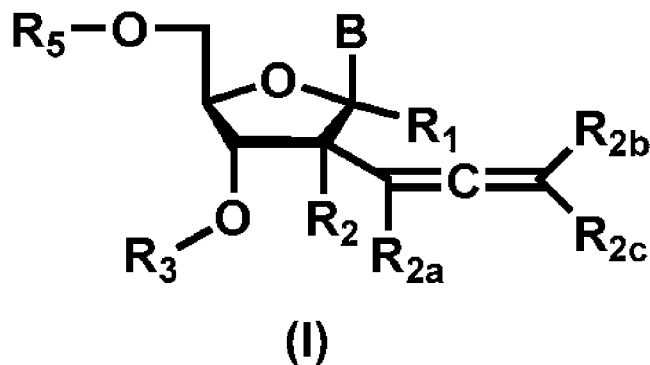




- (51) **International Patent Classification:**
A01N 43/04 (2006.01) *A61K 31/70* (2006.01)
- (21) **International Application Number:**
PCT/US2012/029381
- (22) **International Filing Date:**
16 March 2012 (16.03.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/453,286 16 March 2011 (16.03.2011) US
- (71) **Applicant (for all designated States except US):** ENANTA PHARMACEUTICALS, INC. [US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** OR, Yat, Sun [US/US]; 169 Fayette Street, Watertown, MA 02472 (US). MA, Jun [CN/US]; 53 Hill Road, Apt. 304, Belmont, MA 02478 (US). WANG, Guoqiang [US/US]; 65 Becket Road, Belmont, MA 02478 (US). KIM, In, Jong [KR/US]; 20 Phinney Road, Lexington, MA 02421 (US). LONG, Jiang [CN/US]; 15 Wallace Road, Wayland, MA 01778 (US). QIU, Yao-Ling [US/US]; 29 Linda Road, Andover, MA 01810 (US).
- (74) **Agents:** HARLAN, Edgar W. et al.; Elmore Patent Law Group, 484 Groton Road, Westford, MA 01886 (US).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))

(54) **Title:** 2'-ALLENE-SUBSTITUTED NUCLEOSIDE DERIVATIVES

(57) **Abstract:** The present invention relates to 2'-allene-substituted nucleoside derivatives of the general formula (I): As well as pharmaceutical compositions comprising such compounds and methods to treat or prevent an HIV infection, HBV infection, HCV infection or abnormal cellular proliferation, comprising administering said compounds or compositions. In addition, the present invention includes processes for the preparation of such compounds, and the related β-D and β-L-nucleoside derivatives.

2'-Allene-Substituted Nucleoside Derivatives

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/453,286 filed on March 16, 2011. The entire teachings of the above application are
5 incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical compositions useful as antiviral and antiproliferative agents. Specifically, the present invention relates to nucleoside derivatives with 2'-allenic substitution and methods for
10 their preparation and use.

BACKGROUND OF THE INVENTION

Synthetic nucleosides such as 5-iodouracil and 5-fluorouracil have been used for the treatment of cancer for many years. Since the 1980's, synthetic nucleosides have also been a focus of interest for the treatment of HIV and hepatitis.

15 In 1981, acquired immune deficiency syndrome (AIDS) was identified as a disease that severely compromises the human immune system, and that almost without exception leads to death. In 1983, the etiological cause of AIDS was determined to be the human immunodeficiency virus (HIV). In 1985, it was reported that the synthetic nucleoside 3'-azido-3'-deoxythymidine (AZT) inhibits the
20 replication of human immunodeficiency virus. Since then, a number of other synthetic nucleosides, including 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), and 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), have been proven to be effective against HIV. After cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA,
25 causing chain termination due to the absence of the 3'-hydroxyl group. They can also inhibit the viral enzyme reverse transcriptase.

The success of various synthetic nucleosides in inhibiting the replication of HIV in vivo or in vitro has led a number of researchers to design and test nucleosides that substitute a heteroatom for the carbon atom at the 3'-position of the nucleoside.
30 European Patent Publication No. 0,337,713 and U.S. Pat. No. 5,041,449, assigned to BioChem Pharma, Inc., disclose 2-substituted-4-substituted-1,3-dioxolanes that exhibit antiviral activity. U.S. Pat. No. 5,047,407 and European Patent Publication

No. 0,382,526, also assigned to BioChem Pharma, Inc., disclose that a number of 2-substituted-5-substituted-1,3-oxathiolane nucleosides have antiviral activity, and specifically report that 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (referred to below as BCH-189) has approximately the same activity against HIV as AZT, with
5 little toxicity.

It has also been disclosed that cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ("FTC") has potent HIV activity. Schinazi, et al., "Selective Inhibition of Human Immunodeficiency viruses by Racemates and Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl]-Cytosine" Antimicrobial Agents and
10 Chemotherapy, November 1992, 2423-2431. See also U.S. Pat. Nos. 5,210,085; 5,814,639; and 5,914,331.

Another virus that causes a serious human health problem is the hepatitis B virus (referred to below as "HBV"). HBV is second only to tobacco as a cause of human cancer. The mechanism by which HBV induces cancer is unknown. It is
15 postulated that it may directly trigger tumor development, or indirectly trigger tumor development through chronic inflammation, cirrhosis, and cell regeneration associated with the infection.

After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes
20 abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed.

Patients typically recover from acute hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended or indefinite period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis.
25 Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a
30 primary liver cancer.

In western industrialized countries, high risk groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is very similar to that of acquired immune deficiency syndrome, which accounts for

why HBV infection is common among patients with AIDS or AIDS related complex. However, HBV is more contagious than HIV.

Both FTC and 3TC exhibit activity against HBV. Furman, et al., "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-oxathiolane-5-yl]-Cytosine" Antimicrobial Agents and Chemotherapy, December 1992, pp. 2686-2692; and Cheng, et al., Journal of Biological Chemistry, Volume 267(20), pp. 13938-13942 (1992). Other compounds that exhibit activity against HBV in humans include Clevudine or CLV (L-FMAU) (Pharmasset, Inc. under license from The University of Georgia Research Foundation and Yale University), and L-dT and L-dC (Idenix Pharmaceuticals, Inc.).

HCV is the major causative agent for post-transfusion and for sporadic non A, non B hepatitis (Alter, H. J. (1990) *J. Gastro. Hepatol.* 1:78-94; Dienstag, J. L. (1983) *Gastro* 85:439-462). Despite improved screening, HCV still accounts for at least 25% of the acute viral hepatitis in many countries (Alter, H. J. (1990) *supra*; Dienstag, J. L. (1983) *supra*; Alter M. J. et al. (1990a) *J.A.M.A.* 264:2231-2235; Alter M. J. et al (1992) *N. Engl. J. Med.* 327:1899-1905; Alter, M. J. et al. (1990b) *N. Engl. J. Med.* 321:1494-1500). Infection by HCV is insidious in a high proportion of chronically infected (and infectious) carriers who may not experience clinical symptoms for many years. The high rate of progression of acute infection to chronic infection (70-100%) and liver disease (>50%), its world-wide distribution and lack of a vaccine make HCV a significant cause of morbidity and mortality. Currently, there are three types of interferon and a combination of interferon and ribavirin used to treat hepatitis C. Selection of patients for treatment may be determined by biochemical, virologic, and when necessary, liver biopsy findings, rather than presence or absence of symptoms.

Interferon is given by injection, and may have a number of side effects including flu-like symptoms including headaches, fever, fatigue, loss of appetite, nausea, vomiting, depression and thinning of hair. It may also interfere with the production of white blood cells and platelets by depressing the bone marrow. Periodic blood tests are required to monitor blood cells and platelets. Ribavirin can cause sudden, severe anemia, and birth defects so women should avoid pregnancy while taking it and for 6 months following treatment. The severity and type of side effects differ for each individual. Treatment of children with HCV is not currently approved but is under investigation. While 50-60% of patients respond to treatment initially,

lasting clearance of the virus occurs in only about 10-40% of patients. Treatment may be prolonged and given a second time to those who relapse after initial treatment. Re-treatment with bioengineered consensus interferon alone results in elimination of the virus in 58% of patients treated for one year. Side effects occur but the medication is usually well tolerated. Combined therapy (interferon and ribavirin) shows elimination of the virus in 47% after 6 months of therapy. Side effects from both drugs may be prominent.

A tumor is an unregulated, disorganized proliferation of cell growth. A tumor is malignant, or cancerous, if it has the properties of invasiveness and metastasis.

Invasiveness refers to the tendency of a tumor to enter surrounding tissue, breaking through the basal laminae that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis refers to the tendency of a tumor to migrate to other areas of the body and establish areas of proliferation away from the site of initial appearance.

Cancer is now the second leading cause of death in the United States. Over 8,000,000 persons in the United States have been diagnosed with cancer, with 1,208,000 new diagnoses expected in 1994. Over 500,000 people die annually from the disease in this country.

Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene." Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called protooncogenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene expression and mortality (transformed cells can grow indefinitely).

All of the various cell types of the body can be transformed into benign or malignant tumor cells. The most frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreas and then ovary. Other prevalent types of cancer

include leukemia, central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer.

Cancer is now primarily treated with one or a combination of three means of therapies: surgery, radiation and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon and skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, or in the treatment of disseminated neoplastic conditions such as leukemia.

Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of leukemia, as well as breast, lung, and testicular cancer.

There are five major classes of chemotherapeutic agents currently in use for the treatment of cancer: natural products and their derivatives; anthacyclines; alkylating agents; antiproliferatives (also called antimetabolites); and hormonal agents. Chemotherapeutic agents are often referred to as antineoplastic agents.

The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin and various nitrosoureas. A disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastrointestinal mucosa, and fetal tissue.

Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids.

Several synthetic nucleosides have been identified that exhibit anticancer activity. A well known nucleoside derivative with strong anticancer activity is 5-fluorouracil. 5-Fluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis, leukocytic thrombocytopenia, anorexia, pigmentation and edema. Derivatives of 5-fluorouracil with anti-cancer activity have been described in U.S. Pat. No. 4,336,381, and in Japanese patent publication Nos. 50-50383, 50-50384, 50-64281, 51-146482, and 53-84981.

U.S. Patent No. 4,000,137 discloses that the peroxidate oxidation product of inosine, adenosine or cytidine with methanol or ethanol has activity against lymphocytic leukemia.

5 Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug in the treatment of acute myeloid leukemia. It is also active against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher,
10 R. and Cheng, Y., "Purine and Pyrimidine Antimetabolites" *Cancer Medicine*, Chapter XV-1, 3rd Edition, Edited by J. Holland, et al., Lea and Febigol, publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA) is one of
15 the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F-araA is associated with the accumulation of cells at the G1/S phase boundary and in S phase; thus, it is a cell cycle S phase-specific drug. Incorporation of the active metabolite, F-araATP, retards DNA chain elongation. F-araA is also a potent inhibitor of
20 ribonucleotide reductase, the key enzyme responsible for the formation of dATP.

2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins' lymphoma, and hairy-cell leukemia.

In light of the fact that acquired immune deficiency syndrome, AIDS-related
25 complex, hepatitis B virus and hepatitis C virus have reached epidemic levels worldwide, and have tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat these diseases that have low toxicity to the host. Further, there is a need to provide new antiproliferative agents.

Therefore, it is an object of the present invention to provide a method and
30 composition for the treatment of human patients or other host animals infected with HIV.

It is another object of the present invention to provide a method and composition for the treatment of human patients infected with hepatitis B or C.

It is a further object of the present invention to provide new antiproliferative agents.

It is still another object of the present invention to provide a new process for the preparation of 2'-allene-substituted nucleoside derivatives of the present invention.

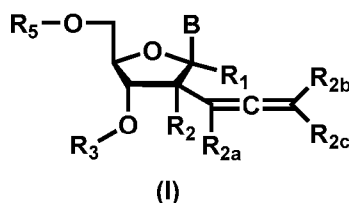
5

SUMMARY OF THE INVENTION

The present invention includes β -D and β -L-nucleoside derivatives, pharmaceutical compositions comprising such compounds, as well as methods to treat or prevent an HIV infection, HBV infection, HCV infection or abnormal cellular proliferation, comprising administering said compounds or compositions. In addition, the present invention includes processes for the preparation of such compounds, and the related β -D and β -L-nucleoside derivatives.

10

The compounds of the invention are 2'-allene-substituted nucleoside derivatives of the general formula (I):



15

or the β -L enantiomer thereof, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof, wherein:

20 R_1 is selected from the group consisting of:

- 1) hydrogen;
- 2) $-\text{CN}$;
- 3) halogen;
- 4) $-\text{N}_3$; and

25 5) Substituted or unsubstituted $-\text{C}_1\text{-C}_8$ alkyl;

R_{2a} , R_{2b} and R_{2c} are each independently selected from the group consisting of: hydrogen, halogen, and substituted or unsubstituted $-\text{C}_1\text{-C}_8$ alkyl;

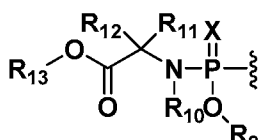
R₂ is selected from the group consisting of:

- 1) halogen;
- 2) -CN;
- 3) -N₃; and
- 5 4) OR₆; where R₆ is selected from the group consisting of: hydrogen, hydroxy protecting group, -C(O)R₇, -C(O)OR₇, and -C(O)NR_{8a}R_{8b}; wherein R₇ is selected from the group consisting of: substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, substituted or unsubstituted -C₂-C₈ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{8a} and R_{8b} are each independently selected from the group consisting of: hydrogen and R₇; or alternatively R_{8a} and R_{8b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;
- 10
- 15 R₃ is R₆; or alternatively R₂ is -OR₆ and R₃ and R₆ together form a group selected from: -C(Me)₂-, -C(CH₂)₄-, -CH(Ph)-, -CH(OMe)- and -P(O)(OH)-.

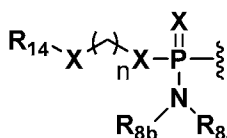
- B is selected from the group consisting of: substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic;
- 20 preferably a heterocycle containing at least one nitrogen atom.

