; HCV) consists of a number of closely related but genotypically distinguishable viruses that infect humans. There are at least 6 HCV genotypes and more than 50 subtypes. Due to the similarities between pestiviruses and hepaciviruses, combined with the poor ability of hepaciviruses to grow efficiently in cell culture, bovine viral diarrhea virus (BVDV) is often used as a surrogate to study the HCV virus.

[0008] The genetic organization of pestiviruses and hepaciviruses is very similar. These

positive stranded RNA viruses possess a single large open reading frame (ORF) encoding all the viral proteins necessary for virus replication. These proteins are expressed as a polyprotein that is co- and post-translationally processed by both cellular and virus-encoded proteinases to yield the mature viral proteins. The viral proteins responsible for the replication of the viral genome RNA are located within approximately the carboxy-terminal. Two-thirds of the ORF are termed nonstructural (NS) proteins. The genetic organization and polyprotein processing of the nonstructural protein portion of the ORF for pestiviruses and hepaciviruses is very similar. For both the pestiviruses and hepaciviruses, the mature nonstructural (NS) proteins, in sequential order from the amino-terminus of the nonstructural protein coding region to the carboxy-terminus of the ORF, consist of p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

[0009] The NS proteins of pestiviruses and hepaciviruses share sequence domains that are characteristic of specific protein functions. For example, the NS3 proteins of viruses in both groups possess amino acid sequence motifs characteristic of serine proteinases and of helicases (Gorbalenya et al., Nature, 1988, 333, 22; Bazan and Fletterick Virology , 1989,171,637-639; Gorbalenya et al., Nucleic Acid Res., 1989, 17, 3889-3897). Similarly, the NS5B proteins of pestiviruses and hepaciviruses have the motifs characteristic of RNA-directed RNA polymerases (Koonin, E.V. and Dolja, V.V., Crir. Rev. Biochem. Molec. Biol. 1993, 28, 375-430).

[0010] The actual roles and functions of the NS proteins of pestiviruses and hepaciviruses in the lifecycle of the viruses are directly analogous. In both cases, the NS3 serine proteinase is responsible for all proteolytic processing of polyprotein precursors downstream of its position in the ORF (Wiskerchen and Collett, Virology, 1991, 184, 341-350; Bartenschlager et al., J. Virol. 1993, 67, 3835-3844; Eckart et al. Biochem. Biophys. Res. Comm. 1993,192, 399-406; Grakoui et al., J. Virol. 1993, 67, 2832-2843; Grakoui et al., Proc. Natl. Acad Sci. USA 1993, 90, 10583-10587; Hijikata et al., J. Virol. 1993, 67, 4665-4675; Tome et al., J. Virol., 1993, 67, 4017-4026). The NS4A protein, in both cases, acts as a cofactor with the NS3 serine protease (Bartenschlager et al., J. Virol. 1994, 68, 5045-5055; Failla et al., J. Virol. 1994, 68, 3753-3760; Xu et al., J. Virol, 1997, 71:53 12-5322). The NS3 protein of both viruses also functions as a helicase (Kim et al., Biochem. Biophys. Res. Comm., 1995, 215, 160-166; Jin and Peterson, Arch. Biochem. Biophys., 1995, 323, 47-53; Warrener and Collett, J. Virol. 1995, 69,1720-1726). Finally, the NS5B proteins ofpestiviruses and hepaciviruses have the predicted RNA-directed RNA polymerases activity (Behrens et al., EMBO, 1996, 15, 12-22; Lechmann et al., J. Virol., 1997, 71, 8416-8428; Yuan et al., Biochem. Biophys. Res. Comm. 1997, 232, 231-235; Hagedorn, PCT WO 97/12033; Zhong et al, J. Virol., 1998, 72, 9365-9369).

[0011] Currently, there are limited treatment options for individuals infected with hepatitis C virus. The current approved therapeutic option is the use of immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin. This therapy is limited in its clinical effectiveness and only 50% of treated patients respond to therapy. Therefore, there is significant need for more effective and novel therapies to address the unmet medical need posed by HCV infection.

[0012] A number of potential molecular targets for drug development of direct acting antivirals as anti -HCV therapeutics have now been identified including, but not limited to, the NS2-NS3 autoprotease, the N3 protease, the N3 helicase and the NS5B polymerase. The RNA-dependent RNA polymerase is absolutely essential for replication of the single-stranded, positive sense, RNA genome and this enzyme has elicited significant interest among medicinal chemists.

[0013] Inhibitors of HCV NS5B as potential therapies for HCV infection have been reviewed: Tan, S.-L., et al., Nature Rev. Drug Discov., 2002, 1, 867-881; Walker, M.P. et al., Exp. Opin. Investigational Drugs, 2003, 12, 1269-1280; Ni, Z-J., et al., Current Opinion in Drug Discovery and Development, 2004, 7, 446-459; Beaulieu, P. L., et al., Current Opinion in Investigational Drugs, 2004, 5, 838-850; Wu, J., et al., Current Drug Targets-Infectious Disorders, 2003, 3, 207-219; Griffith, R.C., et al, Annual Reports in Medicinal Chemistry, 2004, 39, 223-237; Carrol, S., et al., Infectious Disorders-Drug Targets, 2006, 6, 17-29. The potential for the emergence of resistant HCV strains and the need to identify agents with broad genotype coverage supports the need for continuing efforts to identify novel and more effective nucleosides as HCV NS5B inhibitors.

[0014] Nucleoside inhibitors of NS5B polymerase can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted in *vivo* to a triphosphate to compete for the polymerase nucleotide binding site. This conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable *of in situ* phosphorylation.

[0015] In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in the metabolism of a nucleoside to the active triphosphate analog, the preparation of stable phosphate prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral replication when administered to viral infected whole cells (McGuigan, C., et al., J. Med. Chem., 1996, 39, 1748-1753; Valette, G., et al., J. Med. Chem., 1996, 39, 1981-1990; Balzarini, J., et al., Proc. National Acad Sci USA, 1996, 93, 7295-7299; Siddiqui, A. Q., et al., J. Med. Chem., 1999, 42, 4122-4128; Eisenberg, E. J., et al., Nucleosides, Nucleotides and Nucleic Acids, 2001, 20, 1091-1098; Lee, W.A., et al., Antimicrobial Agents and Chemotherapy, 2005, 49, 1898); US 2006/0241064; and WO 2007/095269.

[0016] Also limiting the utility ofnucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on

their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to administering the parent nucleoside alone. Enzyme-mediated hydrolysis of the phosphate ester moiety produces a nucleoside monophosphate wherein the rate limiting initial phosphorylation is unnecessary.

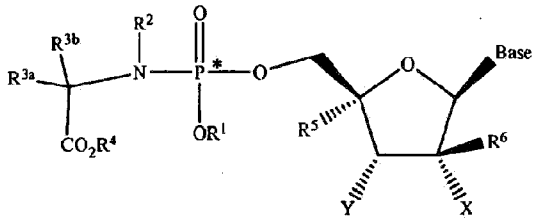
[0017] WO 2005/003147 discloses compositions and methods of treating a *Flaviviviridae* infection, including hepatitis C virus.

[0018] J. Med. Chem., 2005, 48, 5504-5508, Clark et al., discloses 2'-deoxy-2'-fluoro-2'-C-methylcytidine as an inhibitor of Hepatitis C Virus.

SUMMARY OF THE INVENTION

[0019] The present invention is as set out in the claims.

[0020] The present disclosure is directed toward phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections in mammals, which is a compound, its stereoisomers, salts (acid or basic addition salts), hydrates, solvates, or crystalline forms thereof, represented by the following structure:



I

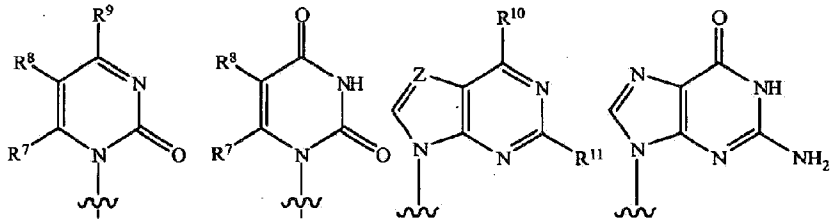
wherein

1. (a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, - $NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and - SO_2C_{1-6} alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is -OR' or $-N(R^{1'})_2$);
2. (b) R^2 is hydrogen, C_{1-10} alkyl, R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, $C(O)CR^{3a}R^{3b}NHR^1$, where n is 2 to 4 and R^1, R^{3a}, and R^{3b};

3. (c) R^{3a} and R^{3b} are (i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, -$(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, -CH_2SH, -$(CH_2)_2S(O)_dMe$,-$(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl,-$(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are $(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is -OR' or -$N(R^{3'})_2$); (vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl; or (viii) R^{3a} is CH_3, -CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is -OR' or -$N(R^{3'})_2$);
4. (d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;
5. (e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), CH_2F, N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I, with the provisos that when X is OH, base is cytosine and R^6 is H, R^5 cannot be N_3 and when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H;
6. (f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, F, or CN;
7. (g) X is H, OH, F, OMe, halogen, NH_2, or N_3;
8. (h) Y is OH, H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, vinyl, N_3, CN, Cl, Br, F, I, NO_2, $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{1-4}$ alkyl), $OC(O)O(C_{2-4}$ alkynyl), $OC(O)O(C_{2-4}$ alkenyl), OC_{1-10} haloalkyl, O(aminoacyl), $O(C_{1-10}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{2-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{2-4}$ alkynyl), $S(C_{2-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{2-4}$ alkynyl), $SO(C_{2-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$

alkenyl), $OS(O)_2(C_{14}$ acyl), $OS(O)_2(C_{1-4}$ alkyl), $OS(O)_2(C_{2-4}$ alkenyl), NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{2-4}$ alkenyl), $NH(C_{2-4}$ alkynyl), $NH(C_{1-4}$ acyl), $N(C_{1-4}$ alkyl)$_2$, $N(C_{1-18}$ acyl)$_2$, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3, CN, one to three halogen (Cl, Br, F, I), NO_2, $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{2-4}$ alkynyl), $C(O)O(C_{2-4}$ alkenyl), $O(C_{1-4}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{2-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{2-4}$ alkynyl), $S(C_{2-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{2-4}$ alkynyl), $SO(C_{2-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{2-4}$ alkynyl), $SO_2(C_{2-4}$ alkenyl), $OS(O)_2(C_{1-4}$ acyl), $OS(O)_2(C_{1-4}$ alkyl), $OS(O)_2(C_{2-4}$ alkenyl), NH_2, $NH(C_{1-4}$ alkyl), $NH(C_{2-4}$ alkenyl), $NH(C_{2-4}$ alkynyl), $NH(C_{1-4}$ acyl), $N(C_{1-4}$ alkyl)$_2$, $N(C_{1-4}$ acyl)$_2$;

the base is a naturally occurring or modified purine or pyrimidine base represented by the following structures:



a **b** **c** **d**

wherein

Z is N or CR^{12};

R^7, R^8,R^9, R^{10}, and R^{11} are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$,

wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted C_{1-20} alkyl, an optionally substituted C_{1-10} alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an optionally substituted alkynyl of C_2-C_6, an optionally substituted lower alkenyl of C_2-C_6, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, $C(O)(C_{1-20}$ alkyl), $C(O)(C_{1-10}$ alkyl), or C(O)(lower alkyl) or alternatively, in the instance of NR'$_2$, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and

R^{12} is H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, NO_2 lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R',

$CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$; with the proviso that when base is represented by the structure c with R^{11} being hydrogen, R^{12} is not a: (i) $-C\equiv C-H$, (ii) $-C=CH_2$, or (iii) $-NO_2$.

DEFINITIONS

[0021] The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

[0022] The phrase "as defined herein above" refers to the first definition provided in the Summary of the Invention.

[0023] The terms "optional" or "optionally" as used herein means that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present, and that the description includes single, double, or triple bonds.

[0024] The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R appears twice and is defined as "independently carbon or nitrogen", both R's can be carbon, both R's can be nitrogen, or one R' can be carbon and the other nitrogen.

[0025] The term "alkenyl" refers to an unsubstituted hydrocarbon chain radical having from 2 to 10 carbon atoms having one or two olefinic double bonds, preferably one olefinic double bond. The term "C_{2-N} alkenyl" refers to an alkenyl comprising 2 to N carbon atoms, where N is an integer having the following values: 3, 4, 5, 6, 7, 8, 9, or 10. The term "C_{2-10} alkenyl" refers to an alkenyl comprising 2 to 10 carbon atoms. The term "C_{2-4} alkenyl" refers to an alkenyl comprising 2 to 4 carbon atoms. Examples include, but are not limited to, vinyl, 1-propenyl, 2-propenyl (allyl) or 2-butenyl (crotyl).

[0026] The term "halogenated alkenyl" refers to an alkenyl comprising at least one of F, Cl, Br, and I.

[0027] The term "alkyl" refers to an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 30 carbon atoms. The term "C_{1M} alkyl" refers to an alkyl comprising 1 to M carbon atoms, where M is an integer having the following values: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30.

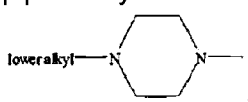
The term "C_{1-4} alkyl" refers to an alkyl containing 1 to 4 carbon atoms. The term "lower alkyl" denotes a straight or branched chain hydrocarbon residue comprising 1 to 6 carbon atoms. "C_{1-20} alkyl" as used herein refers to an alkyl comprising 1 to 20 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl comprising 1 to 10 carbons. Examples of alkyl groups include, but are not limited to, lower alkyl groups include methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl. The term (ar)alkyl or (heteroaryl)alkyl indicate the alkyl group is optionally substituted by an aryl or a heteroaryl group respectively.

[0028] The term "cycloalkyl" refers to an unsubstituted or substituted carbocycle, in which the carbocycle contains 3 to 10 carbon atoms; preferably 3 to 8 carbon atoms; more preferably 3 to 6 carbon atoms (i.e., lower cycloalkyls). Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, 2-methyl-cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0029] The term "cycloalkyl alkyl" refers to an additionally unsubstituted or substituted alkyl substituted by a lower cycloalkyl. Examples of cycloalkyl alkyls include, but are not limited to, any one of methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, t-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl that is substituted with cyclopropyl, 2-methyl-cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0030] The term "cycloheteroalkyl" refers to an unsubstituted or substituted heterocycle, in which the heterocycle contains 2 to 9 carbon atoms; preferably 2 to 7 carbon atoms; more preferably 2 to 5 carbon atoms. Examples of cycloheteroalkyls include, but are not limited to, aziridin-2-yl, *N*-C_{1-3}-alkyl-aziridin-2-yl, azetidinyl, *N*-C_{1-3}-alkyl-azetidin-m'-yl, pyrrolidin-m'-yl, *N*-C_{1-3}-alkyl-pyrrolidin-m'-yl, piperidin-m'-yl, and *N*-C_{1-3}-alkyl-piperidin-m'-yl, where m' is 2, 3, or 4 depending on the cycloheteroalkyl. Specific examples of N-C_{1-3}-alkyl-cycloheteroalkyls include, but are not limited to, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-2-yl, N-methyl-piperidin-3-yl, and N-methyl-piperidin-4-yl. In the instance of R^4, the point of attachment between the cycloheteroalkyl ring carbon and the oxygen occurs at any one of m'

[0031] The term "heterocycle" refers to an unsubstituted or substituted heterocycle containing carbon, hydrogen, and at least one ofN, O, and S, where the C and N can be trivalent or tetravalent, i.e., sp^2- or sp^3-hybridized. Examples of heterocycles include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, imidazole, oxazole, piperazine, etc. In the instance of piperazine, as related to R^{10} for NR'_2, the corresponding opposite nitrogen atom of the piperazinyl is substituted by a lower alkyl represented by the following structure:



Preferably, the opposite nitrogen of the piperazinyl is substituted by a methyl group.

[0032] The term "halogenated alkyl" (or "haloalkyl") refers to an unbranched or branched chain

alkyl comprising at least one of F, Cl, Br, and I. The term "C_{1-M} haloalkyl" refers to an alkyl comprising 1 to M carbon atoms that comprises at least one of F, Cl, Br, and I, where M is an integer having the following values: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30. "C_{1-3} haloalkyl" refers to a haloalkyl comprising 1 to 3 carbons and at least one of F, Cl, Br, and I. The term "halogenated lower alkyl" (or "lower haloalkyl") refers to a haloalkyl comprising 1 to 6 carbon atoms and at least one of F, Cl, Br, and I. Examples include, but are not limited to, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 1-iodoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2-dichloroethyl, 2,2-dibromomethyl, 2-2-diiodomethyl, 3-fluoropropyl, 3-chloropropyl, 3-bromopropyl, 2,2,2-trifluoroethyl or 1,1,2,2,2-pentafluoroethyl.

[0033] The term "alkynyl" refers to an unbranched or branched hydrocarbon chain radical having from 2 to 10 carbon atoms, preferably 2 to 5 carbon atoms, and having one triple bond. The term "C_{2-N} alkynyl" refers to an alkynyl, comprising 2 to N carbon atoms, where N is an integer having the following values: 3, 4, 5, 6, 7, 8, 9, or 10. The term "C C_{2-4} alkynyl" refers to an alkynyl comprising 2 to 4 carbon atoms. The term "C_{2-10} alkynyl" refers to an alkynyl comprising 2 to 10 carbons. Examples include, but are limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl or 3-butynyl.

[0034] The term "halogenated alkynyl" refers to an unbranched or branched hydrocarbon chain radical having from 2 to 10 carbon atoms, preferably 2 to 5 carbon atoms, and having one triple bond and at least one of F, Cl, Br, and I.

[0035] The term "cycloalkyl" refers to a saturated carbocyclic ring comprising 3 to 8 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The term "C_{3-7} cycloalkyl" as used herein refers to a cycloalkyl comprising 3 to 7 carbons in the carbocyclic ring.

[0036] The term "alkoxy" refers to an -O-alkyl group or an -O-cycloalkyl group, wherein alkyl and cycloalkyl are as defined above. Examples of -O-alkyl groups include, but are not limited to, methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" refers to an-O-alkyl wherein alkyl is C_{1-10}. Examples of -O-cycloalkyl groups include, but are not limited to, -O-*c*-propyl, -O-*c*-butyl, -O-*c*-pentyl, and -O-*c*-hexyl.

[0037] The term "halogenated alkoxy" refers to an -0-alkyl group in which the alkyl group comprises at least one of F, Cl, Br, and I.

[0038] The term "halogenated lower alkoxy" refers to an -O-(lower alkyl) group in which the lower alkyl group comprises at least one of F, Cl, Br, and I.

[0039] The term "amino acid" includes naturally occurring and synthetic α, β γ or δ amino acids, and includes but is not limited to, amino acids found in proteins, i.e. glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleucinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleucinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl. When the term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α, β γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in the D and L-configurations.

[0040] The term "aminoacyl" includes N,N-unsubstituted, N,N-monosubstituted, and N,N-disubstituted derivatives of naturally occurring and synthetic α, β γ or δ amino acyls, where the amino acyls are derived from amino acids. The amino-nitrogen can be substituted or unsubstituted. When the amino-nitrogen is substituted, the nitrogen is either mono- or di-substituted, where the substituent bound to the amino-nitrogen is a lower alkyl or an alkaryl. In the instance of its use for Y, the expression "O(aminoacyl)" is used. It is understood that the C3' carbon of the ribose is bound to the oxygen "O", which is then bound to the carbonyl carbon of the aminoacyl.

[0041] The terms "alkylamino" or "arylamino" refer to an amino group that has one or two alkyl or aryl substituents, respectively.

[0042] The term "protected," as used herein and unless otherwise defined, refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. Nonlimiting examples include: C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, *tert*butyldimethylsilyl, *tert*-butyldiphenylsilyl, and 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

[0043] The term "aryl," as used herein, and unless otherwise specified, refers to substituted or unsubstituted phenyl (Ph), biphenyl, or naphthyl, preferably the term aryl refers to substituted or unsubstituted phenyl. The aryl group can be substituted with one or more moieties selected from among hydroxyl, F, Cl, Br, I, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

[0044] The terms "alkaryl" or "alkylaryl" refer to an alkyl group with an aryl substituent, such as benzyl. The terms "aralkyl" or "arylalkyl" refer to an aryl group with an alkyl substituent.

[0045] The term "di(lower alkyl)amino-lower alkyl" refers to a lower alkyl substituted by an amino group that is itself substituted by two lower alkyl groups. Examples include, but are not limited to, $(CH_3)_2NCH_2$, $(CH_3)_2NCH_2CH_2$, $(CH_3)_2NCH_2CH_2CH_2$, etc. The examples above show lower alkyls substituted at the terminus carbon atom with an N,N-dimethyl-amino substituent. These are intended as examples only and are not intended to limit the meaning of the term "di(lower alkyl)amino-lower alkyl" so as to require the same. It is contemplated that the lower alkyl chain can be substituted with an N,N-di(lower alkyl)-amino at any point along the chain, e.g., $CH_3CH(N\text{-(lower alkyl)}_2)CH_2CH_2$.

[0046] The term "halo," as used herein, includes chloro, bromo, iodo and fluoro.

[0047] The term "acyl" refers to a substituent containing a carbonyl moiety and a non-carbonyl moiety. The carbonyl moiety contains a double-bond between the carbonyl carbon and a heteroatom, where the heteroatom is selected from among O, N and S. When the heteroatom is N, the N is substituted by a lower alkyl. The non-carbonyl moiety is selected from straight, branched, and cyclic alkyl, which includes, but is not limited to, a straight, branched, or cyclic $C_{1\text{-}20}$ alkyl, $C_{1\text{-}10}$ alkyl, or lower alkyl; alkoxyalkyl, including methoxymethyl; aralkyl, including benzyl; aryloxyalkyl, such as phenoxymethyl; or aryl, including phenyl optionally substituted with halogen (F, Cl, Br, I), hydroxyl, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy, sulfonate esters, such as alkyl or aralkyl sulphonyl, including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. When at least one aryl group is present in the non-carbonyl moiety, it is preferred that the aryl group comprises a phenyl group.

[0048] The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

[0049] The term "purine" or "pyrimidine" base includes, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-allcylaminopurine, N^6-thioallcyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, ,C^5-iodopyrimidine, C^6-Iodo-pyrimidine, C^5-Br-vinyl pyrimidine, C^6-Br-vinyl pyrimidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-

azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

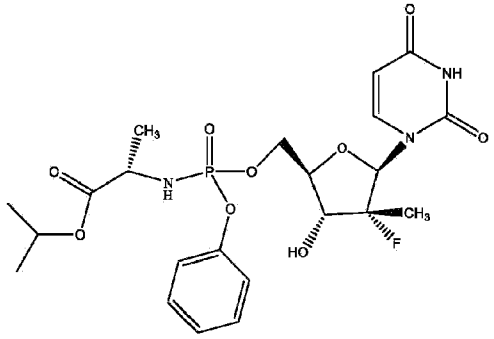
[0050] The term "tautomerism" and "tautomers" have their accepted plain meanings.

[0051] The term "P*" means that the phosphorous atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which have their accepted plain meanings. It is contemplated that compounds of the formula I are racemic because the chirality at phosphorous. Applicants contemplate use of the racemate and/or the resolved enantiomers. In some instances, an asterisk does not appear next to the phosphoroamidate phosphorous atom. In these instances, it is understood that the phosphorous atom is chiral and that one of ordinary skill understands this to be so unless the substituents bound to the phosphorous exclude the possibility of chirality at phosphorous, such as in $P(O)Cl_3$.

DETAILED DESCRIPTION OF THE INVENTION

[0052] The present invention is as set out in the following clauses:

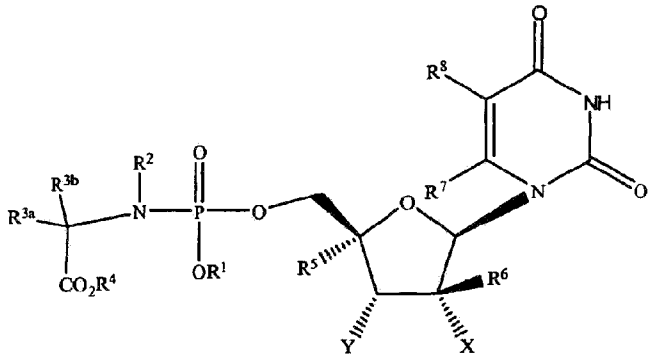
1. 1. A compound represented by the formula



2. 2. A composition comprising the compound of clause 1 and a pharmaceutically acceptable medium.

[0053] The following tables contain numeric identifiers associated with various substituent designators that should be viewed in light of the accompanying structure. These structures are contemplated species of the various aspects of the present disclosure. However, it is contemplated that any one of the exemplified nucleoside bases can be used in combination with any one of contemplated species that specify a particular combination of R^1, R^2, R^{3a}, R^{3b},

R^4, R^5, R^6, X, and Y. In each of the presented tables, the phosphoramidate substituent containing the substituents R^{3a} and R^{3b} are depicted without reference to stereochemical structure. It is contemplated that the compounds recited below embody compounds in which R^{3a} projects toward the viewer while R^{3b} projects away from the viewer. Moreover, it is contemplated that the compounds recited below also embody compounds in which R^{3a} projects away from the viewer while R^{3b} projects towards the viewer. Not meant to be limiting, however, it is contemplated that preferred compounds are those in which R^{3a} projects towards the viewer and R^{3b} projects away from the viewer such that the natural L-amino acid (S)-configuration is presented. Additionally, the inventors recognize that the phosphorus atom of the phosphoramidate moiety is another source of chirality. Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zig-zag) line structure the oxo-substitutent projects towards the viewer while the OR^1 substitutent projects away from the viewer, and vice versa, i.e., where the Cahn-Ingold-Prelog stereochemical designation of phosphorous is either R or S. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus.



IX

Table IX-1.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-1-1	CH_3	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-1-2	CH_3	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-1-3	CH_3	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-1-4	CH_3	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-1-5	CH_3	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-1-6	CH_3	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-1-7	CH_3	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-1-8	CH_3	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-2.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^8	X	Y	R^7	R^8
IX-2-1	Et	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-2-2	Et	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-2-3	Et	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-2-4	Et	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-2-5	Et	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-2-6	Et	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-2-7	Et	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-2-8	Et	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-3.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-3-1	^{i}Pr	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-3-2	^{i}Pr	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-3-3	^{i}Pr	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-3-4	^{i}Pr	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-3-5	^{i}Pr	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-3-6	^{i}Pr	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-3-7	^{i}Pr	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-3-8	^{i}Pr	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-4.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-4-1	^{t}Bu	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-4-2	^{t}Bu	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-4-3	^{t}Bu	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-4-4	^{t}Bu	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-4-5	^{t}Bu	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-4-6	^{t}Bu	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-4-7	^{t}Bu	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-4-8	^{t}Bu	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-5.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-5-1	Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-5-2	Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-5-3	Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-5-4	Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-5-5	Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-5-6	Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-5-7	Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-5-8	Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-6.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-6-1	p-Me-Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-6-2	p-Me-Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-6-3	p-Me-Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-6-4	p-Me-Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-6-5	p-Me-Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-6-6	p-Me-Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-6-7	p-Me-Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-6-8	p-Me-Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-7.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-7-1	p-F-Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-7-2	p-F-Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-7-3	p-F-Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-7-4	p-F-Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-7-6	p-F-Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-7-7	p-F-Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-7-8	p-F-Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-7-20	p-F-Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-8.

	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-8-1	p-Cl-Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-8-2	p-Cl-Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-8-3	p-Cl-Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-8-4	p-Cl-Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-8-5	p-Cl-Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-8-6	p-Cl-Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-8-7	p-Cl-Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-8-8	p-Cl-Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-9.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-9-1	p-Br-Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-9-2	p-Br-Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-9-3	p-Br-Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-9-4	p-Br-Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-9-6	p-Br-Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-9-7	p-Br-Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-9-8	p-Br-Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-9-20	p-Br-Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-10.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-10-1	p-I-Ph	H	H	H	CH_3	H	CH_3	F	OH	H	H
IX-10-2	p-I-Ph	H	H	CH_3	CH_3	H	CH_3	F	OH	H	H
IX-10-3	p-I-Ph	H	H	$CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-10-4	p-I-Ph	H	H	$CH_2CH(CH_3)_2$	CH_3	H	CH_3	F	OH	H	H
IX-10-5	p-I-Ph	H	H	CH_2Ph	CH_3	H	CH_3	F	OH	H	H
IX-10-6	p-I-Ph	H	H	CH_2-indol-3-yl	CH_3	H	CH_3	F	OH	H	H
IX-10-7	p-I-Ph	H	H	$CH_2CH_2SCH_3$	CH_3	H	CH_3	F	OH	H	H
IX-10-8	p-I-Ph	*	H	*	CH_3	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-11.