R₅ is selected from the group consisting of:

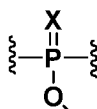
- 1) hydrogen;
- 2) R₆;
- 25 3) -P(O)(OR_{7a})(OR_{7b}); wherein R_{7a} and R_{7b} are each independently selected from the group consisting of a) hydrogen; b) unsubstituted or substituted -C₁-C₈ alkyl;
- 4) -P(O)(OR_{7a})-O-P(O)(OR_{7b})(OR_{7c}); wherein R_{7a} and R_{7b} are previously defined; R_{7c} is selected from the group consisting of a) hydrogen; b)
- 30 unsubstituted or substituted -C₁-C₈ alkyl;
- 5) -P(O)(OR_{7a})-O-P(O)(OR_{7b})-O-P(O)(OR_{7c})(OR_{7d}); wherein R_{7a}, R_{7b} and R_{7c} are previously defined; R_{7d} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted -C₁-C₈ alkyl;



- 6) $\text{R}_{13}-\text{O}-\text{C}(=\text{O})-\text{C}(\text{R}_{12})(\text{R}_{11})-\text{N}(\text{R}_{10})-\text{P}(=\text{X})(\text{O}-\text{R}_9)-$; where X is O or S; R_9 is R_7 wherein R_7 is previously defined; R_{10} , R_{11} and R_{12} are each independently selected from the group consisting of : a) hydrogen; b) unsubstituted or substituted $-\text{C}_1-\text{C}_8$ alkyl; alternatively, (c) R_{11} is hydrogen, and R_{12} and R_{10} are taken together with the atoms to which they are attached to form a heterocyclic ring; or d) R_{11} and R_{12} are taken together with the carbon atom to which they are attached to form a ring; and R_{13} is hydrogen or R_7 , wherein R_7 is previously defined; and



- 7) $\text{R}_{14}-\text{O}-\text{P}(=\text{X})(\text{O}-\text{R}_{14})-\text{N}(\text{R}_{8a})(\text{R}_{8b})-$, where X is O or S; n is 1-4; R_{8a} and R_{8b} are as previously defined; R_{14} is hydrogen or $-(\text{CO})-\text{R}_7$, wherein R_7 is as previously defined.



Or, R_5 and R_3 are taken together to form $\text{O}-\text{P}(=\text{X})(\text{O}-\text{R}_6)-$, where X is O or S; and R_6 is as previously defined.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, prodrug, salt of a prodrug, stereoisomer, tautomer, solvate, or combination thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present invention provides a method of inhibiting the replication of an RNA or DNA containing virus comprising contacting said virus with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt, prodrug, salt of a pro drug, stereoisomer, tautomer, solvate, or combination thereof.

Particularly, this invention is directed to methods of inhibiting the replication of HIV, HBV and HCV.

In still another embodiment, the present invention provides a method of treating or preventing infection caused by an RNA or DNA-containing virus

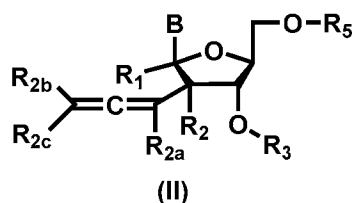
comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, prodrug, salt of a prodrug, stereoisomer, or tautomer, solvate, or combination thereof. Particularly, this invention is directed to methods of treating or preventing infection caused by HIV, HBV and HCV.

Yet another embodiment of the present invention provides the use of a compound or combination of compounds of the present invention, or a therapeutically acceptable salt form, prodrug, salt of a prodrug, stereoisomer or tautomer, solvate, or combination thereof, as defined hereinafter, in the preparation of a medicament for the treatment or prevention of infection caused by RNA or DNA-containing virus, specifically HIV, HBV and HCV.

DETAILED DESCRIPTION OF THE INVENTION

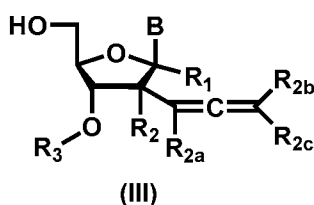
In a first embodiment of the present invention is a compound of Formula (I) as illustrated above, or a pharmaceutically acceptable salt, ester or prodrug thereof.

In a second embodiment of the present invention is the β -L enantiomer of 2'-allene-substituted nucleoside derivative represented by formula (II), or pharmaceutically acceptable salt or prodrug thereof:



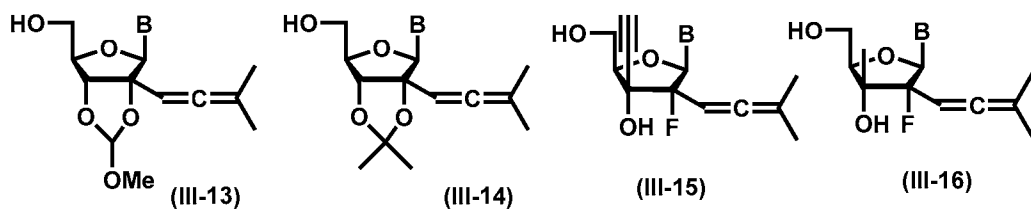
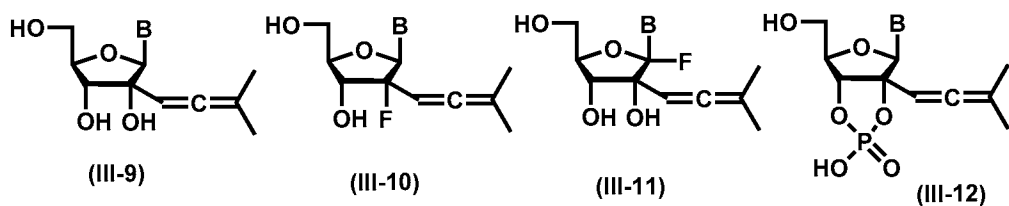
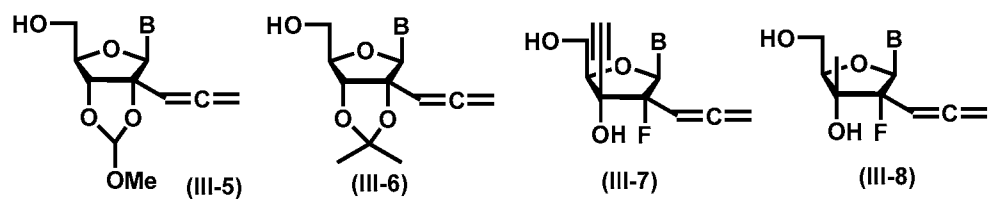
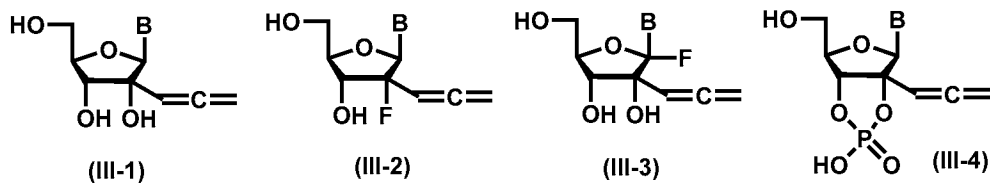
wherein R_1 , R_2 , R_{2a} , R_{2b} , R_{2c} , R_3 , R_5 , B are as previously defined.

In a particular embodiment of the present invention is a β -D 2'-allene-substituted nucleoside derivatives represented by formula (III), or its β -L enantiomer, or pharmaceutically acceptable salt or prodrug thereof:

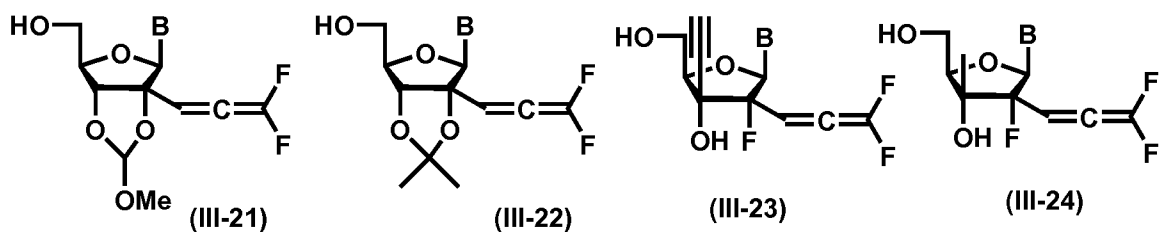
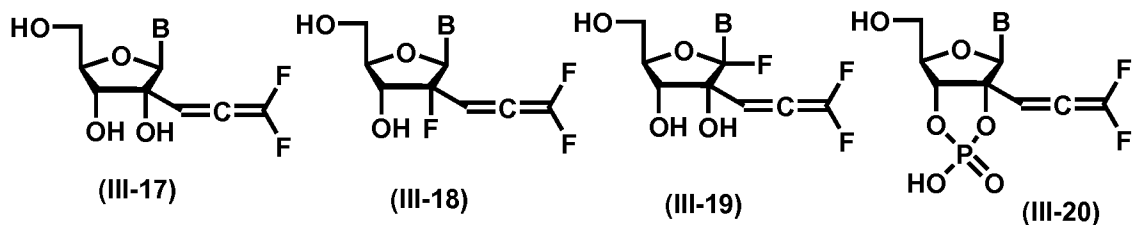


wherein R₁, R₂, R_{2a}, R_{2b}, R_{2c}, R₃, B are as previously defined.

Illustrative structures of formula (III) can be represented, but not limited, by formula (III-1~III-24) and the β-L enantiomers thereof:



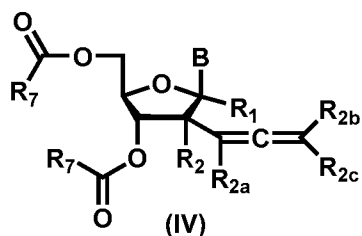
5



wherein B is as previously defined;

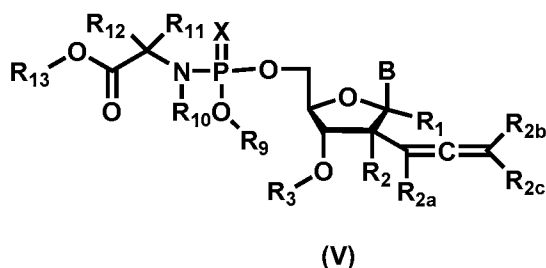
In another particular embodiment of the present invention is a β -D 2'-allene-substituted nucleoside diester derivatives represented by formula (IV), or its β -L

5 enantiomer, or pharmaceutically acceptable salt or prodrug thereof:



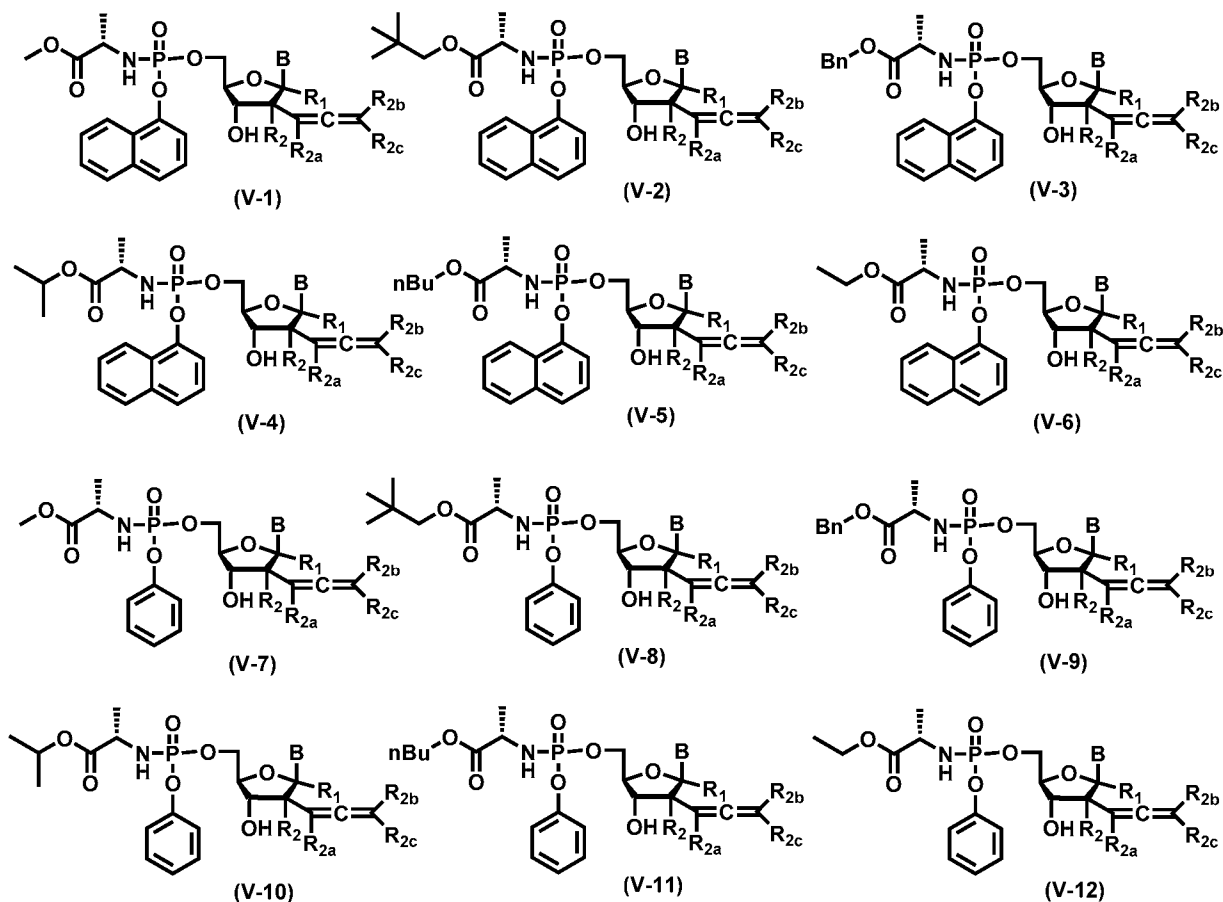
wherein R_1 , R_2 , R_{2a} , R_{2b} , R_{2c} , R_7 , and B are as previously defined.