№	R^1	R^1	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-11-1	CH_3	H	H	H	Et	H	CH_3	F	OH	H	H
IX-11-2	CH_3	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-11-3	CH_3	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-11-4	CH_3	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-11-5	CH_3	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-11-6	CH_3	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-11-7	CH_3	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-11-8	CH_3	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-12.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-12-1	Et	H	H	H	Et	H	CH_3	F	OH	H	H
IX-12-2	Et	H	H	CH_3	Et	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-12-3	Et	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-12-4	Et	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-12-5	Et	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-12-6	Et	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-12-7	Et	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-12-8	Et	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-13.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-13-1	^{i}Pr	H	H	H	Et	H	CH_3	F	OH	H	H
IX-13-2	^{i}Pr	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-13-3	^{i}Pr	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-13-4	^{i}Pr	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-13-5	^{i}Pr	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-13-6	^{i}Pr	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-13-7	^{i}Pr	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-13-8	^{i}Pr	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-14.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-14-1	^{t}Bu	H	H	H	Et	H	CH_3	F	OH	H	H
IX-14-2	^{t}Bu	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-14-3	^{t}Bu	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-14-4	^{t}Bu	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-14-5	^{t}Bu	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-14-6	^{t}Bu	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-14-7	^{t}Bu	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-14-8	^{t}Bu	*	H	*	Et	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-15.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-15-1	Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-15-2	Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-15-3	Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-15-4	Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-15-5	Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-15-6	Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-15-7	Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-15-8	Ph	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-16.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-16-1	p-Me-Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-16-2	p-Me-Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-16-3	p-Me-Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-16-4	p-Me-Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-16-5	p-Me-Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-16-6	p-Me-Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-16-7	p-Me-Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-16-8	p-Me-Ph	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-17.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-17-1	p-F-Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-17-2	p-F-Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-17-3	p-F-Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-17-4	p-F-Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-17-5	p-F-Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-17-6	p-F-Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-17-7	p-F-Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-17-8	p-F-Ph	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-18.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-18-1	p-Cl-Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-18-2	p-Cl-Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-18-3	p-Cl-Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-18-4	p-Cl-Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-18-5	p-Cl-Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-18-6	p-Cl-Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-18-7	p-Cl-Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-18-8	p-Cl-Ph	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-19.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-19-1	p-Br-Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-19-2	p-Br-Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-19-3	p-Br-Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-19-4	p-Br-Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-19-5	p-Br-Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-19-6	p-Br-Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-19-7	p-Br-Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-19-8	p-Br-Ph	*	H	*	Et	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-20.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-20-1	p-I-Ph	H	H	H	Et	H	CH_3	F	OH	H	H
IX-20-2	p-I-Ph	H	H	CH_3	Et	H	CH_3	F	OH	H	H
IX-20-3	p-I-Ph	H	H	$CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-20-4	p-I-Ph	H	H	$CH_2CH(CH_3)_2$	Et	H	CH_3	F	OH	H	H
IX-20-5	p-I-Ph	H	H	CH_2Ph	Et	H	CH_3	F	OH	H	H
IX-20-6	p-I-Ph	H	H	CH_2-indol-3-yl	Et	H	CH_3	F	OH	H	H
IX-20-7	p-I-Ph	H	H	$CH_2CH_2SCH_3$	Et	H	CH_3	F	OH	H	H
IX-20-8	p-I-Ph	*	H	*	Et	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-21.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-21-1	CH_3	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-21-2	CH_3	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H
IX-21-3	CH_3	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-21-4	CH_3	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-21-5	CH_3	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-21-6	CH_3	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-21-7	CH_3	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-21-8	CH_3	*	H	*	^iPr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-22.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-22-1	Et	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-22-2	Et	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-22-3	Et	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-22-4	Et	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-22-5	Et	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-22-6	Et	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-22-7	Et	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-22-8	Et	*	H	*	^iPr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-23.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-23-1	^iPr	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-23-2	^iPr	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H
IX-23-3	^iPr	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-23-4	^iPr	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-23-5	^iPr	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-23-6	^iPr	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-23-7	^iPr	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-23-8	^iPr	*	H	*	^iPr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-24.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-24-1	^tBu	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-24-2	^tBu	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H
IX-24-3	^tBu	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-24-4	^tBu	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-24-5	^tBu	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-24-6	^tBu	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-24-7	^tBu	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-24-8	^tBu	*	H	*	^iPr	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-25.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-25-1	Ph	H	H	H	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-2	Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-3	Ph	H	H	$CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-4	Ph	H	H	$CH_2CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-5	Ph	H	H	CH_2Ph	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-6	Ph	H	H	CH_2-indol-3-yl	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-7	Ph	H	H	$CH_2CH_2SCH_3$	^{i}Pr	H	CH_3	F	OH	H	H
IX-25-8	Ph	*	H	*	^{i}Pr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-26.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-26-1	p-Me-Ph	H	H	H	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-2	p-Me-Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-3	p-Me-Ph	H	H	$CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-4	p-Me-Ph	H	H	$CH_2CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-5	p-Me-Ph	H	H	CH_2Ph	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-6	p-Me-Ph	H	H	CH_2-indol-3-yl	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-7	p-Me-Ph	H	H	$CH_2CH_2SCH_3$	^{i}Pr	H	CH_3	F	OH	H	H
IX-26-8	p-Me-Ph	*	H	*	^{i}Pr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-27.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-27-1	p-F-Ph	H	H	H	^{i}Pr	H	CH_3	F	OH	H	H
IX-27-2	p-F-Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-27-3	p-F-Ph	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-27-4	p-F-Ph	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-27-5	p-F-Ph	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-27-6	p-F-Ph	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-27-7	p-F-Ph	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-27-8	p-F-Ph	*	H	*	^iPr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-28.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-28-1	p-Cl-Ph	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-28-2	p-Cl-Ph	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H
IX-28-3	p-Cl-Ph	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-28-4	p-Cl-Ph	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-28-5	p-Cl-Ph	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-28-6	p-Cl-Ph	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-28-7	p-Cl-Ph	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-28-8	p-Cl-Ph	*	H	*	^iPr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-29.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-29-1	p-Br-Ph	H	H	H	^iPr	H	CH_3	F	OH	H	H
IX-29-2	p-Br-Ph	H	H	CH_3	^iPr	H	CH_3	F	OH	H	H
IX-29-3	p-Br-Ph	H	H	$CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-29-4	p-Br-Ph	H	H	$CH_2CH(CH_3)_2$	^iPr	H	CH_3	F	OH	H	H
IX-29-5	p-Br-Ph	H	H	CH_2Ph	^iPr	H	CH_3	F	OH	H	H
IX-29-6	p-Br-Ph	H	H	CH_2-indol-3-yl	^iPr	H	CH_3	F	OH	H	H
IX-29-7	p-Br-Ph	H	H	$CH_2CH_2SCH_3$	^iPr	H	CH_3	F	OH	H	H
IX-29-8	p-Br-Ph	*	H	*	^iPr	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-30.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-30-1	p-I-Ph	H	H	H	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-2	p-I-Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-3	p-I-Ph	H	H	$CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-4	p-I-Ph	H	H	$CH_2CH(CH_3)_2$	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-5	p-I-Ph	H	H	CH_2Ph	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-6	p-I-Ph	H	H	CH_2-indol-3-yl	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-7	p-I-Ph	H	H	$CH_2CH_2SCH_3$	^{i}Pr	H	CH_3	F	OH	H	H
IX-30-8	p-I-Ph	*	H	*	^{i}Pr	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-31.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-31-1	CH_3	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-2	CH_3	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-3	CH_3	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-4	CH_3	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-5	CH_3	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-6	CH_3	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-7	CH_3	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-31-8	CH_3	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-32.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-32-1	Et	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-32-2	Et	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-32-3	Et	H	H	$CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-32-4	Et	H	H	$CH_2CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-32-5	Et	H	H	CH_2Ph	^nBu	H	CH_3	F	OH	H	H
IX-32-6	Et	H	H	CH_2-indol-3-yl	^nBu	H	CH_3	F	OH	H	H
IX-32-7	Et	H	H	$CH_2CH_2SCH_3$	^nBu	H	CH_3	F	OH	H	H
IX-32-8	Et	*	H	*	^nBu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-33.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-33-1	^iPr	H	H	H	^nBu	H	CH_3	F	OH	H	H
IX-33-2	^iPr	H	H	CH_3	^nBu	H	CH_3	F	OH	H	H
IX-33-3	^iPr	H	H	$CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-33-4	^iPr	H	H	$CH_2CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-33-5	^iPr	H	H	CH_2Ph	^nBu	H	CH_3	F	OH	H	H
IX-33-6	^iPr	H	H	CH_2-indol-3-yl	^nBu	H	CH_3	F	OH	H	H
IX-33-7	^iPr	H	H	$CH_2CH_2SCH_3$	^nBu	H	CH_3	F	OH	H	H
IX-33-8	^iPr	*	H	*	^nBu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-34.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-34-1	^tBu	H	H	H	^nBu	H	CH_3	F	OH	H	H
IX-34-2	^tBu	H	H	CH_3	^nBu	H	CH_3	F	OH	H	H
IX-34-3	^tBu	H	H	$CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-34-4	^tBu	H	H	$CH_2CH(CH_3)_2$	^nBu	H	CH_3	F	OH	H	H
IX-34-5	^tBu	H	H	CH_2Ph	^nBu	H	CH_3	F	OH	H	H
IX-34-6	^tBu	H	H	CH_2-indol-3-yl	^nBu	H	CH_3	F	OH	H	H
IX-34-7	^tBu	H	H	$CH_2CH_2SCH_3$	^nBu	H	CH_3	F	OH	H	H
IX-34-8	^tBu	*	H	*	^nBu	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-35.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-35-1	Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-2	Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-3	Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-4	Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-5	Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-6	Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-7	Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-35-8	Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-36.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-36-1	p-Me-Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-2	p-Me-Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-3	p-Me-Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-4	p-Me-Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-5	p-Me-Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-6	p-Me-Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-7	p-Me-Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-36-8	p-Me-Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-37.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-37-1	p-F-Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-2	p-F-Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-37-3	p-F-Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-4	p-F-Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-5	p-F-Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-6	p-F-Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-7	p-F-Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-37-8	p-F-Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-38.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-38-1	p-Cl-Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-2	p-Cl-Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-3	p-Cl-Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-4	p-Cl-Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-5	p-Cl-Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-6	p-Cl-Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-7	p-Cl-Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-38-8	p-Cl-Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-39.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-39-1	p-Br-Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-2	p-Br-Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-3	p-Br-Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-4	p-Br-Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-5	p-Br-Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-6	p-Br-Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-7	p-Br-Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-39-8	p-Br-Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-40.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-40-1	p-I-Ph	H	H	H	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-2	p-I-Ph	H	H	CH_3	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-3	p-I-Ph	H	H	$CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-4	p-I-Ph	H	H	$CH_2CH(CH_3)_2$	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-5	p-I-Ph	H	H	CH_2Ph	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-6	p-I-Ph	H	H	CH_2-indol-3-yl	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-7	p-I-Ph	H	H	$CH_2CH_2SCH_3$	^{n}Bu	H	CH_3	F	OH	H	H
IX-40-8	p-I-Ph	*	H	*	^{n}Bu	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-41.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-41-1	CH_3	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-41-2	CH_3	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-41-3	CH_3	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-41-4	CH_3	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-41-5	CH_3	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-41-6	CH_3	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-41-7	CH_3	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-41-8	CH_3	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-42.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-42-1	Et	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-42-2	Et	H	H	CH_3	Bz	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-42-3	Et	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-42-4	Et	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-42-5	Et	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-42-6	Et	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-42-7	Et	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-42-8	Et	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-43.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-43-1	^{i}Pr	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-43-2	^{i}Pr	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-43-3	^{i}Pr	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-43-4	^{i}Pr	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-43-5	^{i}Pr	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-43-6	^{i}Pr	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-43-7	^{i}Pr	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-43-8	^{i}Pr	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-44.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-44-1	^{t}Bu	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-44-2	^{t}Bu	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-44-3	^{t}Bu	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-44-4	^{t}Bu	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-44-5	^{t}Bu	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-44-6	^{t}Bu	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-44-7	^{t}Bu	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-44-8	^{t}Bu	*	H	*	Bz	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-45.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-45-1	Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-45-2	Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-45-3	Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-45-4	Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-45-5	Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-45-6	Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-45-7	Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-45-8	Ph	*	H	*	Bz	H	CH_3	F	OH	H	H
№ *R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-46.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-46-1	p-Me-Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-46-2	p-Me-Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-46-3	p-Me-Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-46-4	p-Me-Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-46-5	p-Me-Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-46-6	p-Me-Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-46-7	p-Me-Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-46-8	p-Me-Ph	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-47.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-47-1	p-F-Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-47-2	p-F-Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-47-3	p-F-Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-47-4	p-F-Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-47-5	p-F-Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-47-6	p-F-Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-47-7	p-F-Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-47-8	p-F-Ph	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-48.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-48-1	p-Cl-Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-48-2	p-Cl-Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-48-3	p-Cl-Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-48-4	p-Cl-Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-48-5	p-Cl-Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-48-6	p-Cl-Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-48-7	p-Cl-Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-48-8	p-Cl-Ph	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-49.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-49-1	p-Br-Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-49-2	p-Br-Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-49-3	p-Br-Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-49-4	p-Br-Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-49-5	p-Br-Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-49-6	p-Br-Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-49-7	p-Br-Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-49-8	p-Br-Ph	*	H	*	Bz	H	CH_3	F	OH	H	H

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

Table IX-50.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-50-1	p-I-Ph	H	H	H	Bz	H	CH_3	F	OH	H	H
IX-50-2	p-I-Ph	H	H	CH_3	Bz	H	CH_3	F	OH	H	H
IX-50-3	p-I-Ph	H	H	$CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-50-4	p-I-Ph	H	H	$CH_2CH(CH_3)_2$	Bz	H	CH_3	F	OH	H	H
IX-50-5	p-I-Ph	H	H	CH_2Ph	Bz	H	CH_3	F	OH	H	H
IX-50-6	p-I-Ph	H	H	CH_2-indol-3-yl	Bz	H	CH_3	F	OH	H	H
IX-50-7	p-I-Ph	H	H	$CH_2CH_2SCH_3$	Bz	H	CH_3	F	OH	H	H
IX-50-8	p-I-Ph	*	H	*	Bz	H	CH_3	F	OH	H	H
*R^2 and R^{3b} joined together by $(CH_2)_3$ to form five-membered ring.											

DOSAGE, ADMINISTRATION, AND USE

[0054] A further aspect of the present disclosure is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and a compound, that is intended to include its salts (acid or basic addition salts), hydrates, solvates, and crystalline forms can be obtained, represented by formula **I**.

[0055] It is contemplated that the formulation according to this aspect of the present disclosure can contain any of the compounds contemplated in any other aspect of the present disclosure or those specifically recited in the tables above or exemplified herein, either alone or in combination with another compound of the present invention.

[0056] The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by suppository administration, among other routes of administration. The most convenient manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the severity of the disease and the patient's response to the antiviral medication.

[0057] A compound or compounds of the present invention, as well as their pharmaceutically acceptable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the desired dose and pharmacokinetic parameters.

[0058] The term "excipient" as used herein refers to a compound that is used to prepare a pharmaceutical composition, and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

[0059] A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound as used herein means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like or (2) basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Na^+, K^+, Mg^{2+}, Ca^{2+}, and $NH_gR'''_{4-g}{}^+$, in which R''' is a C_{1-3} alkyl and g is a number selected from among 0, 1, 2, 3, or 4. It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

[0060] Solid form preparations include powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0061] Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs and aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

[0062] The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0063] The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0064] Suitable formulations along with pharmaceutical carriers, diluents and expcipients are described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. The compounds of the present invention can also be encapsulated in liposomes, such as those disclosed in U.S. Patent Nos. 6,180,134, 5,192,549, 5,376,380, 6,060,080, 6,132,763. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

[0065] The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (e.g., salt formulation), which are well within the ordinary skill in the art. It is also well within the ordinary

skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

[0066] A further aspect of the present disclosure is directed to a use of the compounds of the present invention in the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus.

[0067] The term "medicament" means a substance used in a method of treatment and/or prophylaxis of a subject in need thereof, wherein the substance includes, but is not limited to, a composition, a formulation, a dosage form, and the like, comprising the compounds of the present invention.

[0068] The term "subject" means a mammal, which includes, but is not limited to, cattle, pigs, sheep, chicken, turkey, buffalo, llama, ostrich, dogs, cats, and humans, preferably the subject is a human.

[0069] The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.1 and about 10 g, including all values in between, such as 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 9.5, per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.5 and about 7.5 g per day, more preferred 1.5 and about 6.0 g per day. Generally, treatment is initiated with a large initial "loading dose" to rapidly reduce or eliminate the virus following by a decreasing the dose to a level sufficient to prevent resurgence of the infection. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

[0070] Therapeutic efficacy can be ascertained from tests of liver function including, but not limited to protein levels such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ-glutaminyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism. Alternatively the therapeutic effectiveness may be monitored by measuring HCV-RNA. The results of these tests will allow the dose to be optimized.

[0071] A further aspect of the present disclosure, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to the subject a therapeutically effective of a compound represented by compounds of the present invention and a therapeutically effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours. Examples of "another antiviral agents" include, but are not limited to: HCV NS3 protease inhibitors (see WO 2008010921, WO 2008010921, EP 1881001, WO 2007015824, WO 2007014925, WO 2007014926, WO 2007014921, WO 2007014920, WO 2007014922, US 2005267018, WO 2005095403, WO 2005037214, WO 2004094452, US 2003187018, WO 200364456, WO 2005028502, and WO 2003006490); HCV NS5B Inhibitors (see US 2007275947, US20072759300, WO2007095269, WO 2007092000, WO 2007076034, WO 200702602, US 2005-98125, WO 2006093801, US 2006166964, WO 2006065590, WO 2006065335, US 2006040927, US 2006040890, WO 2006020082, WO 2006012078, WO 2005123087, US 2005154056, US 2004229840, WO 2004065367, WO 2004003138, WO 2004002977, WO 2004002944, WO 2004002940, WO 2004000858, WO 2003105770, WO 2003010141, WO 2002057425, WO 2002057287, WO 2005021568, WO 2004041201, US 20060293306, US 20060194749, US 20060241064, US 6784166, WO 2007088148, WO 2007039142, WO 2005103045, WO 2007039145, WO 2004096210, and WO 2003037895); HCV NS4 Inhibitors (see WO 2007070556 and WO 2005067900); HCV NS5a Inhibitors (see US 2006276511, WO 2006120252, WO 2006120251, WO 2006100310, WO 2006035061); Toll-like receptor agonists (seeWO 2007093901); and other inhibitors (see WO 2004035571, WO 2004014852, WO 2004014313, WO 2004009020, WO 2003101993, WO 2000006529).