In another particular embodiment of the present invention is a β -D 2'-allene-substituted nucleoside phosphoramidate derivative represented by formula (V), or its β -L enantiomer, or a pharmaceutically acceptable salt or prodrug thereof:



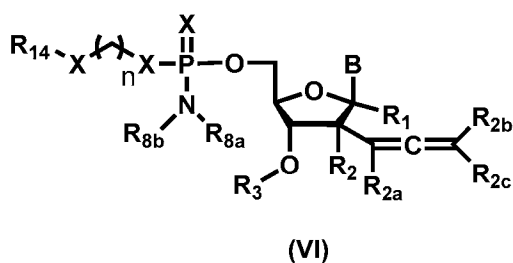
wherein R_1 , R_2 , R_{2a} , R_{2b} , R_{2c} , R_3 , R_7 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , and B are as previously defined. X is O or S.

15 Illustrative structures of formula (V) can be represented, but not limited, by formula (V-1~V-12):



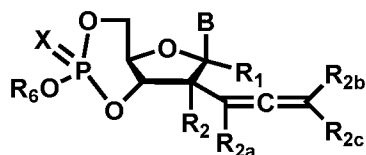
wherein R_1 , R_2 , R_{2a} , R_{2b} , R_{2c} , and B are as previously defined.

In another particular embodiment of the present invention is a β -D 2'-allene-substituted nucleoside phosphate derivative represented by formula (VI), or its β -L enantiomer, or a pharmaceutically acceptable salt or prodrug thereof:



wherein R_1 , R_2 , R_{2a} , R_{2b} , R_{2c} , R_3 , R_{8a} , R_{8b} , R_{14} , and B are as previously defined. X is O or S. n is 1~4.

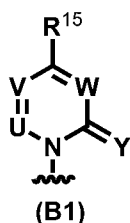
In still another particular embodiment of the present invention is a β -D 2'-allene-substituted nucleoside phosphate derivative represented by formula (VII), or its β -L enantiomer, or a pharmaceutically acceptable salt or prodrug thereof:



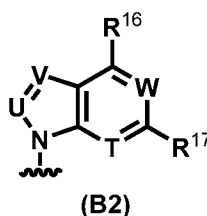
(VII)

wherein R₁, R₂, R_{2a}, R_{2b}, R_{2c}, R₆, and B are as previously defined. X is O or S.

In yet another particular embodiment of the present invention is a β-D 2'-allene-substituted nucleoside derivative represented by formula (I), or its β-L enantiomer, or pharmaceutically acceptable salt or prodrug thereof, with B at each occurrence is an optionally substituted aryl, heteroaryl, or heterocyclic; preferably a heterocycle moiety containing at least one nitrogen, most preferably a pyrimidinyl, purinyl group or the like of the general formula of (B1) and (B2):



(B1)



(B2)

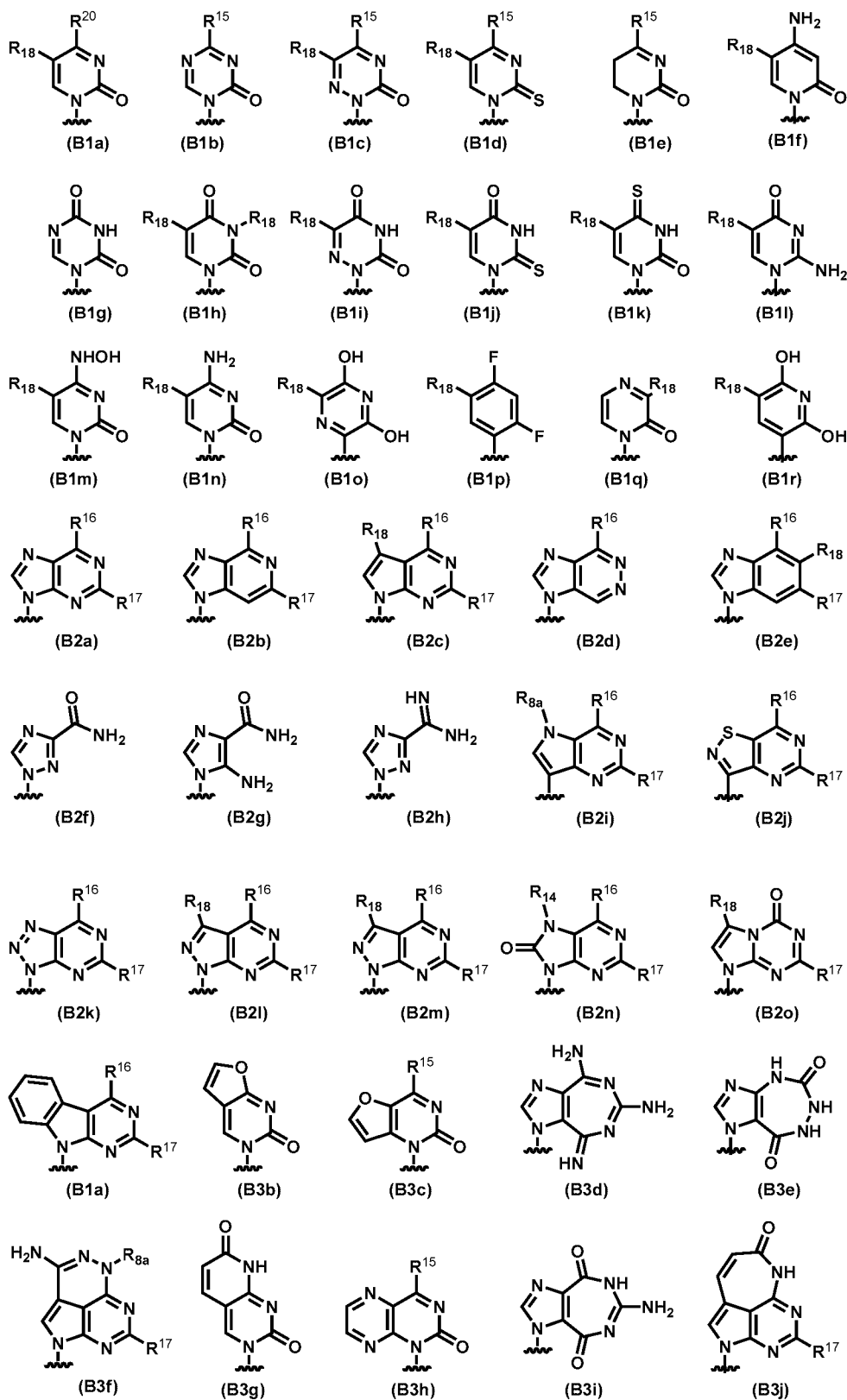
wherein:

Y is selected from a group consisting of: O, S, NR_{8a}, NC(O)R₇, NC(O)OR₇ and NC(O)NR_{8a}R_{8b};

T, U, V and W are independently N or CR₁₈; wherein R₁₈ is selected from a group consisting of: hydrogen, halogen, -CN, -C(O)R₇, -C(O)NR_{8a}R_{8b}, -NO₂, -N₃, -OR₇, -SR₇, -NR_{8a}R_{8b}, -OC(O)R₇, -OC(O)OR₇, -NHC(O)R₇, -NHC(O)OR₇ and -NHC(O)NR_{8a}R_{8b}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic, substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, substituted or unsubstituted -C₂-C₈ alkynyl;

R¹⁵, R¹⁶ and R¹⁷ at each occurrence are independently selected from a group consisting of: hydrogen, halogen, -CN, -C(O)R₇, -C(O)NR_{8a}R_{8b}, -NO₂, -N₃, -OR₇, -SR₇, -NR_{8a}R_{8b}, -OC(O)R₇, -OC(O)OR₇, -NHC(O)R₇, -NHC(O)OR₇ and -NHC(O)NR_{8a}R_{8b}, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic, substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, substituted or unsubstituted -C₂-C₈ alkynyl.

Illustrative structures of B are represented by formula (B1a~B1r), (B2a~B2o), and (B3a~B3j):

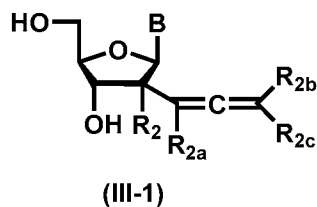


5

wherein R_{8a} , R_{18} , R^{15} , R^{16} and R^{17} are as previously defined.

Representative compounds of the invention include, but are not limited to, the following compounds illustrated in Table 1 to Table 5.

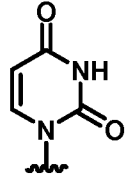
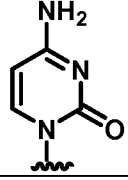
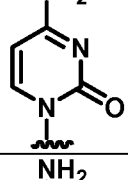
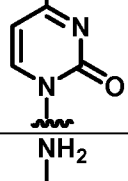
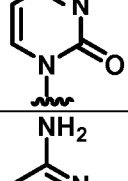
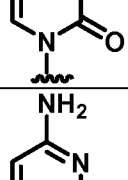
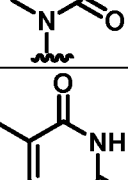
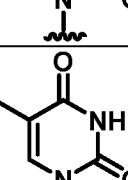
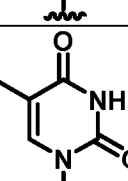
Compounds in Table 1 are represented by Formula (III-1) wherein R_{2a} , R_{2b} , R_{2c} , and B are delineated for each example in Table 1.

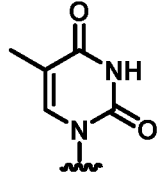
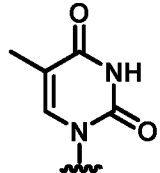
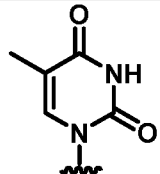
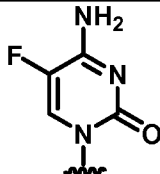
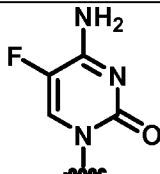
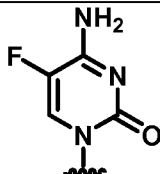
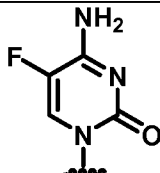
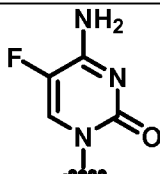
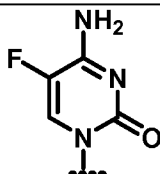
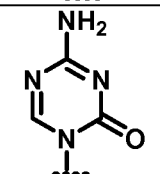


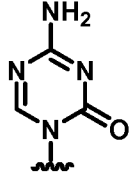
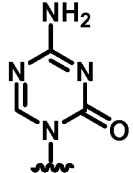
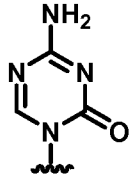
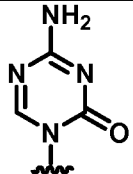
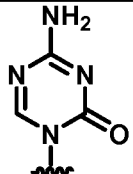
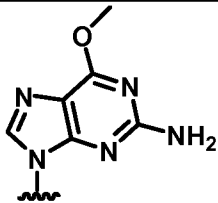
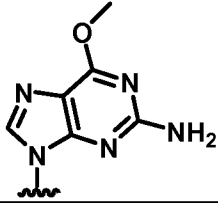
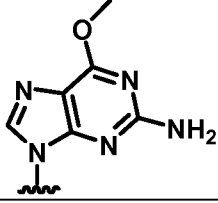
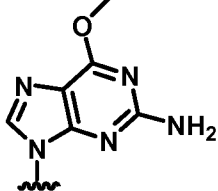
5

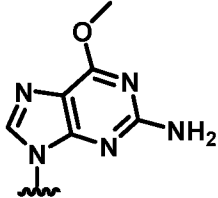
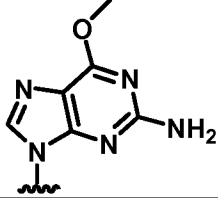
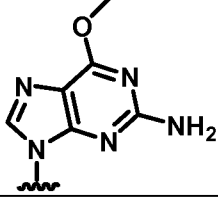
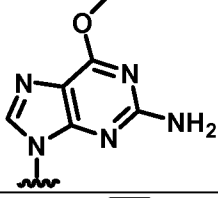
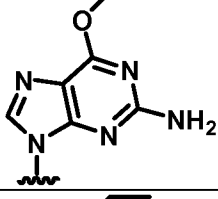
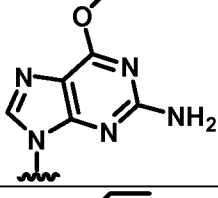
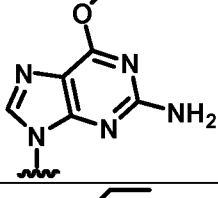
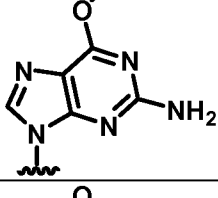
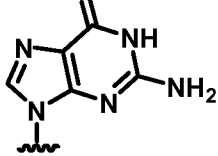
TABLE 1

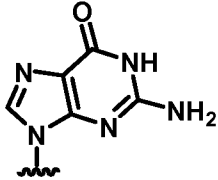
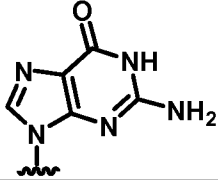
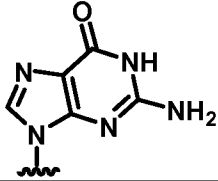
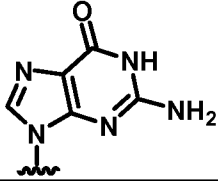
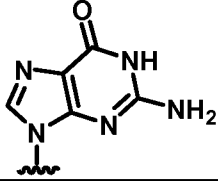
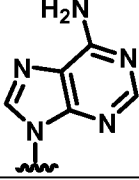
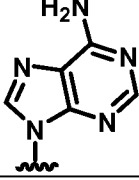
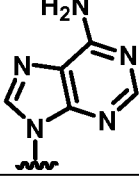
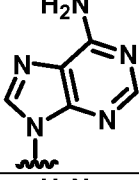
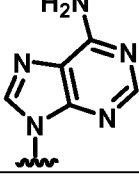
Example#	R_{2a}	R_{2b}	R_{2c}	R_2	B
1	H	H	H	OH	
2	H	H	H	F	
3	H	Me	Me	OH	
4	H	Me	Me	F	
5	H	F	F	OH	