[0072] A further aspect of the present disclosure, is directed to a method of treatment in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of a compound according to the present invention and another antiviral agent to the subject. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

[0073] A further aspect of the present disclosure, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to the subject a therapeutically effective of at least one compound according to the present invention and a therapeutically effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

[0074] A further aspect of the present disclosure, is directed to a method of treatment in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of at least one compound according to the present invention and

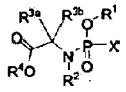
another antiviral agent to the subject. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

[0075] It is contemplated that the another antiviral agent includes, but is not limited to interferon-α, interferon-β, pegylated interferon-α, ribavirin, levovirin, viramidine, another nucleoside HCV polymerase inhibitor, a HCV non-nucleoside polymerase inhibitor, a HCV protease inhibitor, a HCV helicase inhibitor or a HCV fusion inhibitor. When the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound. When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the nucleoside derivatives. "Concurrent administration" as used herein thus includes administration of the agents at the same time or at different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients or by substantially simultaneous administration of two or more dosage forms with a single active agent.

[0076] It will be understood that references herein to treatment extend to prophylaxis as well as to the treatment of existing conditions. Furthermore, the term "treatment" of a HCV infection, as used herein, also includes treatment or prophylaxis of a disease or a condition associated with or mediated by HCV infection, or the clinical symptoms thereof.

PROCESS FOR PREPARATION

[0077] An aspect of the present disclosure is directed to a process for preparing the compounds, which comprises reacting a suitably substituted phosphochloridate compound 4 with a nucleoside analog 5



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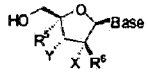

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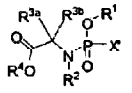
wherein the substituents R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, X, Y, R^6, and base have their meanings as disclosed in the Detailed Description of the Invention and X' is a leaving group, such as Cl, Br, I, tosylate, mesylate, trifluoroacetate, trifluorosulfonate, pentafluorophenoxide, p-NO_2-phenoxide, or other commonly used leaving groups as disclosed in Advanced Organic Chemistry by March, Fourth Edition. Leaving groups and methods that can be used to effect the formation of a phosphoramidate nucleoside conjugate are found in US 20060142238 and WO 2007095269. Preferably, the leaving group is Cl.

[0078] This reaction is performed in an anhydrous aprotic solvent such tetrahydrofuran, dioxane, or both tetrahydrofuran and dioxane, or any functional equivalent thereof, with tetrahydrofuran being the preferred solvent. The reaction is typically initiated at a temperature range from -78°C to 40°C with the preferred reaction temperature being between 0°C and room temperature. The nucleoside is first stirred with a base (5 to 12 equivalents) such as N-

methylimidazole, collidine, pyridine, 2,6-lutidine, 2, 6-^{t}Bu-pyridine, etc. a tertiary amine base, such as triethylamine, diisopropylethylamine, etc., or an alkyl Grignard reagent, such as tBuMgCl, tBuMgBr, MeMgCl, MeMgBr, etc. The phosphorochloridate (3-10 equivalents) is dissolved in the reaction solvent and added to the mixture of the nucleoside and base. The reaction is then allowed to stir over a period of time at a temperature between room temperature and 40°C for a period of 30 min to 24 hr. with the preferred reaction temperature being room temperature and time being 24 hr. The solvent is removed from the reaction mixture and the product is purified by chromatography on silica gel.

[0079] An aspect of the present disclosure is directed to a product obtained by a process which comprises reacting a suitably substituted phosphochloridate compound **4** with a nucleoside analog **5**



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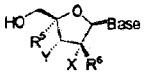

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wherein the substituents R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, X, Y, R^6, X', and base have their meanings as disclosed in the Detailed Description of the Invention.

[0080] This reaction can be performed in an anhydrous aprotic solvent or other suitable solvent, such as tetrahydrofuran, dioxane, or a mixture of tetrahydrofuran and dioxane, with tetrahydrofuran being the preferred solvent. The reaction is typically initiated at a temperature range from -78°C to 40°C with the preferred reaction temperature being between 0°C and room temperature. The nucleoside is first stirred with a base (5 to 12 equivalents) such as N-methylimidazole, a tertiary amine base or tButyl Magnesium Chloride. A phosphorochloridate (3-10 equivalents (or suitable "phosphoro-(leaving group)-date")) is dissolved in the reaction solvent and added to the mixture of the nucleoside and base. The reaction is then allowed to stir over a period of time at a temperature between room temperature and 40°C for a period of 30 min to 24 hr. with the preferred reaction temperature being room temperature and time being 24 hr. The solvent is removed from the reaction mixture and the product is purified by chromatography on silica gel.

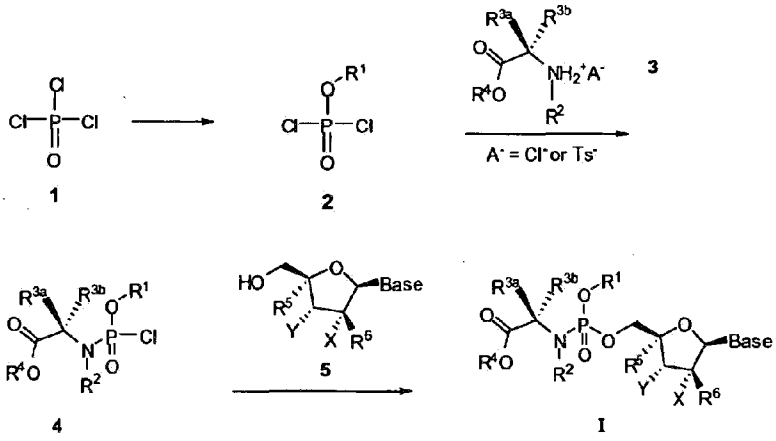
Compounds and Preparation

[0081] Phosphoramidate compounds of the present invention can be prepared by condensation of a nucleoside analog 5 with a suitably substituted phosphochloridate compound 4 (Scheme 1). The nucleoside analog is made by conventional procedures disclosed in any one of U.S. Published Application Nos. 2005/0009737, 2006/0199783, 2006/0122146, and 2007/0197463.

[0082] Disclosed 1H-NMR values were recorded on a Varian AS-400 instrument. Mass spectral data were obtain using either a Micromass-Quattromicro API or a Waters Acquity.

[0083] Thus, by way of example only, a suitably substituted phenol can be reacted with phosphorus oxychloride **(1)** to afford an aryloxy phosphorodichloridate **2** (see Example 1) which is subsequently treated with a acid addition salt of an α-amino acid ester in the presence of TEA to afford an aryloxy phosphorochloridate **4.** This arylalkoxy-amino acid phosphoramidate is reacted with the nucleoside analog to provide the product I (for procedure see, e.g., C. McGuigan et al. Antiviral Res. 1992 17:311-321; D. Curley et al. Antiviral Res. 1990 14:345-356; McGuigan et al. Antiviral Chem. Chemother 1990 1(2):107-113).

Scheme 1



[0084] The preparation of nucleoside phosphoramidates requires reacting an appropriately substituted phosphochloridate with a nucleoside containing a free 5'-hydroxyl moiety. In cases where only one hydroxyl group is present, preparation of the phosphoramidate usually proceeds smoothly when the phosphochloridate is reacted with the desired nucleoside. In cases where the nucleoside contains more than one free hydroxyl group, preparation of the appropriately protected nucleoside might be required. Silyl, acetonide or other alcohol protecting groups known in the art might be warranted for protection of the sugar moiety. For protection of the nucleoside base, protecting a free amino group may require amidine protection strategy.

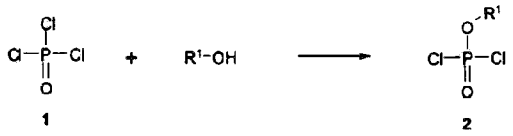
[0085] Condensation of the phosphochloridate can be carried out on the unprotected nucleoside. Since the 5'-OH group of a nucleoside is much less hindered than the 3'-OH group, selective phosphoramidation is possible under carefully controlled conditions. After condensation to form a protected phosphoramidate nucleoside, deprotection to obtain the free phosphoramidate nucleoside can be carried out using standard protocols for nucleic acid chemistry. In many cases, the desired product is readily separated from the starting material using column chromatography on silica gel. The synthetic scheme is summarized in Scheme 1.

[0086] A further understanding of the present disclosure will be appreciated by consideration of the following examples, which are only meant to be illustrative, and not limit the disclosed invention.

EXAMPLE 1

General Procedure for Preparation of phosphorodichloridates

[0087]

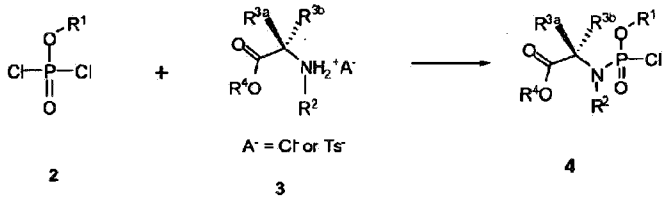


[0088] A solution of the appropriate phenol **R^1-OH** (1eq) and triethylamine (1 eq.) in anhydrous ether was added dropwise to a stirred solution of phosphoryl trichloride 1 (1eq) at 0 °C over a period of 3 hours under nitrogen. Then the temperature was warmed to room temperature, and the reaction was stirred overnight. The triethylamine salt was quickly removed with suction filtration and the filtrate concentrated *in vacuo* to dryness to afford **2** as an oil which was used without further purification.

EXAMPLE 2

General Procedure for Preparation of phosphorochloridates

[0089]

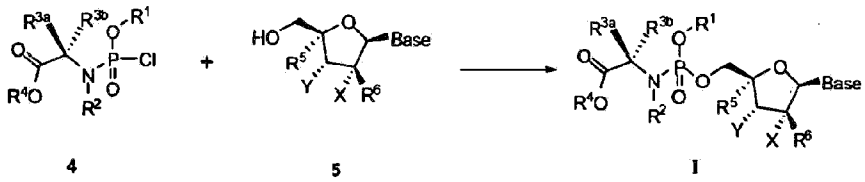


[0090] A solution of triethylamine (2eq) in anhydrous dichloromethane was added dropwise to a solution of aryloxy-phosphodichloridate **2** (1 eq) and the appropriate amino ester **3** (1 eq) in anhydrous dichloromethane with vigorous stirring at -78 °C over a period of 30 to 120 minutes. Then the reaction temperature was allowed to warm to room temperature and stirred over night. Solvent was removed. The residue was washed with ethyl ether and filtered, the filtrate was dried over reduced pressure to give **4.**

EXAMPLE 3

General Procedures for nucleoside phosphoramidate derivatives

[0091]



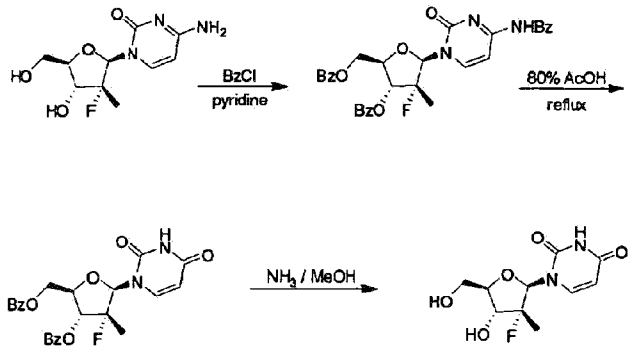
4 5 I

[0092] A solution of the appropriate phosphorochloridate **4** (6.5 equivalents) in anhydrous tetrahydrofuran (THF) was added to a mixture of nucleoside **5** (1 equivalent) and N-methylimidazole (8 equivalents) in anhydrous THF with vigorous stirring at room temperature and the reaction mixture was stirred overnight. The solvent was removed *in vacuo* and the crude was purified by column chromatography and/or preparative thin layer chromatography to give **I.**

EXAMPLE 4

Preparation of 2'-deoxy-2'-fluoro-2'-*C*-methyluridine

[0093]



[0094] 2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine (1.0g, 1 eq) (Clark, J., et al., J. Med. Chem., 2005, 48, 5504-5508) was dissolved in 10 ml of anhydrous pyridine and concentrated to dryness in vacuo. The resulting syrup was dissolved in 20 ml of anhydrous pyridine under nitrogen and cooled to 0°C with stirring. The brown solution was treated with benzoyl chloride (1.63g, 3eq) dropwise over 10 min. The ice bath was removed and stirring continued for 1.5h whereby thin-layer chromatography (TLC) showed no remaining starting material. The mixture was quenched by addition of water (0.5 ml) and concentrated to dryness. The residue was dissolved in 50 mL of dichloromethane (DCM) and washed with saturated $NaHCO_3$ aqueous solution and H_2O. The organic phase was dried over $NaSO_4$ and filtered, concentrated to

dryness to give N^4,3',5'-tribenzoyl-2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine (2.0 g, Yield: 91%).

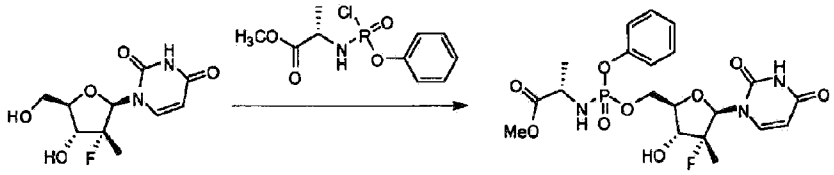
[0095] N^4,3',5'-tribenzoyl-2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine (2.0g, 1 eq) was refluxed in 80% aqueous AcOH overnight. After cooling and standing at room temperature (15 °C), most of the product precipitated and then was filtered through a sintered funnel. White precipitate was washed with water and co-evaporated with toluene to give a white solid. The filtrate was concentrated and co-evaporated with toluene to give additional product which was washed with water to give a white solid. Combining the two batches of white solid gave 1.50g of 3',5'-dibenzoyl-2'-Deoxy-2'-fluoro-2'-*C*-methyluridine (Yield: 91%).

[0096] To a solution of 3',5'-dibenzoyl-2'-Deoxy-2'-fluoro-2'-*C*-methyluridine (1.5 g, 1eq) in MeOH (10 mL) was added a solution of saturated ammonia in MeOH (20mL). The reaction mixture was stirred at 0 °C for 30 min, and then warmed to room temperature slowly. After the reaction mixture was stirred for another 18 hours, the reaction mixture was evaporated under reduced pressure to give the residue, which was purified by column chromatography to afford pure compound 2'-deoxy-2'-fluoro-2'-*C*-methyluridine (500 mg, Yield: 60 %).

EXAMPLE 5

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methyluridine 5'-(phenyl methoxy-alanyl phosphate)

[0097]

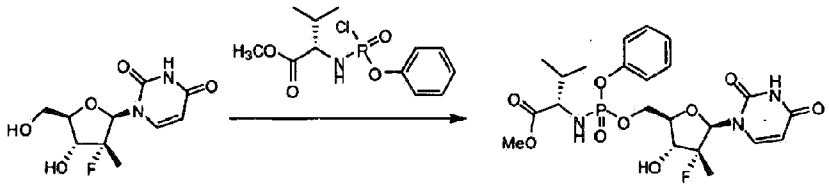


[0098] Phenyl methoxyalaninyl phosphorochloridate (1 g, 6.5 eq) dissolved in 3 mL of THF was added to a mixture of 2'-Deoxy-2'-fluoro-2'-*C*-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (50.1 mg, 15.6%). ^{1}H NMR (DMSO-d_6) δ 1.20-1.27 (m, 6H), 3.58 (d, J = 16.0 Hz, 3H), 3.75-3.92 (m, 2H), 4.015-4.379 (m, 2H), 5.54 (t, J = 10.2 Hz, 1H), 5.83-5.91 (m, 1H), 6.00-6.16 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.22 (s, 1H), 7.35 (t, J = 4.4 Hz, 2H), 7.55 (s, 1H), 11.52 (s, 1H); MS, *m/e* 502 $(M+1)^+$.