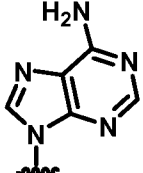
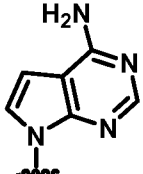
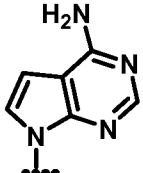
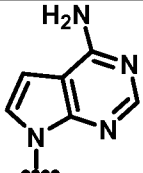
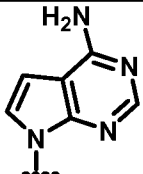
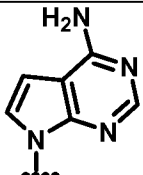
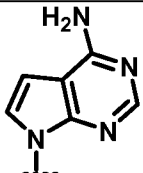
6	H	F	F	F	
7	H	H	H	OH	
8	H	H	H	F	
9	H	Me	Me	OH	
10	H	Me	Me	F	
11	H	F	F	OH	
12	H	F	F	F	
13	H	H	H	OH	
14	H	H	H	F	
15	H	Me	Me	OH	

16	H	Me	Me	F	
17	H	F	F	OH	
18	H	F	F	F	
19	H	H	H	OH	
20	H	H	H	F	
21	H	Me	Me	OH	
22	H	Me	Me	F	
23	H	F	F	OH	
24	H	F	F	F	
25	H	H	H	OH	

26	H	H	H	F	
27	H	Me	Me	OH	
28	H	Me	Me	F	
29	H	F	F	OH	
30	H	F	F	F	
31	H	H	H	OH	
32	H	H	H	F	
33	H	Me	Me	OH	
34	H	Me	Me	F	

35	H	F	F	OH	
36	H	F	F	F	
37	H	H	H	OH	
38	H	H	H	F	
39	H	Me	Me	OH	
40	H	Me	Me	F	
41	H	F	F	OH	
42	H	F	F	F	
43	H	H	H	OH	

44	H	H	H	F	
45	H	Me	Me	OH	
46	H	Me	Me	F	
47	H	F	F	OH	
48	H	F	F	F	
49	H	H	H	OH	
50	H	H	H	F	
51	H	Me	Me	OH	
52	H	Me	Me	F	
53	H	F	F	OH	

54	H	F	F	F	
55	H	H	H	OH	
56	H	H	H	F	
57	H	Me	Me	OH	
58	H	Me	Me	F	
59	H	F	F	OH	
60	H	F	F	F	

Compounds in Table 2 are represented by Formula (IV-1) wherein R_2 , R_7 , R_{2a} , R_{2b} , R_{2c} , and B are delineated for each example in Table 2.

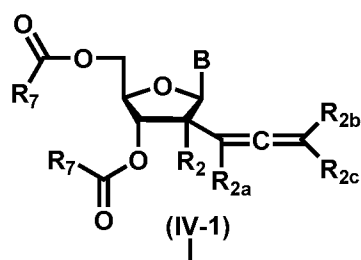
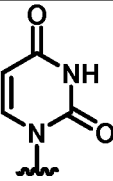
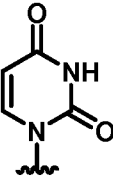
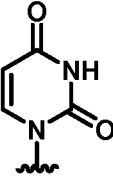
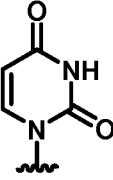
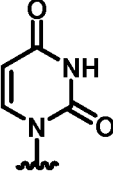
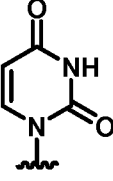
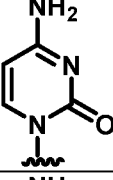
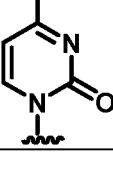
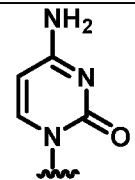
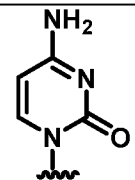
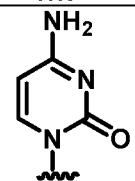
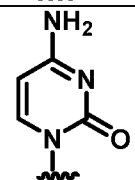
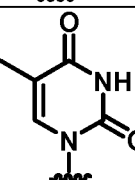
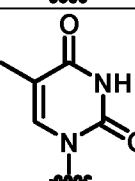
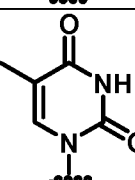
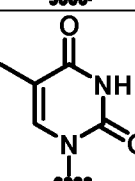
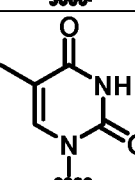
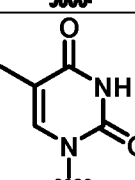
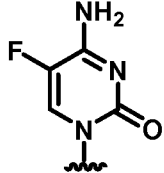
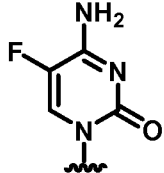
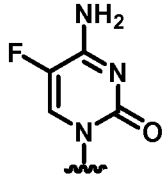
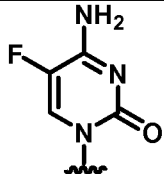
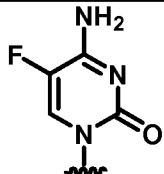
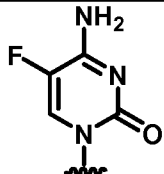
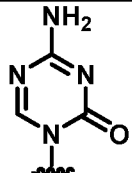
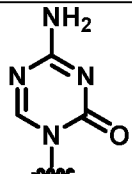
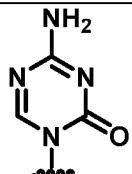
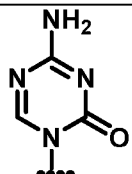
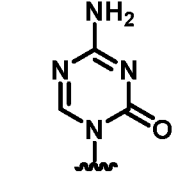
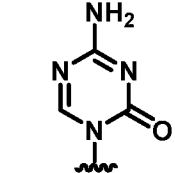
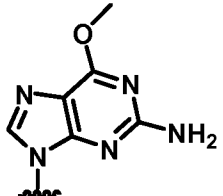
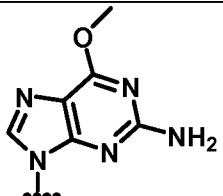
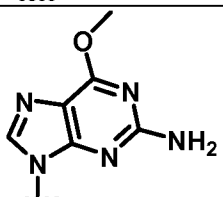
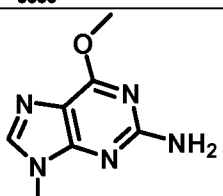
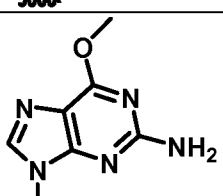
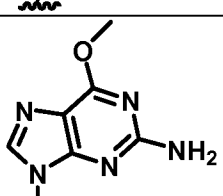
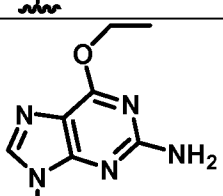


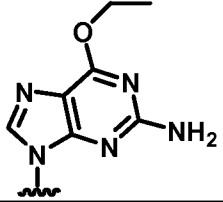
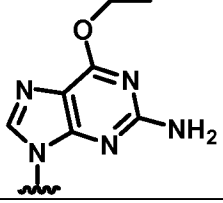
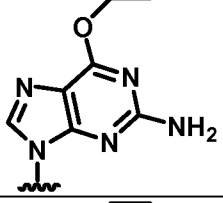
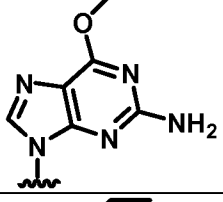
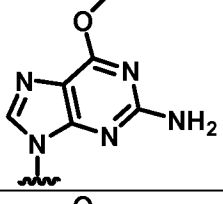
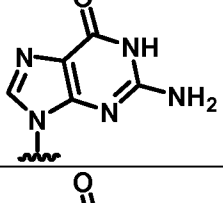
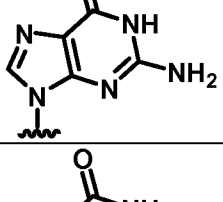
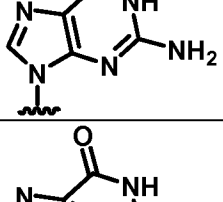
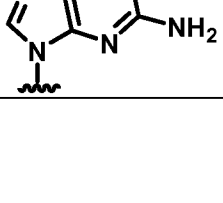
TABLE 2

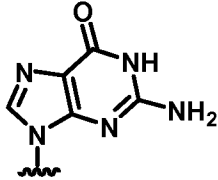
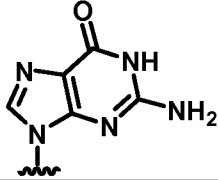
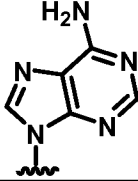
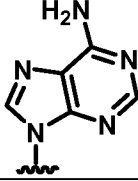
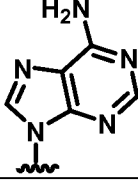
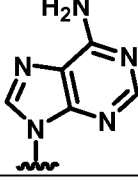
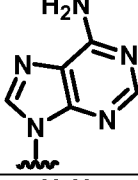
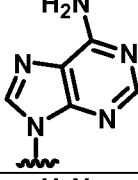
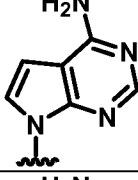
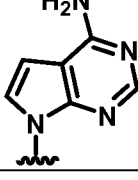
Example#	R _{2a}	R _{2b}	R _{2c}	R ₂	R ₇	B
61	H	H	H	OH	i-Pr	
62	H	H	H	F	i-Pr	
63	H	Me	Me	OH	i-Pr	
64	H	Me	Me	F	i-Pr	
65	H	F	F	OH	i-Pr	
66	H	F	F	F	i-Pr	
67	H	H	H	OH	i-Pr	
68	H	H	H	F	i-Pr	

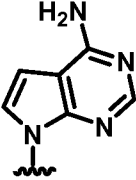
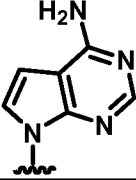
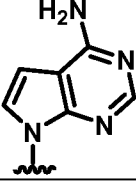
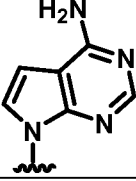
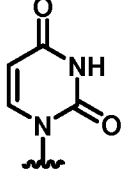
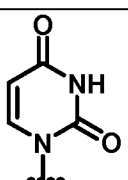
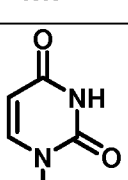
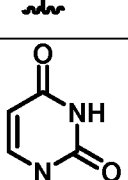
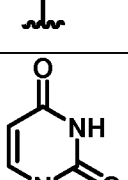
69	H	Me	Me	OH	i-Pr	
70	H	Me	Me	F	i-Pr	
71	H	F	F	OH	i-Pr	
72	H	F	F	F	i-Pr	
73	H	H	H	OH	i-Pr	
74	H	H	H	F	i-Pr	
75	H	Me	Me	OH	i-Pr	
76	H	Me	Me	F	i-Pr	
77	H	F	F	OH	i-Pr	
78	H	F	F	F	i-Pr	

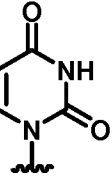
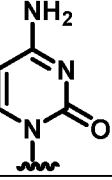
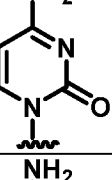
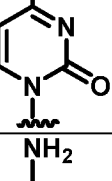
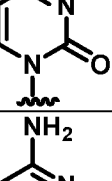
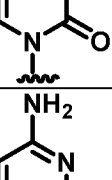
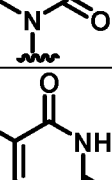
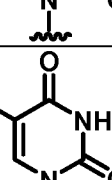
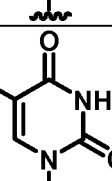
79	H	H	H	OH	i-Pr	
80	H	H	H	F	i-Pr	
81	H	Me	Me	OH	i-Pr	
82	H	Me	Me	F	i-Pr	
83	H	F	F	OH	i-Pr	
84	H	F	F	F	i-Pr	
85	H	H	H	OH	i-Pr	
86	H	H	H	F	i-Pr	
87	H	Me	Me	OH	i-Pr	
88	H	Me	Me	F	i-Pr	

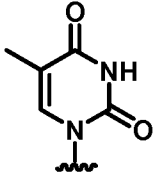
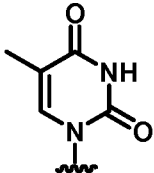
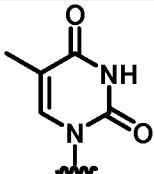
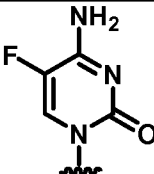
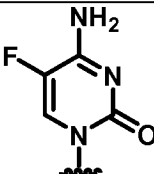
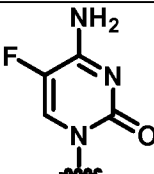
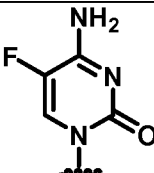
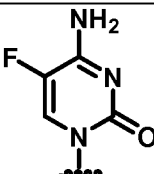
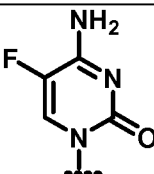
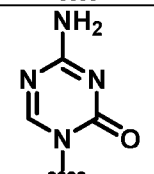
89	H	F	F	OH	i-Pr	
90	H	F	F	F	i-Pr	
91	H	H	H	OH	i-Pr	
92	H	H	H	F	i-Pr	
93	H	Me	Me	OH	i-Pr	
94	H	Me	Me	F	i-Pr	
95	H	F	F	OH	i-Pr	
96	H	F	F	F	i-Pr	
97	H	H	H	OH	i-Pr	

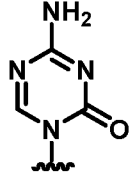
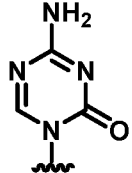
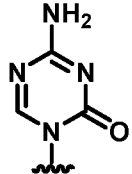
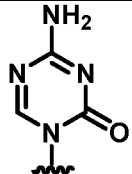
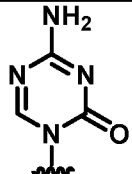
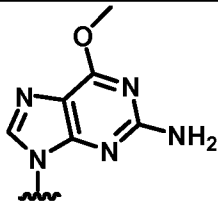
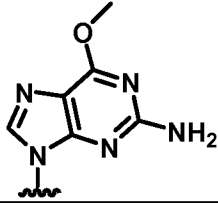
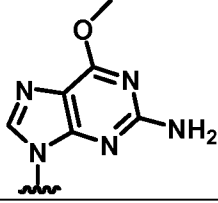
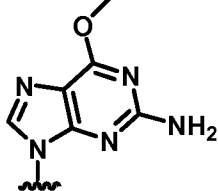
98	H	H	H	F	i-Pr	
99	H	Me	Me	OH	i-Pr	
100	H	Me	Me	F	i-Pr	
101	H	F	F	OH	i-Pr	
102	H	F	F	F	i-Pr	
103	H	H	H	OH	i-Pr	
104	H	H	H	F	i-Pr	
105	H	Me	Me	OH	i-Pr	
106	H	Me	Me	F	i-Pr	