EXAMPLE 6

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methyluridine 5'-(phenyl methoxy-valyl phosphate)

[0099]

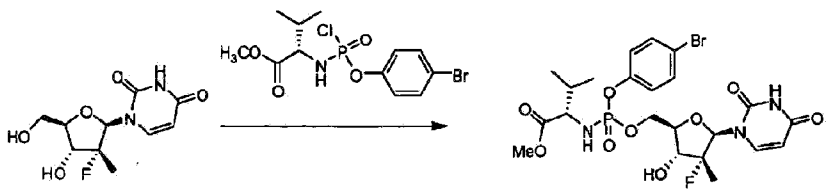


[0100] Phenyl methoxy-valyl phosphorochloridate (0.6 g, 3.6 eq) dissolved in 3 mL of THF was added to a mixture of 2'-Deoxy-2'-fluoro-2'-C-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.44 g, 9 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (60 mg, 20%). ^{1}H NMR (DMSO-d_6) δ 0.74-0.847 (m, 6H), 1.20-1.28 (m, 3H), 1.89-1.92 (m, 1H), 3.50-3.54 (m, 1H), 3.58 (d, J = 10.4Hz, 3H), 3.72-3.95 (m, 1H), 4.03-4.05 (m, 1H), 4.23-4.43 (m, 2H), 5.56 (t, J = 16.0 Hz, 1H), 5.85-5.92 (m, 1H), 6.01-6.07 (m, 1H), 7.16-7.21 (m, 3H), 7.37 (t, J = 8 Hz, 2H), 7.55-7.60 (m, 1H), 11.52 (s, 1H); MS, *m/e* 530 $(M+1)^+$.

EXAMPLE 7

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate)

[0101]



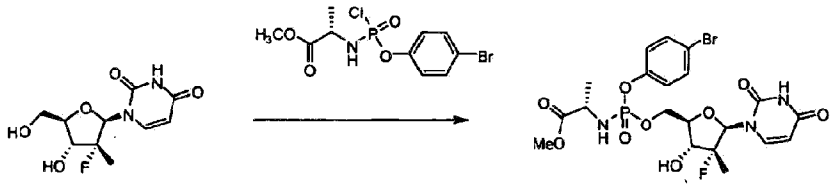
[0102] 4-Bromophenyl methoxy-valyl phosphorochloridate (1 g, 3.4 eq) dissolved in 3 mL of

THF was added to a mixture of 2'-deoxy-2'-fluoro-2'-*C*-methyluridine (0.2 g, 1 eq) and N-methylimidazole (0.35 g, 6 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed reduced pressure to give the desired product (120 mg, 26%). ^{1}H NMR (DMSO-d_6) δ 0.72-0.82 (m, 6H), 1.19-1.26 (m, 3H), 1.86-1.92 (m, 1H), 3.48-3.50 (m, 1H), 3.56 (d, J = 12.0 Hz, 3H), 3.72-3.89 (m, 1H), 3.96-4.03 (m, 1H), 4.22-4.37 (m, 2H), 5.54-5.60 (m, 1H), 5.85-5.91 (m, 1H), 5.98-6.13 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.49-7.56 (m, 3H), 11.53 (s, 1H); MS, *m/e* 608 $(M+1)^+$.

EXAMPLE 8

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate)

[0103]

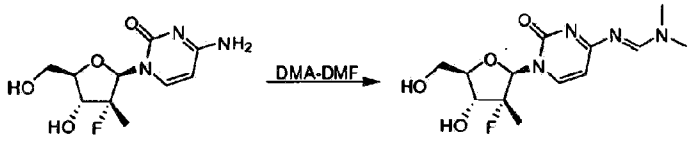


[0104] 4-Bromophenyl methoxy-alanyl phosphorochloridate (0.6 g, 5 eq) dissolved in 3 mL of THF was added to a mixture of 2'-deoxy-2'-fluoro-2'-*C*-methyluridine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (40 mg, 12 %); ^{1}H NMR (DMSO-d_6) δ 1.20-1.26 (m, 6H), 3.57 (d, J = 2.8 Hz, 3H), 3.84 (s, 1H), 3.97-4.03 (m, 1H), 4.21-4.25 (m, 1H), 4.33-4.37 (m, 2H), 5.54-5.60 (m, 1H), 5.83-5.89 (m, 1H), 5.98-6.19 (m, 1H), 7.16 (t, J = 10.2 Hz, 2H), 7.52-7.57 (m, 3H), 11.52 (s, 1 H); MS, *m/e* 580$(M+1)^+$.

EXAMPLE 9

Preparation of N^4-(*N,N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine

[0105]

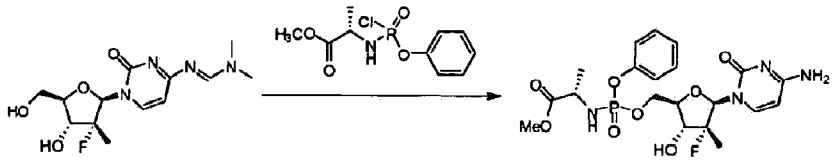


[0106] 2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine (500 mg, 1.9 mmol) was stirred with dimethylformamide dimethyl acetal in DMF (10 mL). The resulting mixture was stirred at room temperature overnight. After solvent removal the crude product was used for next step without further purification.

EXAMPLE 10

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine 5'-(phenyl methoxy-alanyl phosphate)

[0107]



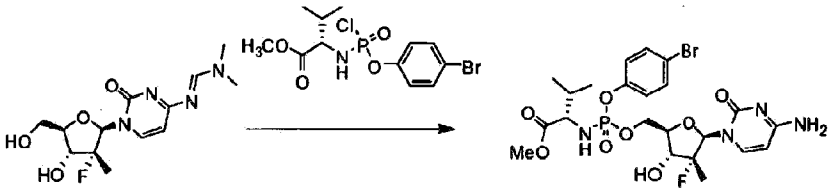
[0108] Phenyl methoxyalaninyl phosphorochloridate (0.6 g, 6 eq) dissolved in 3 mL of THF was added to a mixture of N^4-(*N*,*N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product (62 mg, 20.6%). ^{1}H NMR (DMSO-d_6) δ 1.16 (d, *J* = 23.2 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 3.56 (S, 3H), 3.69-3.75 (d, *J* = 25.6 Hz, 1H), 3.82-3.86 (m, 1H), 3.96-3.98 (m, 1H), 4.21-4.34 (m, 2H), 5.68 (d, *J* = 7.2 Hz, 1H), 5.75-5.77 (m, 1H), 6.07-6.16 (m, 1H), 7.15-7.19 (m, 3H), 7.2 (d, *J* = 9.2 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 1H); MS, *m/e* 501(M+1)$^+$.

EXAMPLE 11

Preparation of 2'-Deoxy-2'-fluoro-2'-*C*-methylcytidine 5'-(4-bromophenyl methoxy-valyl

phosphate)

[0109]

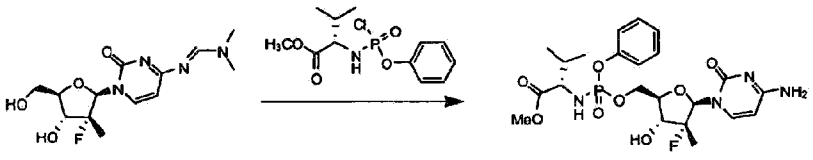


[0110] 4-Bromophenyl methoxy-valyl phosphorochloridate (1.0 g, 3.4 eq.) dissolved in 3 mL of THF was added to a mixture of N^4-(*N*,*N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine (0.2 g, 1 eq.) and N-methylimidazole (0.35 g, 6 eq.) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure. The resulting crude product was dissolved in methanol purified by prep-HPLC on a YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product as a white solid (59 mg, 13%); ^{1}H NMR (DMSO-d_6) δ 0.74-0.83 (m, 6H), 1.12-1.20 (m, 3H), 1.89-1.92 (m, 1H), 3.49-3.51 (m, 1H), 3.55 (s, 3H), 3.59-3.68 (m, 1H), 3.72-.383 (m, 1H), 4.21-4.39 (m, 2H), 5.70-5.72 (m, 1H), 5.76-5.83 (m, 1H), 6.04-6.16 (m, 1H), 7.15 (d, *J* = 13.0 Hz, 2H), 7.26 (s, 1H), 7.33 (s, 1H), 7.46-7.55 (m, 1H), 7.56 (d, *J* = 4.4 Hz, 2H); MS, *m/e* 607 $(M+1)^+$.

EXAMPLE 12

Preparation of 2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate)

[0111]

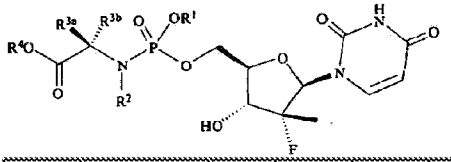


[0112] Phenyl methoxy-valyl phosphorochloridate (0.6 g, 6 eq) dissolved in 3 mL of THF was added to a mixture of N^4-(*N*,*N*-dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (0.15 g, 1 eq) and N-methylimidazole (0.3 g, 7.8 eq) in 3 mL THF with vigorous stirring at room temperature, then the reaction was stirred overnight. Solvent was removed by reduced pressure The resulting crude product was dissolved in methanol purified by prep-HPLC on a

YMC 25x30X2 mm column using a water / acetonitrile gradient elution mobile phase. The acetonitrile and water were removed under reduced pressure to give the desired product as a white solid (86 mg, 42.9 %). ^{1}H NMR (DMSO-d_6) δ 0.72-0.80 (m, 6H), 1.09-1.18 (m, 3H), 1.87-1.92 (m, 1H), 3.47-3.51 (m, 1H), 3.58 (s, 3H), 3.71-3.75 (m, 1H), 3.97 (t, J = 11.2 Hz,1H), 4.22-4.37 (m, 2H), 5.70 (d, J = 8.0 Hz,1H), 5.76-5.84 (m, 1H), 6.01-6.15 (m, 1H), 7.13-7.18 (m, 3H), 7.27 (s, 2H), 7.34 (d, J = 4.0 Hz, 2H), 7.46-7.50 (m, 1H); MS, m/e 529 $(M+1)^+$.

EXAMPLES

[0113] Example numbers **13-54** and **56-66** are prepared using similar procedures described for examples **5-8.** The example number, compound identification, and NMR/MS details are shown below:



Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
13	Ph	H	H	Me	Et	1H NMR (DMSO-d_6) δ 1.12-1.16 (m, 3H), 1.20-1.28(m,6H), 3.70-3.90 (m, 2H), 4.00-4.08 (m, 3H), 4.18-4.45 (m, 2H), 5.52-5.58 (m, 1H), 5.85-5.98 (m, 1H), 6.00-6.20 (m, 2H), 7.16-7.23 (m, 3H), 7.37-7.40 (m, 2H), 7.54-7.60 (m, 1H), 11.54 (s.1H); MS, m/e 516.1 (M+1)+
14	1-Napth	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.18-1.30 (m, 6H), 3.78-4.10 (m, 3H), 4.38-4.49 (m, 2H), 4.99-5.11 (m, 2H), 5.28-5.40 (m, 1H), 5.85-6.10 (m, 2H), 6.30-6.41 (m, 1H), 7.28-7.32 (m, 5H), 7.41-7.60 (m, 5H), 7.73-7.76(m, 1H), 7.94-8.11(m, 1H), 8.13-8.15(m, 1H), 11.50 (s.1H); MS, m/e 628.4 (M+1)+
15	Ph	H	H	H	Me	1H NMR (DMSO-d_6) δ 1.22 (d, J=22.4 Hz, 3H), 3.59(s, 3H), 3.63-3.69 (m, 2H), 3.74-3.8(m, 1H), 4.02(d, J=11.2 Hz, 1H), 4.23-4.28(m, 1H), 4.40-4.43 (m, 1H), 5.57-5.60 (m, 1H), 5.89(d, J=6.8 Hz, 1H), 6.00-6.06(m, 2H), 7.15-7.23 (m, 3H), 7.35-7.39 (m, 2H),7.52(d, J=8 Hz, 1H), 11.52(s, 1H); MS, m/e 487.97 (M+1)+
16	2,4-Cl-Ph	H	H	Me	Me	1H NMR (DMSO-d_6) δ 1.22-1.28 (m, 6H), 3.57-3.60 (m, 3H), 3.84-3.92 (m, 2H), 4.00-4.04 (m, 1H), 4.31-4.44 (m, 2H), 5.54-5.61 (m, 1H), 5.85-6.10 (m, 2H),

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						6.32-6.43 (m, 1H), 7.44-7.54 (m, 3H), 7.72-7.75 (m, 1H), 11.54 (s.1H); MS, m/e 570.2 (M+1)+
17	1-Napth	H	H	Me	Me	1H NMR (DMSO-d_6) δ 1.15-1.27 (m, 6H), 3.51-3.55 (d, 3H), 3.85-3.96 (m, 2H), 4.00-4.10(m, 1H), 4.30-0.46 (m, 2H), 5.31-5.39 (m, 1H), 5.89-6.05 (m, 2H), 6.22-6.34 (m, 1H), 7.44-7.60 (m, 5H), 7.73-7.77 (m, 1H), 7.93-7.96 (m, 1H), 8.12-8.14 (m, 1H), 11.50(s. 1H); MS, m/e 552.1 (M+1)+
18	Ph	*	H	*	Me	1H NMR (DMSO-d_6) δ 1.19 (d, J=22.8 Hz, 3H), 1.69-1.84 (m, 3H), 1.99-2.04 (m, 1H), 3.16-3.21 (m, 2H), 3.58 (s, 3H), 3.68-3.8 (m, 1H), 4.00 (m, 1H), 4.01-4.13 (m, 1H), 4.22-4.25 (m, 1 H), 4.5 (d, J = 11.2 Hz, 1H), 5.54 (d, J = 8.0 Hz, 1H), 5.86 (s, 1H), 5.6 (d, J = 19.6 Hz, 1H), 7.15-7.2 (m, 3H), 7.34 (t, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 11.38 (s, 1H); MS, m/e 527.93(M+1)+
19	Ph	H	H	Me	n-Bu	1H NMR (DMSO-d_6) δ 0.80-0.90 (m, 3H), 1.20-1.35 (m, 8H), 1.48-1.55 (m, 2H), 3.78-3.88 (m, 2H), 3.95-0.08 (m, 3H), 4.22-4.45 (m, 2H), 5.55-5.57(t, 1H), 5.85-6.18 (m, 3H), 7.14-7.23 (m, 3H), 7.35-7.40 (m, 2H), 7.51-7.60 (d, 1H), 11.50 (s.1H); MS, m/e 544.2 (M+1)+
20	Ph	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.20-1.30 (m, 6H), 3.72-4.05 (m, 3H), 4.23-4.27 (m, 1H), 4.32-4.45 (m, 1H), 5.07-5.10(t, 2H), 5.52-5.56(t, 1H), 5.86-6.10 (m, 2H), 6.13-6.21(m,1H), 7.15-7.21 (m, 3H), 7.29-7.40 (m, 7H), 7.51-7.56 (d, 1H), 11.50 (s,1H); MS, m/e 578.2 (M+1)+
21	4-F-Ph	H	H	Me	Me	1H NMR (DMSO-d_6) δ 1.28-1.34 (m, 6H), 3.65(d, J= 4 Hz, 3H), 3.85-3.96 (m, 2H), 4.06-4.12 (m, 1H), 4.30-4.34 (m,1H), 4.40-4.47 (m, 1H), 5.62-5.67 (m, 1H), 5.94-6.01(m, 1H), 6.09 (d, J=18.8 Hz, 1H), 6.17-6.26 (m, 1H), 7.27-7.33(m, 4H), 7.62 (d, J = 7.6 Hz, 1H), 11.61 (s, 1H) ; MS, m/e 519.94(M+1)+
22	4-Cl-Ph	H	H	Me	Me	1H NMR (DMSO-d_6) δ 1.22-1.28 (m, 6H), 3.58 (d, 2H), 3.70-3.95(m,2H), 3.95-4.08 (m,1H), 4.23-4.45 (m, 2H), 5.55-5.61(t,