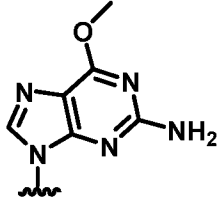
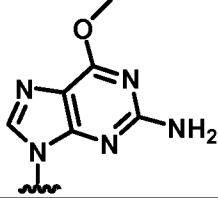
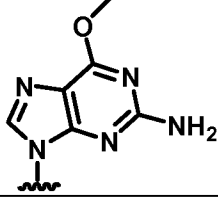
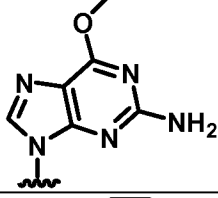
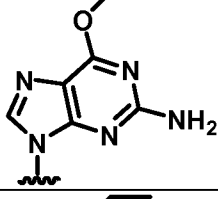
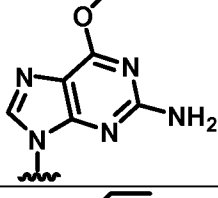
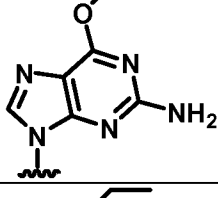
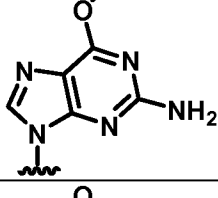
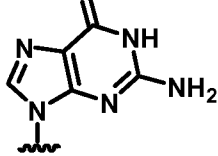
107	H	F	F	OH	i-Pr	
108	H	F	F	F	i-Pr	
109	H	H	H	OH	i-Pr	
110	H	H	H	F	i-Pr	
111	H	Me	Me	OH	i-Pr	
112	H	Me	Me	F	i-Pr	
113	H	F	F	OH	i-Pr	
114	H	F	F	F	i-Pr	
115	H	H	H	OH	i-Pr	
116	H	H	H	F	i-Pr	

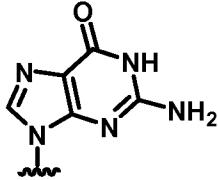
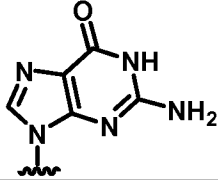
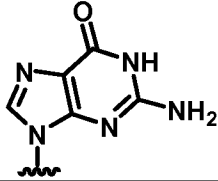
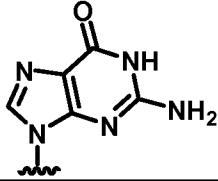
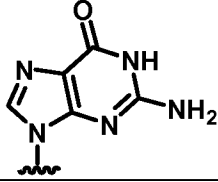
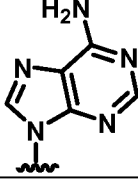
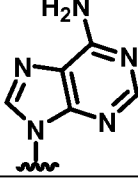
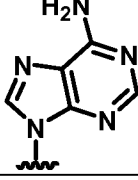
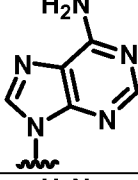
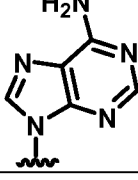
117	H	Me	Me	OH	i-Pr	
118	H	Me	Me	F	i-Pr	
119	H	F	F	OH	i-Pr	
120	H	F	F	F	i-Pr	
121	H	H	H	OH	Et	
122	H	H	H	F	Et	
123	H	Me	Me	OH	Et	
124	H	Me	Me	F	Et	
125	H	F	F	OH	Et	

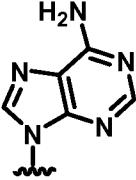
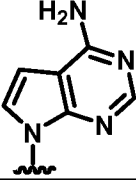
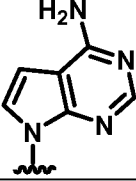
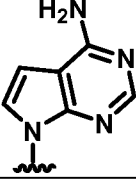
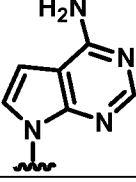
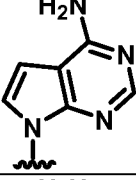
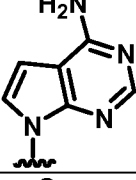
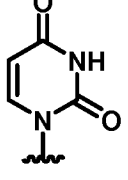
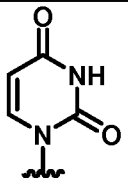
126	H	F	F	F	Et	
127	H	H	H	OH	Et	
128	H	H	H	F	Et	
129	H	Me	Me	OH	Et	
130	H	Me	Me	F	Et	
131	H	F	F	OH	Et	
132	H	F	F	F	Et	
133	H	H	H	OH	Et	
134	H	H	H	F	Et	
135	H	Me	Me	OH	Et	

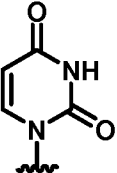
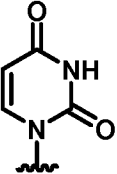
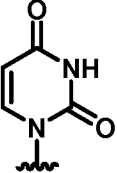
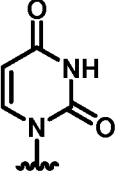
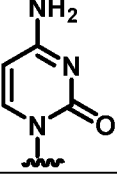
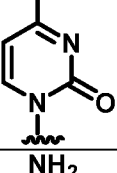
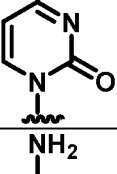
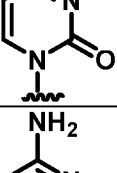
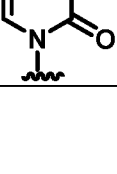
136	H	Me	Me	F	Et	
137	H	F	F	OH	Et	
138	H	F	F	F	Et	
139	H	H	H	OH	Et	
140	H	H	H	F	Et	
141	H	Me	Me	OH	Et	
142	H	Me	Me	F	Et	
143	H	F	F	OH	Et	
144	H	F	F	F	Et	
145	H	H	H	OH	Et	

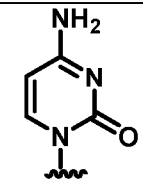
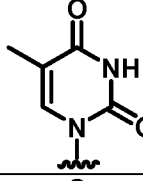
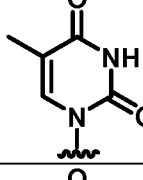
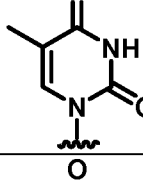
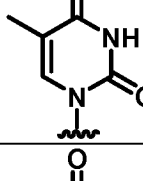
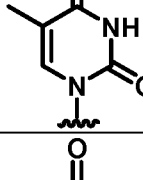
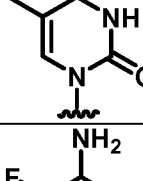
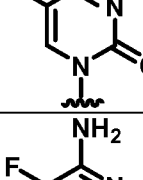
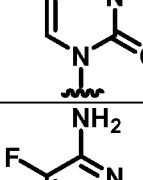
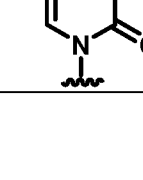
146	H	H	H	F	Et	
147	H	Me	Me	OH	Et	
148	H	Me	Me	F	Et	
149	H	F	F	OH	Et	
150	H	F	F	F	Et	
151	H	H	H	OH	Et	
152	H	H	H	F	Et	
153	H	Me	Me	OH	Et	
154	H	Me	Me	F	Et	

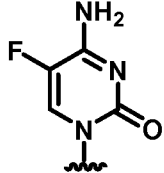
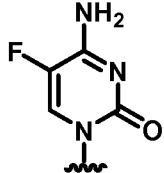
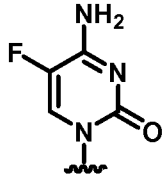
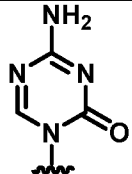
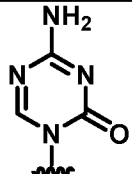
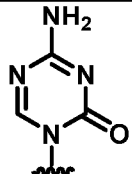
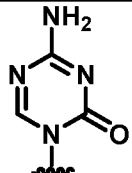
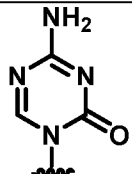
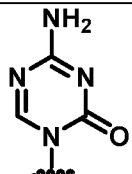
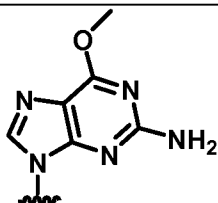
155	H	F	F	OH	Et	
156	H	F	F	F	Et	
157	H	H	H	OH	Et	
158	H	H	H	F	Et	
159	H	Me	Me	OH	Et	
160	H	Me	Me	F	Et	
161	H	F	F	OH	Et	
162	H	F	F	F	Et	
163	H	H	H	OH	Et	

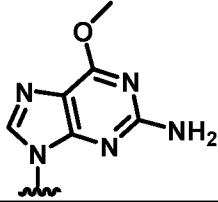
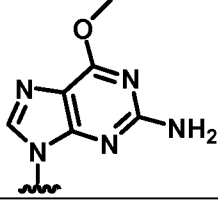
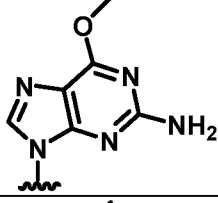
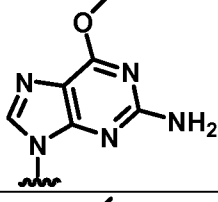
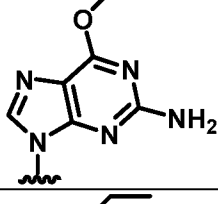
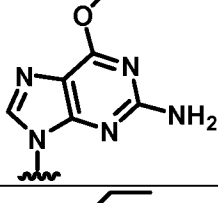
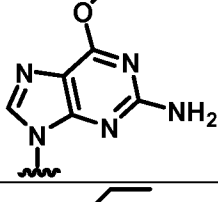
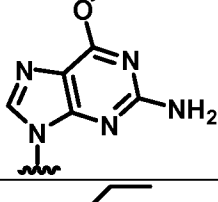
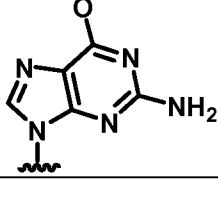
164	H	H	H	F	Et	
165	H	Me	Me	OH	Et	
166	H	Me	Me	F	Et	
167	H	F	F	OH	Et	
168	H	F	F	F	Et	
169	H	H	H	OH	Et	
170	H	H	H	F	Et	
171	H	Me	Me	OH	Et	
152	H	Me	Me	F	Et	
173	H	F	F	OH	Et	

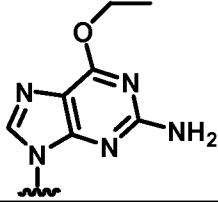
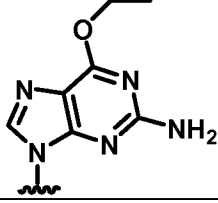
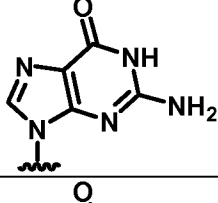
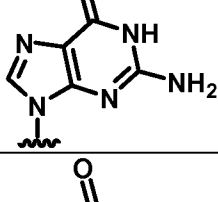
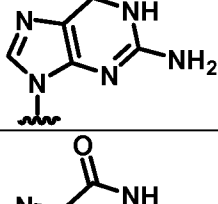
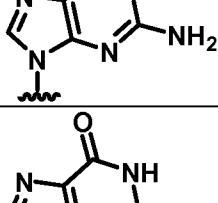
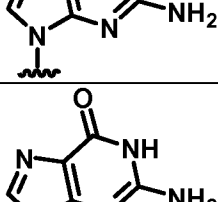
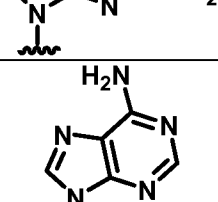
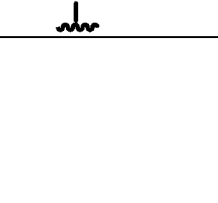
174	H	F	F	F	Et	
175	H	H	H	OH	Et	
176	H	H	H	F	Et	
177	H	Me	Me	OH	Et	
178	H	Me	Me	F	Et	
179	H	F	F	OH	Et	
180	H	F	F	F	Et	
181	H	H	H	OH	i-Bu	
182	H	H	H	F	i-Bu	

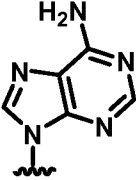
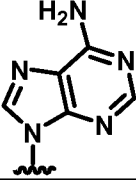
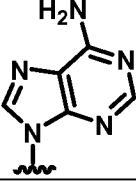
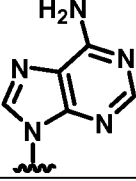
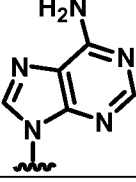
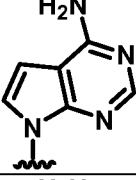
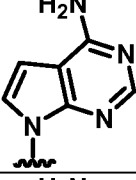
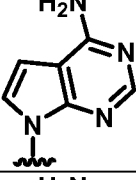
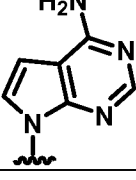
183	H	Me	Me	OH	i-Bu	
184	H	Me	Me	F	i-Bu	
185	H	F	F	OH	i-Bu	
186	H	F	F	F	i-Bu	
187	H	H	H	OH	i-Bu	
188	H	H	H	F	i-Bu	
189	H	Me	Me	OH	i-Bu	
190	H	Me	Me	F	i-Bu	
191	H	F	F	OH	i-Bu	