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						1H), 5.85-6.10 (m, 2H), 6.15-6.23(m,1H), 7.20-7.26 (m, 2H), 7.43-7.46 (m, 2H), 7.54-7.57 (d, 1H), 11.50 (s,1H); MS, m/e 536.1 (M+1)+
23	3,4-Cl-Ph	H	H	Me	Me	1H NMR (DMSO-d_6) δ 1.13 (m, 6H), 3.49 (s, 3H), 3.61-3.85 (m, 2H), 3.90-3.93 (m, 1H), 4.16-4.22 (m, 1H), 4.27-4.31 (m, 1H), 5.47-5.52 (m, 1H), 5.82 (d, J = 11.6 Hz, 1H), 5.93(d, J = 19.2 Hz, 1H), 6.15-6.25 (m, 1H), 7.13 (t, J = 9.6 Hz, 1H), 7.43 (d, J = 12Hz, 2H), 7.57 (d, J = 6.0 Hz, 1H), 11.43(s, 1H); MS, m/e 569.85 (M+1)+
24	Ph	H	H	Me	2-Bu	1H NMR (DMSO-d_6) δ 0.83 (d, J = 6.8 Hz, 6H), 1.20-1.26 (m, 6H), 1.79-1.86 (m, 1H), 3.73-3.90 (m, 4H), 4.01 (t, J = 11.2 Hz, 1H), 4.21-4.28 (m, 1H), 4.33-4.42 (m, 1H), 5.54 (t, J = 7.6 Hz, 1H), 5.85-5.92 (m, 1H), 5.99-6.13 (m, 2H), 7.19 (t, J = 8 Hz, 3H), 7.36 (t, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H), 11.52 (s, 1H); MS, m/e 544.00 (M+1)+
25	Ph	H	H	Me	i-Pr	1H NMR (DMSO-d_6) δ 1.13-1.28 (m, 12H), 3.74-3.81 (m, 2H), 3.95-4.08 (m,1H), 4.20-0.45 (m, 2H), 4.83-4.87 (m, 1H), 5.52-5.58 (m, 1H), 5.84-6.15 (m, 3H), 7.17-7.23 (m, 3H), 7.35-7.39 (m, 2H), 7.54-7.57 (m, 1H), 11.50 (s,1H); MS, m/e 530.2 (M+1)+
26	4-MeOH-Ph	H	H	Me	n-Bu	1HNMR (400MHz, DMSO-d_6): δ =0.78-0.82 (m, 3H), 1.29-1.47 (m, 8H), 1.49-1.54 (m, 2H), 3.66-3.87 (m, 5H), 3.96-4.02 (m, 3H), 4.21-4.39 (m, 2H), 5.57 (t, J= 12.0Hz, 1H), 5.84-6.05 (m, 3H), 6.90 (dd, J1 =8.0Hz, J2=4.0Hz, 2H), 7.09-7.14 (dd, J1=16.0Hz, J2=4.0Hz, 2H), 7.55 (d, J=8.0Hz, 1H), 11.48-11.62 (s, 1H)
27	4-F-Ph	H	H	Me	Et	1H NMR (DMSO-d_6) δ 1.12-1.28 (m, 9H), 3.72-3.94(m,2H),3.98-4.10 (m,3H), 4.21-4.42(m,2H), 5.55-5.61 (t, 1H), 5.85-6.20 (m, 3H), 7.18-7.25 (m,4H), 7.55-7.58 (d, 1H), 11.50 (s,1H); MS, m/e 533.90 (M+1)+
28	4-F-Ph	H	H	Me	i-Pr	1H NMR (DMSO-d_6) δ 1.13-1.30 (m, 12H), 3.74-3.85(m,2H), 3.98-4.06 (m, 1H), 4.23-4.41(m,2H), 4.83-4.87 (m, 1H), 5.55-5.61 (t, 1H), 5.85-6.12 (m, 3H), 7.18-7.24 (m,4H), 7.55-7.58 (d, 1H), 11.50 (s,1H);

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						MS, m/e 547.91 (M+1)+
29	4-F-Ph	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.10-1.23 (m, 6H), 3.65-3.89(m,3H),4.10-4.30 (m,2H), 4.96-5.00(m,2H), 5.46-5.50 (t, 1H), 5.75-5.96 (m, 2H), 6.04-6.12(m,1H), 7.05-7.11 (m,4H), 7.20-7.24 (d, 5H), 7.42-7.45(d,1H), 11.50 (s,1H); MS, m/e 595.94 (M+1)+
30	4-MeO-Ph	H	H	Me	i-Pr	1HNMR (400MHz, DMSO-d_6): δ=1.15-1.27 (m, 12H), 3.71-3.89 (m, 5H), 3.98-4.02 (m, 1H), 4.22-4.25 (m, 1H), 4.33-4.39 (m, 1H), 4.84-4.87 (m, 1H), 5.57 (t, J= 12.0Hz, 1H), 5.91-6.03 (m, 3H), 6.90 (d, J= 8.0Hz, 2H), 7.09-7.14 (m, 2H), 7.55 (d, J= 8.0Hz, 1H), 11.51 (s, 1H)
31	2-Cl-Ph	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.23 (m, 6 H), 3.93-4.00 (m, 3 H), 4.27-4.40 (m, 2H), 5.0(t, J= 7.2 Hz, 2 H), 5.53 (m, I H), 5.80-6.0(m, 2 H), 6.30(m, 1H), 7.15 (d, J= 2.4 Hz, 1 H), 7.27 (m, 6 H), 7.51 (m, 3 H), 11.5 (s, I H) ; MS, m/e 579.87(M+1)+/ 596.78 (M+18)+
32	2,4-Cl-Ph	H	H	Me	n-Bu	1H NMR (DMSO-d_6) δ=0.82 (m, 3 H),1.23 (m, 8 H), 1.47 (m, 2 H), 3.86 (m, 2 H), 3.84 (m, 3 H),4.27-4.43 (m, 2H), 5.5 (m , 1H), 6.02 (m ,2 H), 6.35(m, 1H), 7.44 (m, 3 H), 7.77 (m, 1 H), 11.5 (s, 1 H) ; MS, m/e 611.87(M+1)+
33	4-Me-Ph	H	H	Me	i-Pr	1H NMR (DMSO-d_6) δ 1.14-1.27 (m, 12H), 2.17-2.26 (m, 3H), 3.73-3.82 (m, 1H), 3.99-4.02 (m, 1H), 4.23-4.26 (m, 1H), 4.37 -4.40 (m, 1H), 4.82-4.88 (m, 1H), 5.52-5.58 (m, 1H), 5.85-6.07 (m, 3H), 7.01-7.20 (m, 4H), 7.55 (d, J = 16Hz, 1H), 11.51 (s, 1H); MS, m/e 543.98 (M+1)+; 1108.86 (2M+23)+
34	4-F-Ph	H	H	Me	n-Bu	1H NMR (DMSO-d_6) δ 0.82-0.89 (m,3H), 1.20-1.31 (m, 8H), 1.48-1.53 (m,2H), 3.77-3.90 (m,2H) ,3.95-4.10 (m,3H), 4.21-4.45(m,2H), 5.56-5.61 (t, 1H), 5.83-6.20 (m, 3H), 7.18-7.25 (m,4H), 7.55-7.58 (d, 1H), 11.50 (s,1H); MS, m/e 584.1 (M+23)+
35	3,4-diCl-Ph	H	H	Me	Et	1H NMR (DMSO-d_6) δ1.12-1.31 (m, 9H), 3.77-3.92 (m,2H), 3.95-4.08 (m,3H), 4.21-4.45(m,2H), 5.56-5.62 (t, 1H), 5.80-6.11

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						(m, 2H), 6.18-6.33(m,1H), 7.18-7.25 (m, 1H), 7.49-7.56 (d, 2H), 7.62-7.67(m,1H), 11.50 (s,1H); MS, m/e 606.1 (M+23)+
36	2-Cl-Ph	H	H	Me	i-Pr	1HNMR (400MHz, DMSO-d_6): δ =1.12-1.16 (m, 6H), 1.21-1.27 (m, 6H), 3.79-3.85 (m, 2H), 4.00-4.07 (m, 1H), 4.28-4.32 (m, 1H), 4.38-4.43 (m, 1H), 4.83-4.87 (m, 1H), 5.56 (dd, J1=16.0Hz, J2=8.0Hz, 1H), 5.85-6.12 (m, 2H), 6.20-6.33 (m, 1H), 7.19-7.22 (m, 1H), 7.33 (t, J= 16.0Hz, 1H), 7.48-7.55 (m, 3H), 11.55 (s, 1H)
37	4-Me0-Ph	H	H	Me	Bn	1HNMR(400MHz, DMSO-d_6): δ=1.19-1.26 (m, 6H), 3.69-3.70 (s, 3H), 3.87 (m, 2H), 3.99 (m, 1H), 4.20-4.21 (m, 1H), 4.35 (m, 1H), 5.07-5.09 (m, 2H), 5.54 (t, J = 16.0Hz, 1H), 5.85-5.92 (m, 1H), 6.04-6.10 (m, 2H), 6.86 (d, J= 8.0Hz, 2H), 7.09 (dd, J1=16.0Hz, J2=4.0Hz, 2H), 7.30-7.34 (m, 5H), 7.53 (s, 1H), 11.52(s, 1H)
38	Ph	H	H	Me	n-Pen	1H NMR (DMSO-d_6) δ 0.79-0.81 (m, 3H), 1.17-1.23 (m, 10H), 3.74-3.81 (m, 2H), 3.94-3.96 (m, 3H), 4.19-4.36 (m, 2H), 5.49-5.54 (m, 1H), 5.87-6.08 (m,3H), 7.14-7.33 (m, 3H), 7.31-7.35 (m, 2H), 7.51 (d, J = 8Hz, 1H), 11.51 (s, 1H); MS, m/e 557.9 (M+1)+; 1136.88 (2M+23)+
39	4-Cl-Ph	H	H	Me	i-Pr	1H NMR (DMSO-d_6) δ 1.04-1.19 (m, 12H), 3.76-3.80 (m, 2H), 3.98-4.08 (m, 1H), 4.42-4.42 (m, 2H), 4.82-4.85 (m, 1H), 5.55-5.60 (m, 1H), 5.80-6.20 (m,3H),7.20-7.2 5(m, 2H), 7.43 (d, J = 8.8Hz, 1H), 7.54 (d, J = 8Hz, 1H), 11.51 (s, 1H); MS, m/e 563.88 (M+1)+; 1148.73 (2M+23)+
40	4-Cl-Ph	H	H	Me	n-Bu	1H NMR (DMSO-d_6) δ 0.85 (t, J = 7.2 Hz, 3H), 1.22-1.33 (m, 8H),1.45-1.53 (m, 2H), 3.80-3.87 (m, 2H), 3.96-4.04 (m, 3H), 4.24-4.27 (m, 1H), 4.35-4.39 (m, 1H), 5.56-5.61 (m, 1H), 5.82-6.11 (m, 2H), 6.15-6.18 (m, 1H), 7.20-7.56 (m, 4H), 7.51-7.57 (m,1H), 11.54 (s, 1H); MS, m/e 577.95(M+1)+
41	4-Cl-Ph	H	H	Me	Et	1H NMR (DMSO-d_6) δ 1.14 (t, J = 7.0Hz, 3H), 1.20-1.28 (m, 6H),3.77-3.88 (m, 2H), 3.99-4.07 (m, 3H), 4.24-4.28 (m, 1H), 4.34-4.43 (m, 1H), 5.56-5.61 (m, 1H), 5.86-6.13 (m, 2H), 6.15-6.24 (m, 1H),

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						7.20-7.26 (m, 2H), 7.44 (d, J = 7.6Hz, 2H), 7.55 (d, J = 7.6Hz, 1H), 11.55 (s, 1H); MS, m/e 549.11(M+1)+
42	4-Me-Ph	H	H	Me	n-Bu	1H NMR (DMSO-d_6) δ 0.79-0.83 (m, 3H), 1.17-1.28 (m, 8H), 1.45-1.47 (m, 2H), 2.22 (d, J = 2.8Hz, 1H), 3.70-3.90 (m, 2H), 3.95-3.98 (m, 3H), 4.10-0.40 (m, 2H), 5.51 (t, 1H), 5.80-5.90 (m, 1H), 5.95-6.05 (m, 2H), 7.02-7.06 (m, 2H), 7.51 (t, J = 4.2Hz, 4H), 7.51 (d, 1H), 11.51 (s, 1H); MS, m/e 557.99(M+1)+; 1136.84(2M+23)+
43	4-Me-Phe	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.16-1.24 (m, 6H), 2.22 (s, 3H), 3.65-4.03 (m,3H), 4.11-4.38 (m, 2H), 5.04-5.05 (m, 2H), 5.48-5.50 (m, 1H), 5.77-5.87 (m,1H),5.90-6.11 (m, 2H), 6.98-7.10 (m, 4H), 7.28-7.32 (m, 5H), 7.50 (t, 1H), 11.48 (s, 1H); MS, m/e 592.00 (M+1)+.
44	Ph	H	H	Et	Me	1H NMR (DMSO-d_6) δ 0.70-0.80 (m, 3H), 1.11-1.26 (m, 3H), 1.42-1.61 (m, 2H), 3.50-3.54 (m, 3H), 3.58-3.80 (m, 2H), 3.91-4.02 (m, 1H), 4.12-4.38 (m, 2H), 5.47-5.52 (m,1H),5.90-6.03 (m, 2H), 7.08-7.16 (m, 3H), 7.26-7.35 (m, 2H),7.48 (t,1H), 11.45 (s, 1H); MS, m/e 515.95 (M+1)+; 1052.82 (2M+23)+
45	Ph	H	H	Me	4-F-Bn	^{1}HNMR (400MHz, DMSO-d_6): δ 1.20-1.26 (m, 6H), 3.80-3.93 (m, 2H), 3.98 (s, 1H), 4.25-4.26 (m, 1H), 4.36-4.37 (m, 1H), 5.07 (s, 2H), 5.52-5.55 (m, 1H), 5.86-5.87(m, 1H), 5.98-6.04 (m, 1H), 6.14-6.17 (m, 1H), 7.15-7.20 (m, 5H), 7.36 (dd, *J* = 20.0, 8.0 Hz, 4H), 7.54 (s, 1H), 11.55 (s, 1H)
46	4-Cl-Ph	H	H	Me	n-Bu	^{1}HNMR (400MHz, DMSO-d_6): δ 1.21-1.28 (m, 6H), 3.71-3.88 (m, 1H), 3.91-3.98 (m, 1H), 4.00-4.01 (m, 1H), 4.23-4.27 (m, 1H), 4.35-4.38 (m, 1H), 5.08 (d, *J* = 4.0Hz, 2H), 5.57 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 6.01 (d, *J* = 8.0 Hz, 1H), 6.22-6.24 (m, 1H), 7.17-7.23 (m, 2H), 7.31-7.40 (m, 7H), 7.53 (s, 1H), 11.50 (s, 1H)
47	Ph	H	H	Me	3-Me-1-Bu	^{1}H NMR (DMSO-d_6) δ 0.80-0.82 (m, 6H), 1.18-1.40 (m, 8H), 1.50-1.58 (m, 1H), 3.71-3.82 (m, 3H), 3.97-3.4.01 (m, 3H),