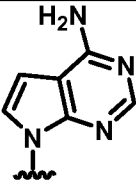
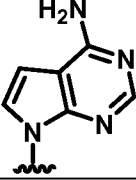
192	H	F	F	F	i-Bu	
193	H	H	H	OH	i-Bu	
194	H	H	H	F	i-Bu	
195	H	Me	Me	OH	i-Bu	
196	H	Me	Me	F	i-Bu	
197	H	F	F	OH	i-Bu	
198	H	F	F	F	i-Bu	
199	H	H	H	OH	i-Bu	
200	H	H	H	F	i-Bu	
201	H	Me	Me	OH	i-Bu	

202	H	Me	Me	F	i-Bu	
203	H	F	F	OH	i-Bu	
204	H	F	F	F	i-Bu	
205	H	H	H	OH	i-Bu	
206	H	H	H	F	i-Bu	
207	H	Me	Me	OH	i-Bu	
208	H	Me	Me	F	i-Bu	
209	H	F	F	OH	i-Bu	
210	H	F	F	F	i-Bu	
211	H	H	H	OH	i-Bu	

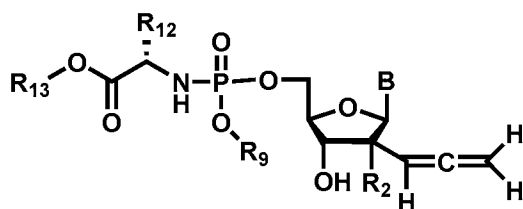
212	H	H	H	F	i-Bu	
213	H	Me	Me	OH	i-Bu	
214	H	Me	Me	F	i-Bu	
215	H	F	F	OH	i-Bu	
216	H	F	F	F	i-Bu	
217	H	H	H	OH	i-Bu	
218	H	H	H	F	i-Bu	
219	H	Me	Me	OH	i-Bu	
220	H	Me	Me	F	i-Bu	

221	H	F	F	OH	i-Bu	
222	H	F	F	F	i-Bu	
223	H	H	H	OH	i-Bu	
224	H	H	H	F	i-Bu	
225	H	Me	Me	OH	i-Bu	
226	H	Me	Me	F	i-Bu	
227	H	F	F	OH	i-Bu	
228	H	F	F	F	i-Bu	
229	H	H	H	OH	i-Bu	

230	H	H	H	F	i-Bu	
231	H	Me	Me	OH	i-Bu	
232	H	Me	Me	F	i-Bu	
233	H	F	F	OH	i-Bu	
234	H	F	F	F	i-Bu	
235	H	H	H	OH	i-Bu	
236	H	H	H	F	i-Bu	
237	H	Me	Me	OH	i-Bu	
238	H	Me	Me	F	i-Bu	

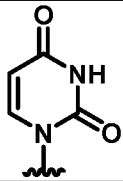
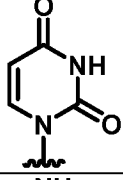
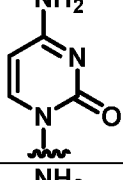
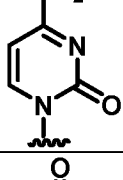
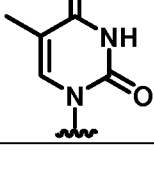
239	H	F	F	OH	i-Bu	
240	H	F	F	F	i-Bu	

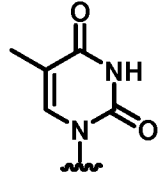
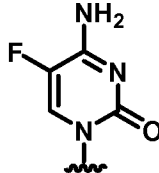
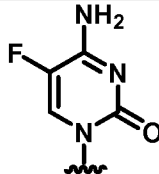
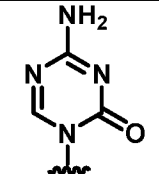
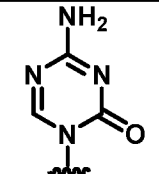
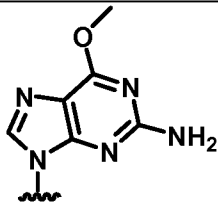
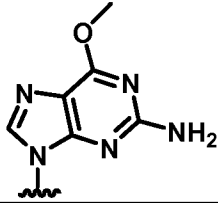
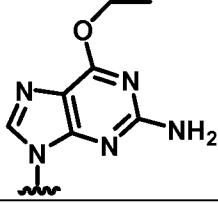
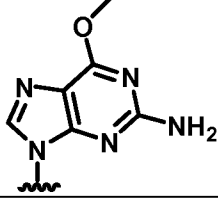
Compounds in Table 3 are represented by Formula (V-1) wherein R_2 , R_9 , R_{12} , R_{13} , and B are delineated for each example in Table 3.

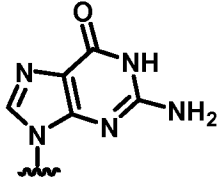
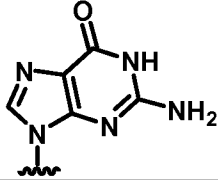
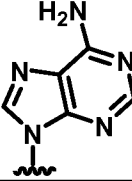
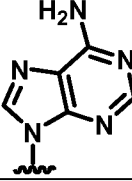
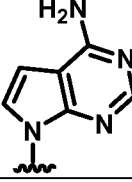
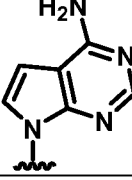
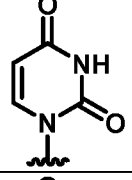
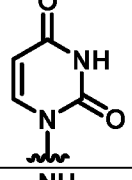
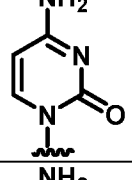
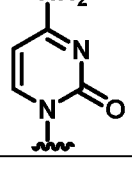


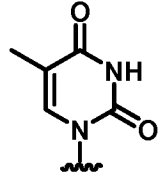
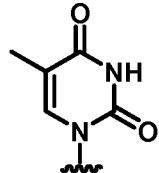
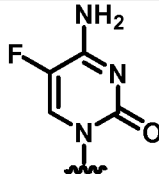
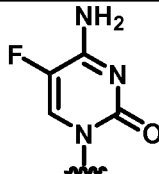
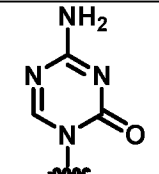
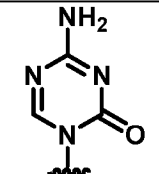
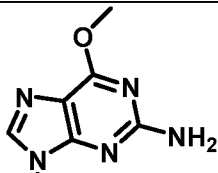
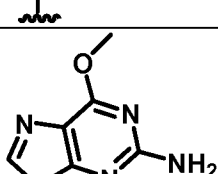
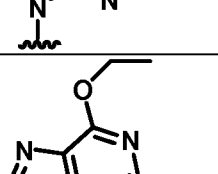
(V-1)

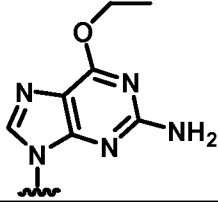
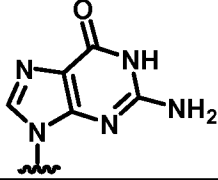
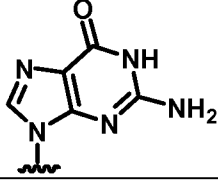
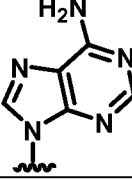
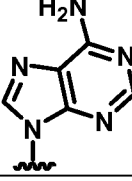
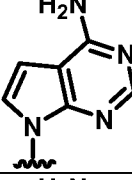
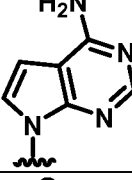
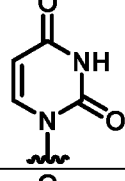
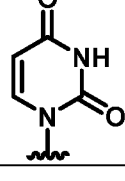
5

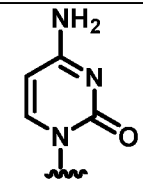
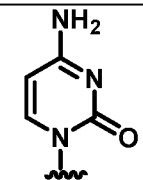
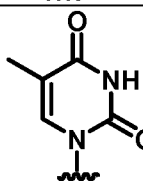
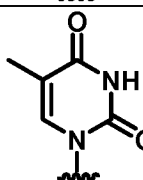
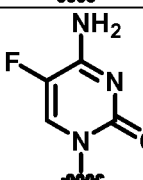
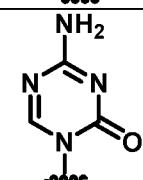
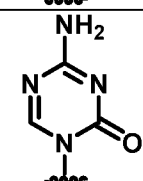
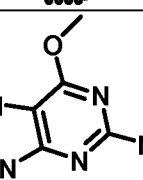
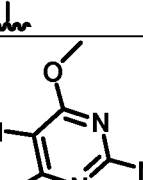
Example#	R_2	R_9	R_{12}	R_{13}	B
241	OH	Ph	Me	Me	
242	F	Ph	Me	Me	
243	OH	Ph	Me	Me	
244	F	Ph	Me	Me	
245	OH	Ph	Me	Me	

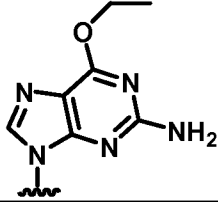
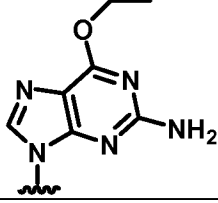
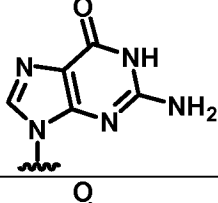
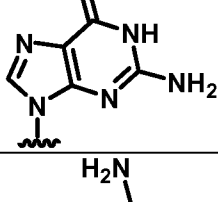
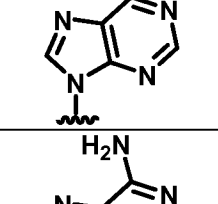
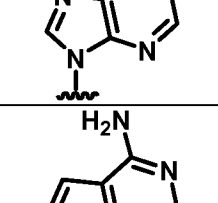
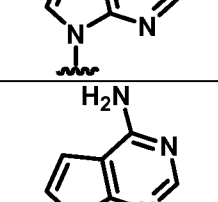
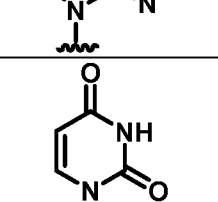
246	F	Ph	Me	Me	
247	OH	Ph	Me	Me	
248	F	Ph	Me	Me	
249	OH	Ph	Me	Me	
250	F	Ph	Me	Me	
251	OH	Ph	Me	Me	
252	F	Ph	Me	Me	
253	OH	Ph	Me	Me	
254	F	Ph	Me	Me	

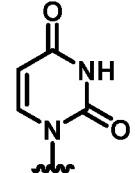
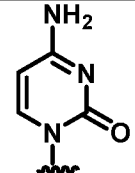
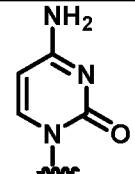
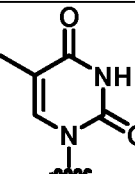
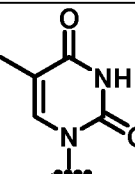
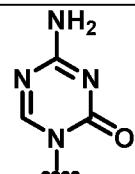
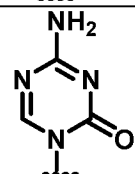
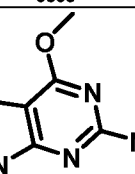
255	OH	Ph	Me	Me	
256	F	Ph	Me	Me	
257	OH	Ph	Me	Me	
258	F	Ph	Me	Me	
259	OH	Ph	Me	Me	
260	F	Ph	Me	Me	
261	OH	1-Naphthyl	Me	Me	
262	F	1-Naphthyl	Me	Me	
263	OH	1-Naphthyl	Me	Me	
264	F	1-Naphthyl	Me	Me	

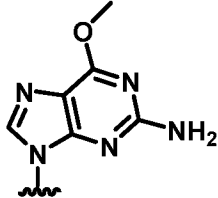
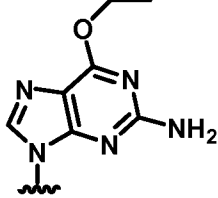
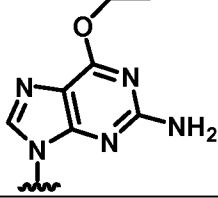
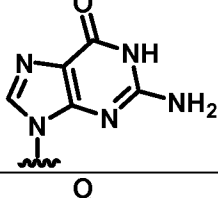
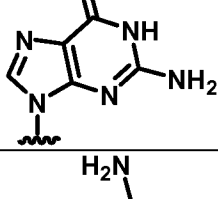
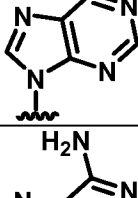
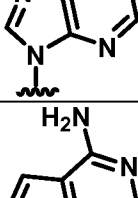
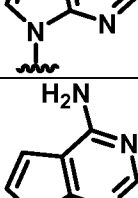
265	OH	1-Naphthyl	Me	Me	
266	F	1-Naphthyl	Me	Me	
267	OH	1-Naphthyl	Me	Me	
268	F	1-Naphthyl	Me	Me	
269	OH	1-Naphthyl	Me	Me	
270	F	1-Naphthyl	Me	Me	
271	OH	1-Naphthyl	Me	Me	
272	F	1-Naphthyl	Me	Me	
273	OH	1-Naphthyl	Me	Me	

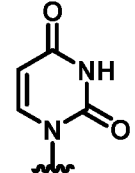
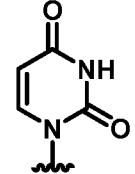
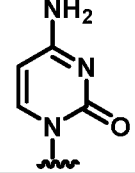
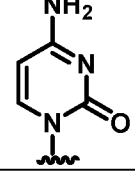
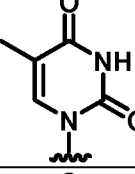
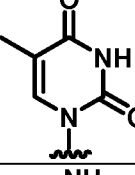
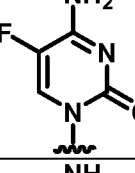
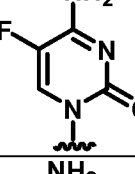
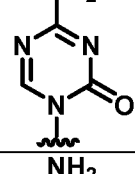
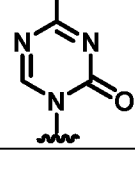
274	F	1-Naphthyl	Me	Me	
275	OH	1-Naphthyl	Me	Me	
276	F	1-Naphthyl	Me	Me	
277	OH	1-Naphthyl	Me	Me	
278	F	1-Naphthyl	Me	Me	
279	OH	1-Naphthyl	Me	Me	
280	F	1-Naphthyl	Me	Me	
281	OH	Ph	H	Me	
282	F	Ph	H	Me	

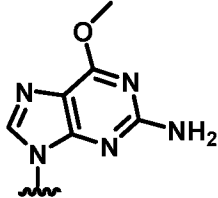
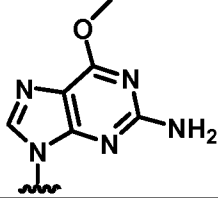
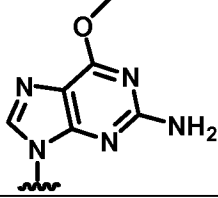
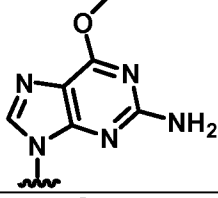
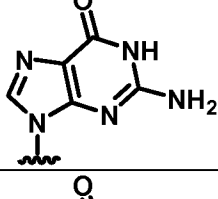
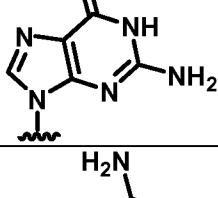
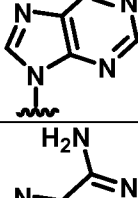
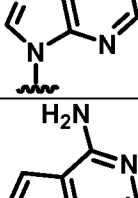
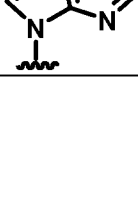
283	OH	Ph	H	Me	
284	F	Ph	H	Me	
285	OH	Ph	H	Me	
286	F	Ph	H	Me	
287	OH	Ph	H	Me	
288	F	Ph	H	Me	
289	OH	Ph	H	Me	
290	F	Ph	H	Me	
291	OH	Ph	H	Me	
292	F	Ph	H	Me	

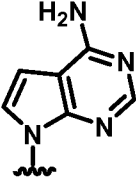
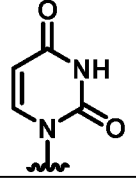
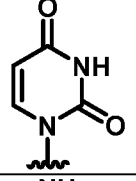
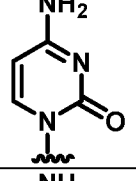
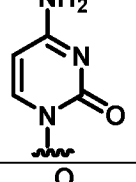
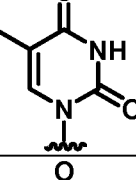
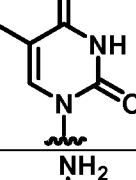
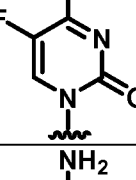
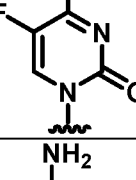
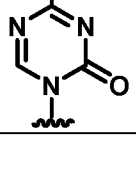
293	OH	Ph	H	Me	
294	F	Ph	H	Me	
295	OH	Ph	H	Me	
296	F	Ph	H	Me	
297	OH	Ph	H	Me	
298	F	Ph	H	Me	
299	OH	Ph	H	Me	
300	F	Ph	H	Me	
301	OH	1-Naphthyl	H	Me	

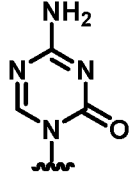
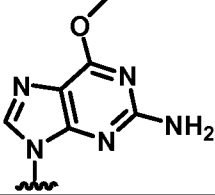
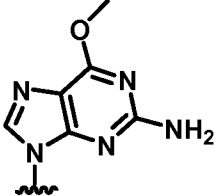
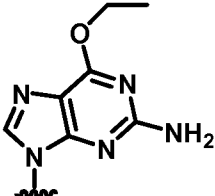
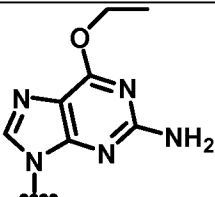
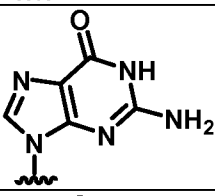
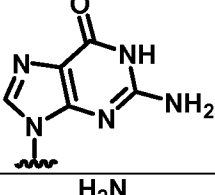
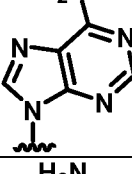
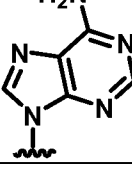
302	F	1-Naphthyl	H	Me	
303	OH	1-Naphthyl	H	Me	
304	F	1-Naphthyl	H	Me	
305	OH	1-Naphthyl	H	Me	
306	F	1-Naphthyl	H	Me	
307	OH	1-Naphthyl	H	Me	
308	F	1-Naphthyl	H	Me	
309	OH	1-Naphthyl	H	Me	
310	F	1-Naphthyl	H	Me	
311	OH	1-Naphthyl	H	Me	

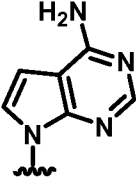
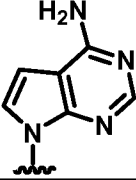
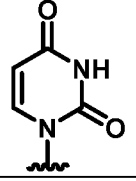
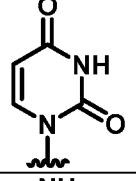
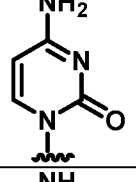
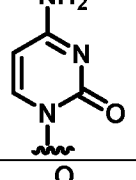
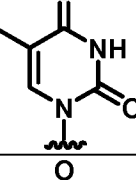
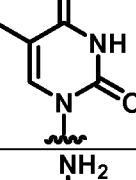
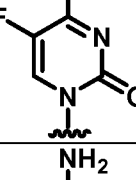
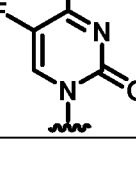
312	F	1-Naphthyl	H	Me	
313	OH	1-Naphthyl	H	Me	
314	F	1-Naphthyl	H	Me	
315	OH	1-Naphthyl	H	Me	
316	F	1-Naphthyl	H	Me	
317	OH	1-Naphthyl	H	Me	
318	F	1-Naphthyl	H	Me	
319	OH	1-Naphthyl	H	Me	
320	F	1-Naphthyl	H	Me	

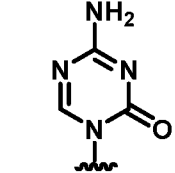
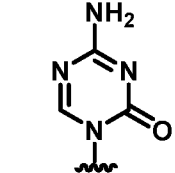
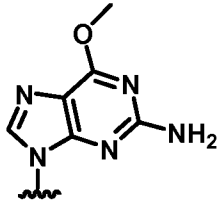
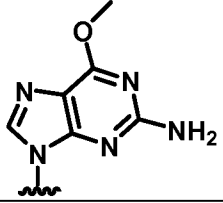
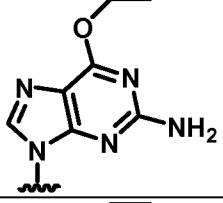
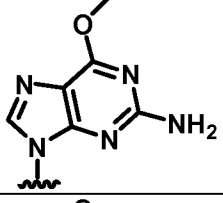
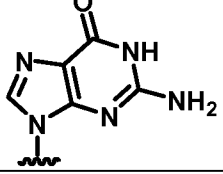
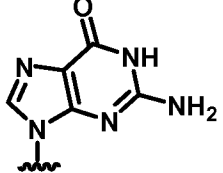
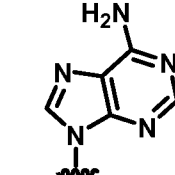
321	OH	Ph	Me	n-Pentyl	
322	F	Ph	Me	n-Pentyl	
323	OH	Ph	Me	n-Pentyl	
324	F	Ph	Me	n-Pentyl	
325	OH	Ph	Me	n-Pentyl	
326	F	Ph	Me	n-Pentyl	
327	OH	Ph	Me	n-Pentyl	
328	F	Ph	Me	n-Pentyl	
329	OH	Ph	Me	n-Pentyl	
330	F	Ph	Me	n-Pentyl	

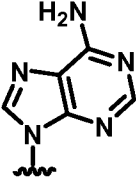
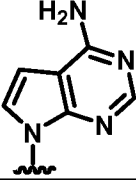
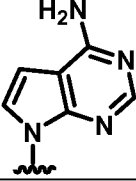
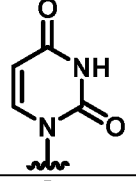
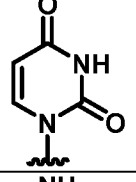
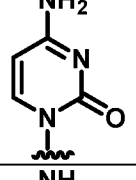
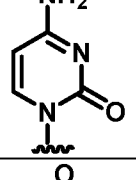
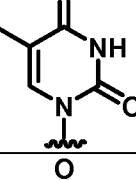
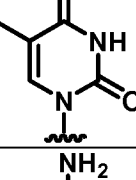
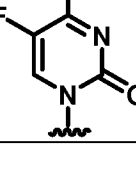
331	OH	Ph	Me	n-Pentyl	
332	F	Ph	Me	n-Pentyl	
333	OH	Ph	Me	n-Pentyl	
334	F	Ph	Me	n-Pentyl	
335	OH	Ph	Me	n-Pentyl	
336	F	Ph	Me	n-Pentyl	
337	OH	Ph	Me	n-Pentyl	
338	F	Ph	Me	n-Pentyl	
339	OH	Ph	Me	n-Pentyl	

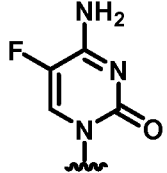
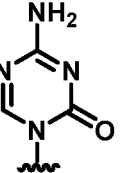
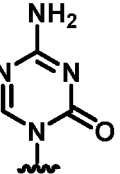
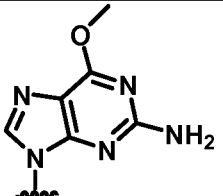
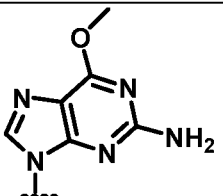
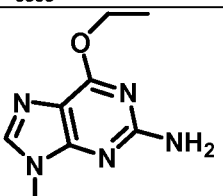
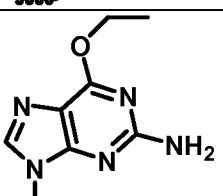
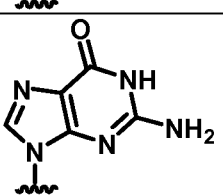
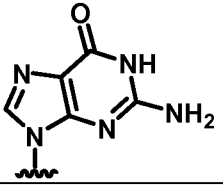
340	F	Ph	Me	n-Pentyl	
341	OH	1-Naphthyl	Me	n-Pentyl	
342	F	1-Naphthyl	Me	n-Pentyl	
343	OH	1-Naphthyl	Me	n-Pentyl	
344	F	1-Naphthyl	Me	n-Pentyl	
345	OH	1-Naphthyl	Me	n-Pentyl	
346	F	1-Naphthyl	Me	n-Pentyl	
347	OH	1-Naphthyl	Me	n-Pentyl	
348	F	1-Naphthyl	Me	n-Pentyl	
349	OH	1-Naphthyl	Me	n-Pentyl	

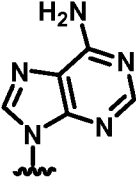
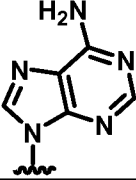
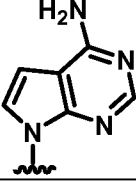
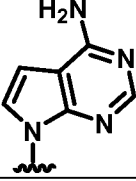
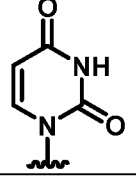
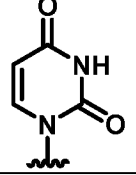
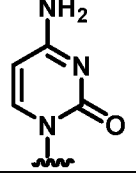
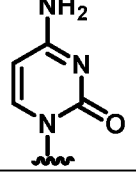
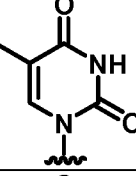
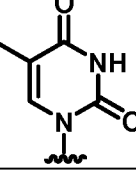
350	F	1-Naphthyl	Me	n-Pentyl	
351	OH	1-Naphthyl	Me	n-Pentyl	
352	F	1-Naphthyl	Me	n-Pentyl	
353	OH	1-Naphthyl	Me	n-Pentyl	
354	F	1-Naphthyl	Me	n-Pentyl	
355	OH	1-Naphthyl	Me	n-Pentyl	
356	F	1-Naphthyl	Me	n-Pentyl	
357	OH	1-Naphthyl	Me	n-Pentyl	
358	F	1-Naphthyl	Me	n-Pentyl	

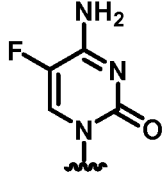
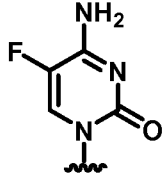
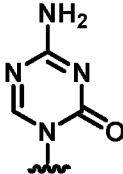
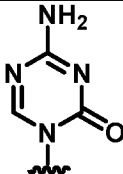
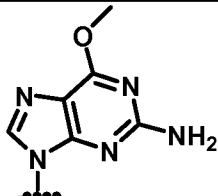
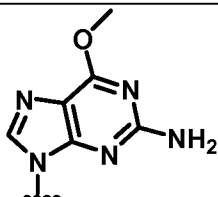
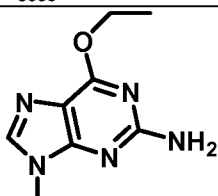
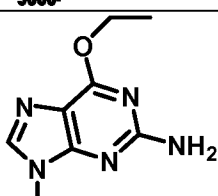
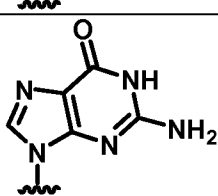
359	OH	1-Naphthyl	Me	n-Pentyl	
360	F	1-Naphthyl	Me	n-Pentyl	
361	OH	Ph	H	n-Pentyl	
362	F	Ph	H	n-Pentyl	
363	OH	Ph	H	n-Pentyl	
364	F	Ph	H	n-Pentyl	
365	OH	Ph	H	n-Pentyl	
366	F	Ph	H	n-Pentyl	
367	OH	Ph	H	n-Pentyl	
368	F	Ph	H	n-Pentyl	