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						4.21-4.40 (m, 2H), 5.30(t, *J*= 8.6 Hz, 1H), 5.81-6.10 (m, 3H), 7.15-7.20 (m, 3H), 7.32-7.36 (m. 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 11.38 (s, 1H); MS, *m/e* 557.98 (M+1)+; 1136.88 (2M+23)+
48	3,4-diCl-Ph	H	H	Me	Bn	1H NMR (DMSO-d_6) δ 1.05-1.37 (m, 6H), 3.71-3.82 (m, 1H), 3.87-4.02 (m, 2H), 4.28-4.29 (m, 1H),4.36-4.38 (m, 1H),5.04 (d, J= 5.2Hz, 2H), 5.55-5.64 (m, 1H), 5.85-5.94 (m, 1H), 6.00-6.05 (m, 1H), 6.29-6.40 (m, 1H),7.17-7.24 (m, 1H), 7.30-7.41 (m, 5H), 7.45-7.58 (m, 2H), 7.61 (d, *J* = 4.0Hz, 1H), 11.53(s, H); MS, *m/e* 545.80(M+1)+;
49	Ph	H	H	Me	c-Hex	^{1}H NMR (DMSO-d_6) δ 1.18-1.41 (m, 12H), 1.59-1.67 (m, 4H), 3.74-13.80 (m, 1H), 3.96-4.02 (m, 1H), 4.19-4.26 (m, 1H), 4.31-4.39 (m, 1H), 4.60 (s, 1H), 5.52 (t, J= 7.8 Hz, 1H), 5.80-6.09 (m, 3H), 7.15-7.20 (m, 3H), 7.32-7.36 (m, 2H), 7.52 (d, *J* = 8 Hz, 1H), 11.50 (s, 1H); MS, 569.98 $(M+1)^+$; 592.14 $(M+23)^+$
50	Ph	H	Me	H	n-Bu	1H NMR (DMSO-d_6) δ 0.76 (t, J = 7.2Hz, 3H), 1.10-1.22 (m, 8H), 1.38-1.43 (m, 2H), 3.72-3.75 (m, 2H), 3.87-3.93 (m, 3H), 4.14-4.21 (m, 1H), 4.23-4.33 (m, 1H), 5.46-5.54 (m, 1H), 5.84-6.11 (m, 3H), 7.09-7.14 (m, 2H), 7.27-7.32 (m, 2H), 7.34-7.51 (m, 1H), 11.47 (s, 1H); MS, m/e 543.98(M+1)+
51	Ph	H	Me	H	i-Pr	1H NMR (DMSO-d_6) δ 1.39 (d, J = 7.2Hz, 6H), 1.19-1.29 (m, 6H), 3.65-3.75 (m, 2H), 3.95-4.05 (m, 1H), 4.20-4.22 (m, 1H), 4.31-4.33 (m, 1H), 4.79-4.82 (m, 1H), 5.48-5.57 (m, 1H), 5.84-5.91 (m, 1H), 5.96-6.07 (m, 2H), 7.12-7.35 (m, 5H), 7.44-7.54 (m,1H), 11.49(s, 1H); MS, m/e 529.96 (M+1)+
52	Ph	H	Me	H	Bn	^{1}HNMR (DMSO-d_6) δ 1.18-1.28 (m, 6H), 3.70-3.83 (m, 1H), 3.87-3.94 (m, 1H), 3.99-4.01 (m, 1H), 4.23-4.26 (m, 1H), 4.33-4.37 (m, 1H), 5.03-5.12 (m, 2H), 5.51-5.59 (m, 1H), 5.87-5.90 (m, 1H), 5.95-6.07 (m, 1H), 6.10-6.27 (m, 1H), 7.15-7.23 (m, 3H), 7.31-7.38 (m, 7H), 7.47-7.56 (m, 1H), 11.50 (s, 1H); MS, m/e

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						577.99 (M+1)+
53	2-Cl-Ph	H	H	Me	n-Bu	^{1}HNMR (400MHz, DMSO-d_6): δ 0.81-0.86 (m, 3H), 1.21-1.31 (m, 8H), 1.46-1.52 (m, 2H), 3.84-3.90 (m, 2H), 3.97-4.04 (m, 3H), 4.27-4.41 (m, 2H), 5.53-5.58 (m, 1H), 5.82-5.95 (m, 1H), 5.96-6.10 (m, 1H), 6.27-6.31 (m, 1H), 7.19-7.22 (m, 1H), 7.34 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.47-7.55 (m, 3H), 11.55 (s, 1H)
54	4-Br-Ph	H	H	Me	i-Pr	^{1}HNMR (400MHz, DMSO-d_6): δ 1.10-1.14 (m, 6H), 1.20-1.27 (m, 6H), 3.74-3.81 (m, 2H), 3.99-4.01 (m, 1H), 4.21-4.25 (m, 1H), 4.37-4.38 (m, 1H), 4.81-4.85 (m, 1H), 5.58 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.82-5.95 (m, 1H), 5.96-6.09 (m, 1H), 6.10-6.13 (m, 1H), 7.18 (dd, *J* = 12.0, 8.0 Hz, 2H), 7.53-7.57 (m, 3H), 11.52 (s, 1H)
55	4-F-Ph	H	H	Me	c-Hex	^{1}H NMR (DMSO-d_6) δ 1.20-1.44 (m, 12H), 1.60-1.71 (m, 4H), 3.75-4.02 (m, 2H), 3.94-4.02 (m, 1H), 4.19-4.26 (m, 2H), 4.59-4.61 (m, 1H), 5.57 (t, *J* = 8.4 Hz, 1H), 5.85-6.06 (m, 3H), 7.17-7.23 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 1H), 11.50 (s, 1H); MS, *m/e* 587.92 $(M+1)^+$
56	4-Br-Ph	H	H	Me	c-Hex	^{1}HNMR (400MHz, DMSO-d_6): δ =1.18-1.46 (m, 12H), 1.61-1.69 (m, 4H), 3.75-3.82 (m, 2H), 3.95-4.08 (m, 1H), 4.25-4.28 (m, 1H), 4.38 (s, 1H), 4.60-4.62 (m, 1H), 5.56-5.60 (m, 1H), 5.82-5.95 (m, 1H), 6.02-6.20 (m, 2H), 7.09-7.20 (m, 2H), 7.53-7.57 (m, 3H), 11.52 (s, 1H) MS, m/e 650.0 $(M+3)^+$
57	Ph	H	H	Et	i-Pr	^{1}HNMR (400MHz, DMSO-d_6): δ =0.75-0.82 (m, 3H), 1.12-1.26 (m, 9H), 1.52-1.59 (m, 2H), 3.55-3.68 (m, 1H), 3.72-3.85 (m, 1H), 3.95-4.08 (m, 1H), 4.18-4.28 (m, 1H), 4.32-4.41 (m, 1H), 4.83-4.86 (m, 1H), 5.55 (m, *J*= 7.6Hz, 1H), 5.99-6.04 (m, 2H), 6.05-6.10 (m, 1H), 7.14-7.21 (m, 3H), 7.33-7.37 (m, 2H), 7.52-7.54 (m, 1H), 11.53 (s, 1H); MS, *m/e* 566.07$(M+23)^+$
58	Ph	H	H	Et	c-Hex	^{1}HNMR (400MHz, DMSO-d_6): δ 0.75-0.88 (m, 3H), 1.26-1.46 (m, 9H), 1.52-1.69 (m, 6H), 3.60-3.63 (m, 1H), 3.72-3.90 (m, 1H),

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						4.02-4.03 (m, 1H), 4.24-4.27 (m, 1H), 4.37-4.38 (m, 1H), 4.63-4.65 (m, 1H), 5.55 (dd, *J* = 8.0Hz, 4.4Hz, 1H), 5.80-5.95 (m, 1H), 6.00-6.07 (m, 2H), 7.15-7.22 (m, 3H), 7.34-7.38 (m, 2H), 7.54 (d, *J* =8.0Hz, 1H), 11.55 (s, 1H); MS, *m/e* 584.01 $(M+1)^+$; 606.17 $(M+23)^+$
59	4-F-Ph	H	H	Et	c-Hex	^{1}H NMR (DMSO-d_6) δ 0.75-0.84 (m, 3H), 1.24 (d, *J* = 22.8Hz, 3H), 1.29-1.47 (m, 6H), 1.51-1.70 (m, 6H), 3.59-3.66 (m, 1H), 3.77-3.84 (m, 1H), 3.98-4.04 (m, 1H), 4.21-4.27 (m, 1H), 4.34-4.41 (m, 1H), 4.60-4.65 (m, 1H), 5.56-5.60 (m, 1H), 5.84-5.90 (m, 1H), 6.00-6.08 (m, 2H), 7.20-7.24 (m, 4H), 7.56(d, *J* = 8.0Hz, 1H), 11.49 (s, 1H); MS, *m/e* 602.00$(M+1)^+$
60	Ph	H	H	Me	F-CH_2-CH_2-	^{1}H NMR (DMSO-d_6) δ 1.18-1.25(m, 6H), 3.71-3.89 (m, 2H), 3.92-3.99 (m, 1H), 4.19-4.27 (m, 4H), 4.48-4.61 (m, 2H), 3.94-3.98 (m, 2H), 4.11-4.23 (m, 4H), 5.47-5.52 (m, 1H), 6.01-6.11 (m, 1H), 5.90-6.14 (m, 2H), 7.15-7.21 (m, 3H), 7.32-7.36 (m, 2H), 7.46-7.57 (m, 1H), 11.49 (s,1H); MS, *m/e* 533.86 $(M+1)^+$
61	Ph	H	H	Me	F_2CH-CH_2-	^{1}H NMR (DMSO-d_6) δ 1.17-1.24 (m, 6H), 3.67-3.81 (m, 1H), 3.89-3.98 (m, 2H),4.21-4.36 (m, 4H), 5.48-5.53 (m, 1H), 5.82-6.05 (m, 2H), 6.18-6.22 (m, 2H), 7.15-7.20 (m, 3H), 7.32-7.36 (m, 2H), 7.51 (s, 1H),11.50 (s, 1H); MS, *m/e* 551.92 $(M+1)^+$;
62	Ph	H	H	Me	$(CF_3)_2$-CH-	^{1}H NMR (DMSO-d_6) δ 1.13-1.29 (m, 6H), 3.67-3.81 (m, 1H), 3.94-4.32 (m, 4H), 5.47 (t, *J* = 8 Hz 1H), 5.82-6.01 (m, 2H), 6.33-6.36 (m, 1H), 6.70-6.78 (m, 1H), 7.09-7.15 (m, 3H), 7.28-7.32 (m, 2H), 7.43-7.46 (m, 1H),11.44 (s, 1H) ; MS, *m/e* 637.90 $(M+1)^+$
63	Ph	H	H	Me	$(CH_2F)_2$ -CH-	^{1}H NMR (DMSO-d_6) δ 1.20-1.29 (m, 6H), 3.70-3.90 (m, 1H), 3.91-4.12 (m, 2H), 4.20-4.33 (m, 1H), 4.35-4.48 (m, 1H), 4.52-4.55 (m, 2H), 4.63-4.67 (m, 2H), 5.20-5.35 (m, 1H), 5.56 (t, *J* = 8.4 Hz, 1H), 5.80-5.95 (m, 1H), 5.95-6.10 (m, 1H),

Ex.	R^1	R^2	R^{3a}	R^{3b}	R^4	NMR/MS
						6.18-6.21 (m, 1H), 7.18-7.23 (m, 3H), 7.35-7.39 (m , 2H), 7.54 (s, 1H), 11.55 (s, 1H); MS, *m/e* 565.98 $(M+1)^+$
64	Ph	H	H	Me	c-Pr-CH_2-	^{1}H NMR (DMSO-d_6) δ 0.20-0.24(m, 2H), 0.47-0.48(m, 2H), 0.76-0.84(m, 3H), 1.03-1.05(m, 1H), 1.23(dd, *J* = 22.4 6.8 *Hz* 3H), 1.55-1.60(m, 2H), 3.61-3.68(m, 1H), 3.81-3.89 (m, 3H), 3.98-4.03(m, 1H), 4.23-4.29(m, 1H), 4.35-4.41(m, 1H), 5.56-6.00(m, 1H), 5.88-5.91(m, 1H), 6.04-6.10(m, 2H), 7.20-7.24(m, 4H), 7.55 (d, *J*= 7.6 Hz 1H). 11.53 (s, 1H); MS, *m/e* 573.17 $(M+1)^+$
65	Ph	H	H	Et	c-Pen	^{1}H NMR (DMSO-d_6) δ 0.75-0.83 (m, 3H), 1.20-1.28 (m, 3H), 1.49-1.63 (m, 8H), 1.76-1.80 (m, 2H), 3.58-3.60 (m, 1H), 3.70-3.82 (m, 1H), 3.98-4.05 (m, 1H), 4.24-4.26 (m, 1H), 4.37-4.42 (m, 1H), 5.03 (s, 1H), 5.54-5.57 (m, 1H), 5.90-6.00 (m, 1H), 6.02-6.07 (m, 2H), 7.15-7.22 (m, 3H), 7.35-7.39 (m, 2H) 7.55 (d, *J* = 8.0 *Hz*, 1H), 11.55 (s, 1H); MS, *m/e* 570.03 (M+1)+
*R^2 and R^{3b} together are -($CH_2)_3$-as derived from L-proline						

The purification procedure by Prep-HPLC:

[0114] Crude products were dissolved in methanol. Injection volumes of these solutions were 5 mL.

[0115] The preparative HPLC system including 2 sets of Gilson 306 pumps, a Gilson 156 UV/V is detector, a Gilson 215 injector & fraction collector, with Unipoint control software. A Ymc 25×30×2 mm column was used. The mobile phase was HPLC grade water (A), and HPLC grade acetonitrile (B). Fractions were collected into 100*15mm glass tubes.

[0116] HPLC gradient is shown in Table 1. Once the gradient was selected, acetonitrile solution was injected into HPLC system, and then fractions collected according to UV peaks. After the separation, each glass tubes were run MS test to collect the desired compounds. The fractions with target MS were combined in a well-weighted flask. Most of acetonitrile was removed under reduce pressure and the remaining solution was freeze-dried to give desired compound.

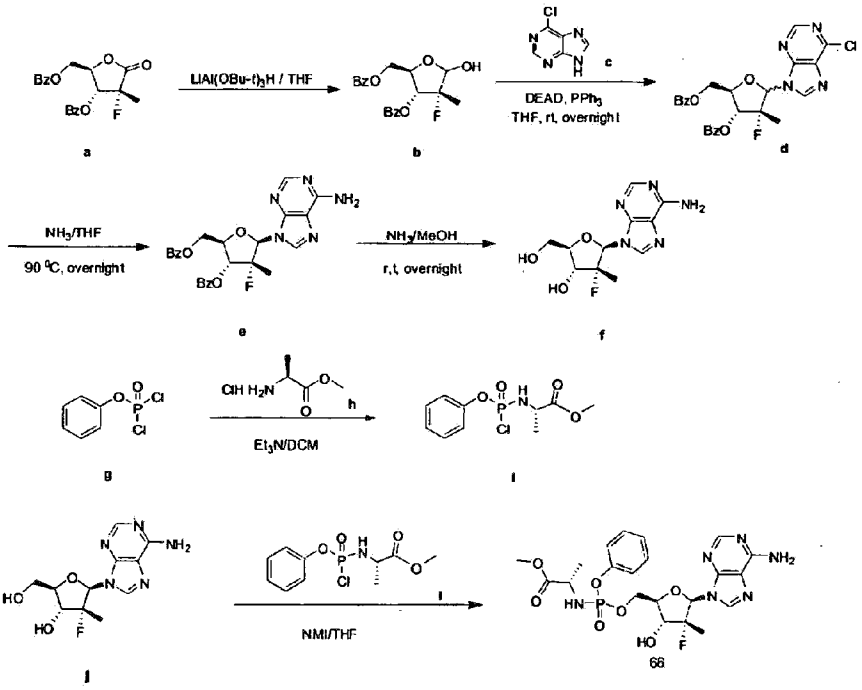
Table 1:

Preparative HPLC gradient			
Time (min)	Flow rate (mL/min)	% A	% B
0	15	90	10
30	15	60	40

Preparation of Example 66

[0117]

Scheme



Preparation of compound (b)

[0118] To a solution of compound **a** (1 g, 2.69 mmol) in anhydrous THF (30 mL) was added dropwise 1 M solution of LiAl(OBu-*t*)$_3$H in THF (2.69 mL, 2.69 mmol) at -20 °C. The reaction mixture was stirred for 2-3 h at the same temperature. EtOAc (100 mL) was added followed by saturated NH_4Cl solution (10 mL) and reaction mixture was slowly brought to room temperature. Reaction mixture was extracted with EtOAc and washed with 1N HCl and water. Combined organic phase was evaporated to give 0.8 g of crude compound **b** as transparent oil, which was used directly for next reaction.

Preparation of compound (d)

[0119] To a solution of compound b (0.8 g, 2.1mmol), compound c (0.45 g, 2.5 mmol) and Ph_3P (0.56 g, 2.1 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added DEAD (1.8 mL). The reaction mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduce pressure. The residue was separated by preparative layer chromatography (hexanes:EtOAc = 3:1) to give crude compound **d** (0.8 g). The crude compound **d** was used to the next step without further purification.

Preparation of compound (e)

[0120] Compound **d** (0.8 g, 1.57 mmol) was dissolved in THF (2 mL) and THF saturated with ammonia (5 mL) was then added to this solution. The reaction mixture was heated to 90 °C overnight. After 18 hours, the solution was cooled to room temperature by ice water, then the solvent was removed under reduced pressure and the residue was purified by column to give compound **e** (0.75 g) for the next step.

Preparation of compound (f)

[0121] Compound e (0.5 g, 1.01 mmol) was dissolved in methanol (2 mL) and methanol was saturated with ammonia (5 mL) was then added to this solution. The reaction mixture was stirred at room temperature overnight. After 18 hours, the solvent was removed under reduced pressure and the residue was purified by column to give crude compound f (0.15 g) for the next step.

Preparation of compound (i)

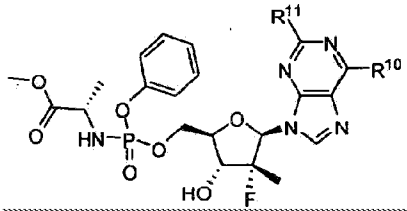
[0122] A solution of triethylamine (1.07 g, 10.6 mmol) in anhydrous dichloromethane (15 mL) was added dropwise to a solution of compound **g** (1.16 g, 5.3 mmol) and compound **h** (1.31 g, 5.3 mmol) in dichloromethane (10 mL) with vigorous stirring at -78 °C over a period of 2 hours. After completion of addition, the reaction temperature was allowed to warm to room temperature gradually and stirred over night. Then the solvent was removed under vacuum and anhydrous ether 20 mL was added and the precipitated salt was filtered and the precipitate was washed with ether. The combined organic phase was concentrated to give the colorless oil of compound **i** (1.0 g).

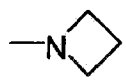
Preparation of Compound 66

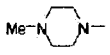
[0123] To a solution of compound **j** (0.1 g, 0.35 mmol) dissolved in 10 mL of anhydrous THF,

stirred and added 0.4g NMI till the solution became clear, added compound **i** (0.8 g, 2.89 mmol) in 10 mL THF dropwise, stirred at r.t. overnight. Compound purity and identification was confirmed by LCMS. The solvent was evaporated and purified by Prep-HPLC to afford **66.** (25 mg, Yield: 13.6%). ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 22.8 Hz, 3H), 1.17-1.24 (m, 3H), 3.50-3.52 (m, 3H), 3.78-3.83 (m, 1H), 4.10-4.13 (m, 1H), 4.24-4.44 (m, 2H), 5.85-5.92 (m, 1H), 6.01-6.11 (m, 1H), 6.2.-6.27 (m, 1H), 7.08-7.19 (m, 4H), 7.31-7.38 (m, 3H), 8.15 (s, 1H), 8.26 (s, 1H); MS, *m/e* 525 $(M+1)^+$.

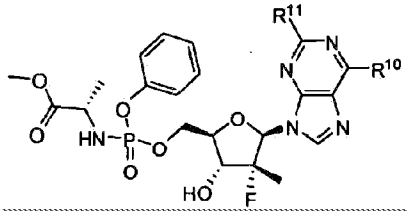
[0124] Example numbers **67-74**, identified below, were prepared using similar procedures disclosed for Example **66,** above.

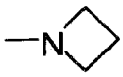


Example	R^{11}	R^{10}	NMR/MS
67	OH	NH_2	^{1}H NMR (DMSO-d_6) δ 1.06-1.13 (m, 3H), 1.20-1.24 (m, 3H), 3.27-3.33(m, 3H), 3.56 (s, 1H), 3.82-3.88 (m, 1H), 4.07-4.13 (m, 1H), 4.25-4.40 (m, 2H), 5.85-5.87 (m, 1H), 5.98-6.09 (m, 2H), 6.59 (s, 32H), 7.14-7.37 (m, 3H), 7.35-7.37 (m, 2H), 7.79 (d, J=7.2 Hz, 1H), 10.69 (s, 1H); MS, *m/e* 541 $(M+1)^+$;
68	NH_2	NH_2	^{1}H NMR (DMSO-d_6) δ 1.07 (d, J=22.8 Hz, 3H), 1.19 (d, J=7.2 Hz, 3H), 3.51 (s, 3H), 3.62 (s, 1H), 3.75-3.81 (m, 1H), 4.05-4.11 (m, 1H), 4.27-4.42 (m, 2H), 5.79-5.83 (m, 1H), 5.92 (s, 2H), 6.00-6.09 (m, 2H), 6.75 (s, 2H), 7.08-7.17 (m, 3H), 7.31-7.35 (m, 2H), 7.78 (s, 1H); MS, *m/e* 540 $(M+1)^+$;
69	NH_2	c-Pentyl-NH-	^{1}H NMR (DMSO-d_6) δ 1.05 (d, J=22.8 Hz, 3H), 1.09-1.19 (m, 3H), 1.48 (s, 4H), 1.66 (s, 1H), 1.86 (s, 1H), 3.54 (d, J=14 Hz, 3H), 3.65 (s, 1H), 4.25-4.43 (m, 4H), 5.71-5.82 (m, 1H), 5.94-6.04 (m, 4H), 7.11-7.24 (m, 3H), 7.26-7.34 (m, 2H), 7.77(d, J=3.6 Hz, 1H); MS, *m/e* 608$(M+1)^+$
70	NH_2		^{1}H NMR (DMSO-d_6) δ 1.07 (d, J=22.4 Hz, 3H), 2.35-2.38 (m, 2H), 3.54 (d, J=9.2 Hz, 3H), 3.59-3.62 (m, 2H), 3.65 (s, 1H), 3.75-3.82 (m, 1H), 4.01-4.13 (m, 2H), 4.22-4.40 (m, 6H), 5.75-5.85 (m, 1H), 6.00-6.07 (m, 4H), 7.15-7.21 (m, 3H), 7.32-7.35 (m, 2H), 7.79 (d, J=4.0 Hz, 1H); MS, *m/e* 580 $(M+1)^+$
71	NH_2	Et_2N-	^{1}H NMR (DMSO-d_6) δ 1.06-1.28 (m, 12H), 3.55 (d, J=4.8 Hz, 3H), 3.79-3.87 (m, 4H), 4.07-4.12 (m, 2H), 4.29-4.42 (m, 3H), 5.75-5.82 (m, 1H), 5.94 (s, 2H),

Example	R^{11}	R^{10}	NMR/MS
			6.04-6.10 (m, 2H), 7.14-7.22 (m, 3H), 7.31-7.37 (m, 2H), 7.82 (d, *J*=4.4 Hz, 1H); MS, *m/e* 596 $(M+1)^+$
72	NH_2	n-Propyl-NH-	^1H NMR (DMSO-d_6) δ 0.84 (t, *J*=7.2 Hz, 3H), 1.01-1.01 (m, 3H), 1.09-1.12 (m, 3H), 1.51-1.56 (m, 2H), 3.48 (d, *J*=15.2 Hz, 3H), 3.79-3.82 (m, 1H), 4.04-4.05 (m, 1H), 4.27-4.38 (m, 3H), 5.72-5.79 (m, 1H), 5.98-6.04 (m, 4H), 7.13-7.20 (m, 3H), 7.26-7.32 (m, 2H), 7.76 (d, *J*=5.2 Hz, 1H); MS, *m/e* 582 $(M+1)^+$
73	NH_2	c-Butyl-NH-	^1H NMR (DMSO-d_6) δ 1.02-1.08 (m, 3H), 1.18 (d, *J*=4.8 Hz, 3H), 1.44-1.61 (m, 2H), 2.02-2.17 (m, 4H), 3.51 (d, *J*=10.8 Hz, 3H), 3.78-3.83 (m, 1H), 4.03-4.06 (m, 1H), 4.27-4.38 (m, 2H), 4.53-4.62 (m, 1H), 5.68-5.79 (m, 1H), 5.95-6.04 (m, 4H), 7.11-7.18 (m, 3H), 7.29-7.35 (m, 2H), 7.51-7.58 (m, 1H), 7.78 (d, *J*=5.2 Hz, 1H); MS, *m/e* 594 $(M+1)^+$
74	NH_2		^1H NMR (DMSO-d_6) δ 0.97-1.20 (m, 6H), 2.18 (s, 3H), 2.19 (s, 4H), 3.43-3.47(m, 3H), 3.75 (s, 1H), 4.01-4.06 (m, 4 H), 4.22-4.35 (m, 3H), 5.69-5.75 (m, 1H), 5.98-6.05 (m, 3H), 7.09-7.15 (m, 3H), 7.25-7.29 (m, 2H), 7.77 (d, *J*=3.6 Hz, 1H); MS, *m/e* 623 $(M+1)^+$

[0125] Example numbers 75-80 are prepared using similar procedures disclosed for Example **66**, above.



Example	R^{11}	R^{10}
75	H	n-propyl-NH-
76	H	c-Butyl-NH-
77	H	c-Pentyl-NH-
78	H	
79	H	
80	H	

EXAMPLE 81

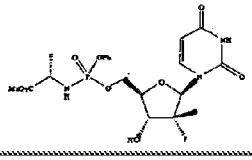
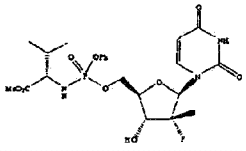
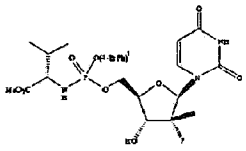
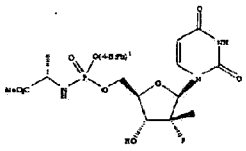
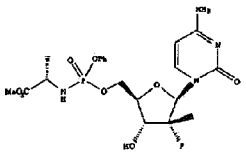
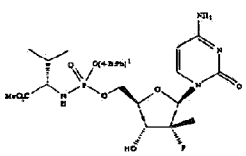
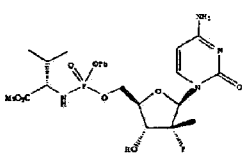
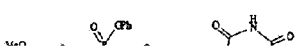
[0126] Certain exemplified compounds were obtained as mixture of diastereomers because of the chirality at phosphorous. The diastereomers were separated on a Chiralpak-AS-H (2 X 25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. The absolute stereochemistry of the P-chiral center of the diastereromers were not determined. However, chromatographic resolution of these two diastereomers provides for isomers that are characterized as fast eluting and slow eluting isomers. Some examples are shown below.

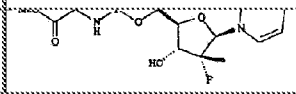
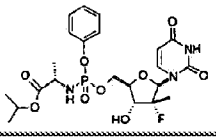
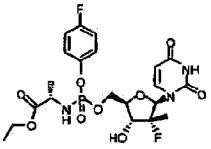
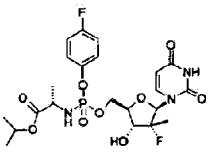
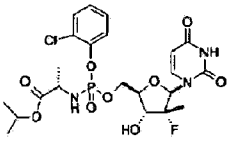
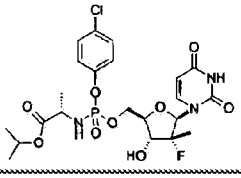
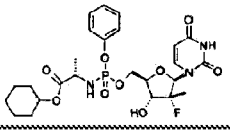
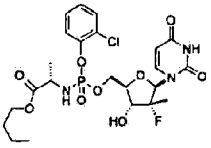
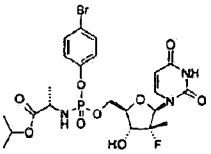
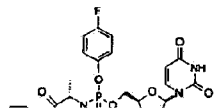
Compound	**EC90 (μM)**
Example 15 (Diastereomeric mixture)	0.86
Fast Moving isomer of **Example 15**	1.35
Slow Moving isomer of **Example 15**	0.26
Example 39 (Diastereomeric mixture)	0.47
Fast Moving isomer of **Example 39**	0.78
Slow Moving isomer of **Example 39**	0.02
Example 49 (Diastereomeric mixture)	0.126
Fast Moving isomer **of Example 49**	0.03
Slow Moving isomer of **Example 49**	5.78

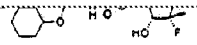
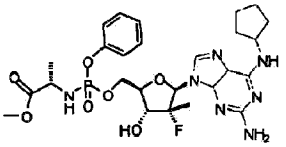
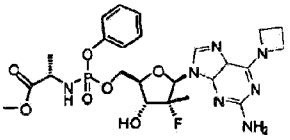
EXAMPLE 82

[0127] HCV replicon assay. HCV replicon RNA-containing Huh7 cells (clone A cells; Apath, LLC, St. Louis, Mo.) were kept at exponential growth in Dulbecco's modified Eagle's medium (high glucose) containing 10% fetal bovine serum, 4 mM L-glutamine and 1 mM sodium pyruvate, 1×nonessential amino acids, and G418 (1,000 μg/ml). Antiviral assays were performed in the same medium without G418. Cells were seeded in a 96-well plate at 1,500 cells per well, and test compounds were added immediately after seeding. Incubation time 4 days. At the end of the incubation step, total cellular RNA was isolated (RNeasy 96 kit; Qiagen). Replicon RNA and an internal control (TaqMan rRNA control reagents; Applied Biosystems) were amplified in a single-step multiplex RT-PCR protocol as recommended by the manufacturer. The HCV primers and probe were designed with Primer Express software (Applied Biosystems) and covered highly conserved 5'-untranslated region (UTR) sequences (sense, 5'-AGCCATGGCGTTAGTA(T)GAGTGT-3', and antisense, 5'-TTCCGCAGACCACTATGG-3'; probe, 5'-FAM-CCTCCAGGACCCCCCCTCCC-TAMRA-3').

[0128] To express the antiviral effectiveness of a compound, the threshold RT-PCR cycle of the test compound was subtracted from the average threshold RT-PCR cycle of the no-drug control (ΔCt_{HCV}). A ΔCt of 3.3 equals a 1-log 10 reduction (equal to the 90% effective concentration [EC_{90}]) in replicon RNA levels. The cytotoxicity of the test compound could also be expressed by calculating the ΔCt_{rRNA} values. The ΔΔCT specificity parameter could then be introduced (ΔCt_{HCV} - ΔCt_{rRNA}), in which the levels of HCV RNA are normalized for the rRNA levels and calibrated against the no-drug control.

Ex #	Compound	Log10 Reduction at 50μM	EC90 (μM)
5		-1.21	3.0
6		-0.45	ND
7		0.31	ND
8		-1.48	2.11
10		-1.25	19.15
11		-0.55	ND
12		0.31	ND
15		ND	0.86

Ex #	Compound	Log10 Reduction at 50μM	EC90 (μM)
			
25		-2.22	0.39
27		-2.25	0.66
28		-2.16	0.75
36		-1.64	21.9
39		-1.78	0.47
49		-2.69	0.126
53		-1.33	<0.3
54		-1.55	0.57
55		-2.38	<0.3

Ex #	Compound	Log10 Reduction at 50µM	EC90 (µM)
			
69		-2.25	< 0.3
70		-2.25	<0.3
[1](4-BrPh): 4-bromo-phenyl.			

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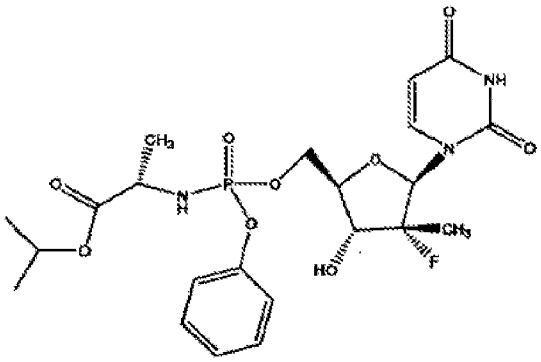
NUKLEOSID-PHOSPHORAMIDAT-PRODRUGS

PATENTKRAV

1. Forbindelse, der repræsenteres af formlen



2. Sammensætning omfattende forbindelsen ifølge krav 1 og et farmaceutisk acceptabelt medium.