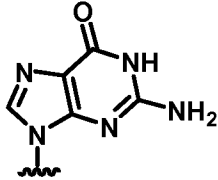
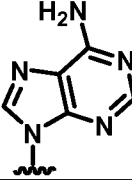
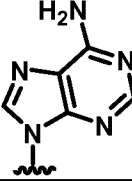
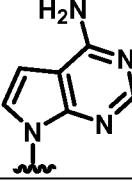
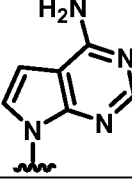
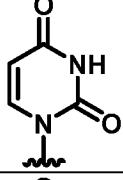
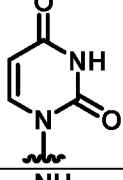
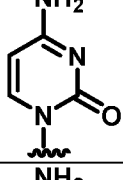
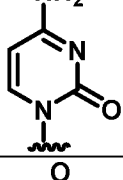
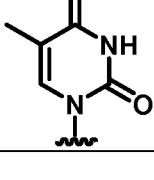
369	OH	Ph	H	n-Pentyl	
370	F	Ph	H	n-Pentyl	
371	OH	Ph	H	n-Pentyl	
372	F	Ph	H	n-Pentyl	
373	OH	Ph	H	n-Pentyl	
374	F	Ph	H	n-Pentyl	
375	OH	Ph	H	n-Pentyl	
376	F	Ph	H	n-Pentyl	
377	OH	Ph	H	n-Pentyl	

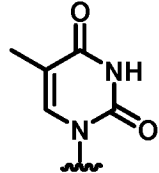
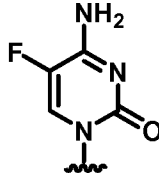
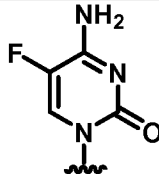
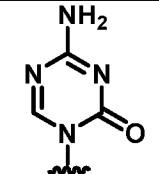
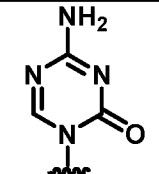
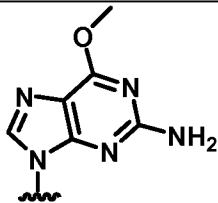
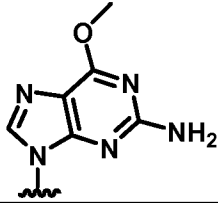
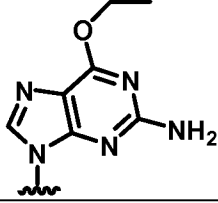
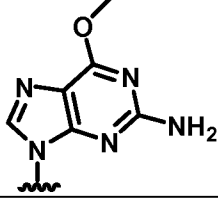
378	F	Ph	H	n-Pentyl	
379	OH	Ph	H	n-Pentyl	
380	F	Ph	H	n-Pentyl	
381	OH	1-Naphthyl	H	n-Pentyl	
382	F	1-Naphthyl	H	n-Pentyl	
383	OH	1-Naphthyl	H	n-Pentyl	
384	F	1-Naphthyl	H	n-Pentyl	
385	OH	1-Naphthyl	H	n-Pentyl	
386	F	1-Naphthyl	H	n-Pentyl	
387	OH	1-Naphthyl	H	n-Pentyl	

388	F	1-Naphthyl	H	n-Pentyl	
389	OH	1-Naphthyl	H	n-Pentyl	
390	F	1-Naphthyl	H	n-Pentyl	
391	OH	1-Naphthyl	H	n-Pentyl	
392	F	1-Naphthyl	H	n-Pentyl	
393	OH	1-Naphthyl	H	n-Pentyl	
394	F	1-Naphthyl	H	n-Pentyl	
395	OH	1-Naphthyl	H	n-Pentyl	
396	F	1-Naphthyl	H	n-Pentyl	

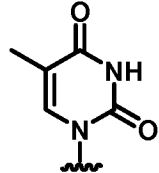
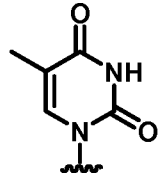
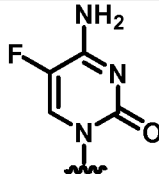
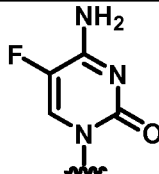
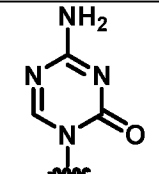
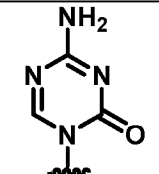
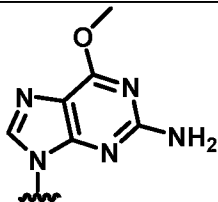
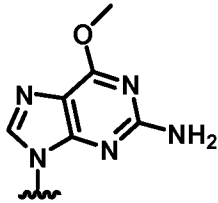
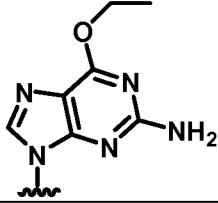
397	OH	1-Naphthyl	H	n-Pentyl	
398	F	1-Naphthyl	H	n-Pentyl	
399	OH	1-Naphthyl	H	n-Pentyl	
400	F	1-Naphthyl	H	n-Pentyl	
401	OH	Ph	Me	i-Pr	
402	F	Ph	Me	i-Pr	
403	OH	Ph	Me	i-Pr	
404	F	Ph	Me	i-Pr	
405	OH	Ph	Me	i-Pr	
406	F	Ph	Me	i-Pr	

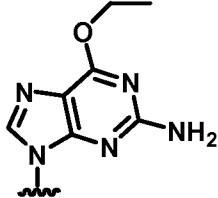
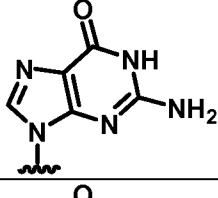
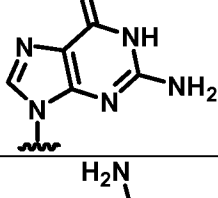
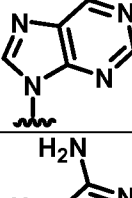
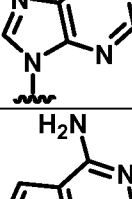
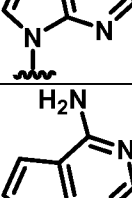
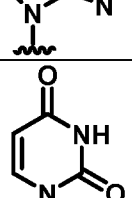
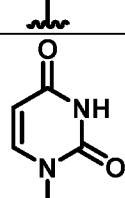
407	OH	Ph	Me	i-Pr	
408	F	Ph	Me	i-Pr	
409	OH	Ph	Me	i-Pr	
410	F	Ph	Me	i-Pr	
411	OH	Ph	Me	i-Pr	
412	F	Ph	Me	i-Pr	
413	OH	Ph	Me	i-Pr	
414	F	Ph	Me	i-Pr	
415	OH	Ph	Me	i-Pr	

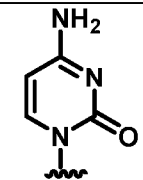
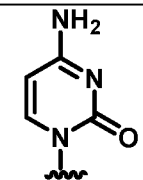
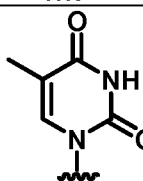
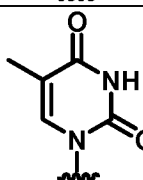
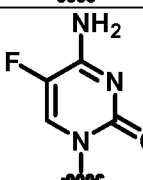
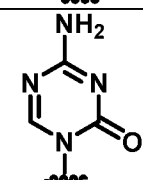
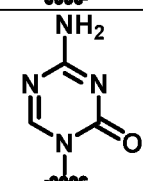
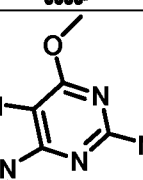
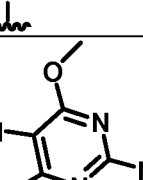
416	F	Ph	Me	i-Pr	
417	OH	Ph	Me	i-Pr	
418	F	Ph	Me	i-Pr	
419	OH	Ph	Me	i-Pr	
420	F	Ph	Me	i-Pr	
421	OH	1-Naphthyl	Me	i-Pr	
422	F	1-Naphthyl	Me	i-Pr	
423	OH	1-Naphthyl	Me	i-Pr	
424	F	1-Naphthyl	Me	i-Pr	
425	OH	1-Naphthyl	Me	i-Pr	

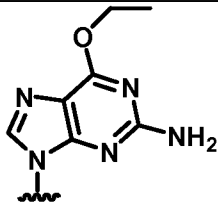
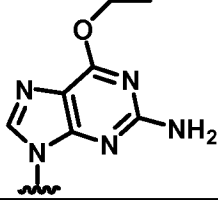
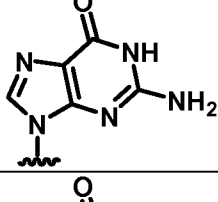
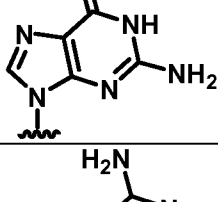
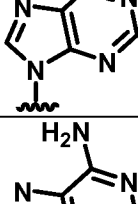
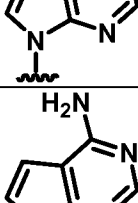
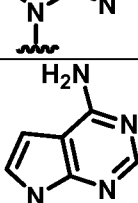
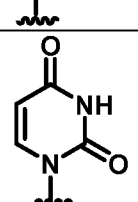
426	F	1-Naphthyl	Me	i-Pr	
427	OH	1-Naphthyl	Me	i-Pr	
428	F	1-Naphthyl	Me	i-Pr	
429	OH	1-Naphthyl	Me	i-Pr	
430	F	1-Naphthyl	Me	i-Pr	
431	OH	1-Naphthyl	Me	i-Pr	
432	F	1-Naphthyl	Me	i-Pr	
433	OH	1-Naphthyl	Me	i-Pr	
434	F	1-Naphthyl	Me	i-Pr	

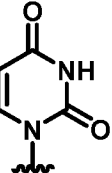
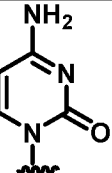
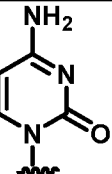
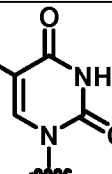
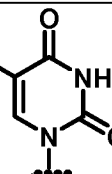
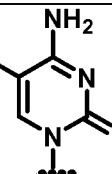
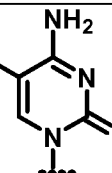
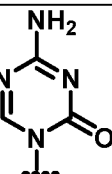
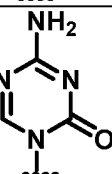
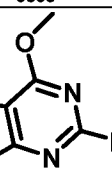
435	OH	1-Naphthyl	Me	i-Pr	
436	F	1-Naphthyl	Me	i-Pr	
437	OH	1-Naphthyl	Me	i-Pr	
438	F	1-Naphthyl	Me	i-Pr	
439	OH	1-Naphthyl	Me	i-Pr	
440	F	1-Naphthyl	Me	i-Pr	
441	OH	Ph	H	i-Pr	
442	F	Ph	H	i-Pr	
443	OH	Ph	H	i-Pr	
444	F	Ph	H	i-Pr	

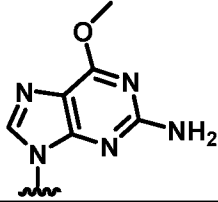
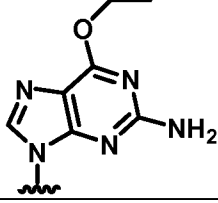
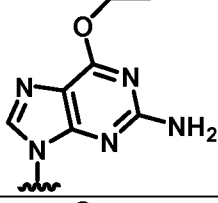
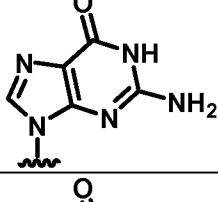
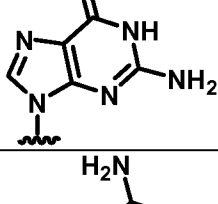
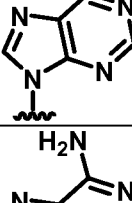
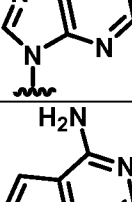
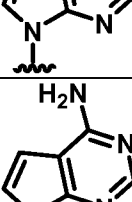
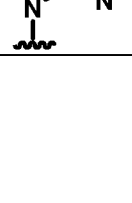
445	OH	Ph	H	i-Pr	
446	F	Ph	H	i-Pr	
447	OH	Ph	H	i-Pr	
448	F	Ph	H	i-Pr	
449	OH	Ph	H	i-Pr	
450	F	Ph	H	i-Pr	
451	OH	Ph	H	i-Pr	
452	F	Ph	H	i-Pr	
453	OH	Ph	H	i-Pr	

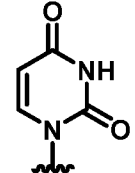
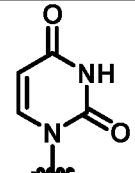
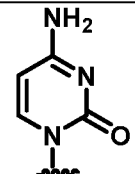
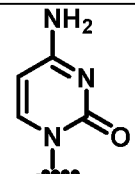
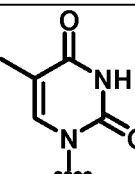
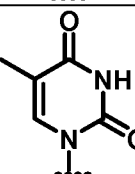
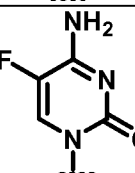
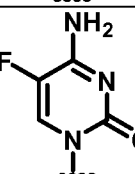
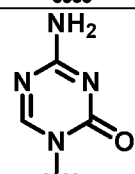
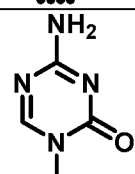
454	F	Ph	H	i-Pr	
455	OH	Ph	H	i-Pr	
456	F	Ph	H	i-Pr	
457	OH	Ph	H	i-Pr	
458	F	Ph	H	i-Pr	
459	OH	Ph	H	i-Pr	
460	F	Ph	H	i-Pr	
461	OH	1-Naphthyl	H	i-Pr	
462	F	1-Naphthyl	H	i-Pr	

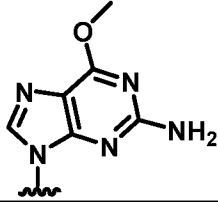
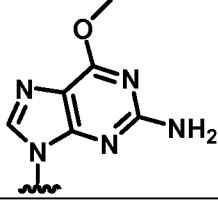
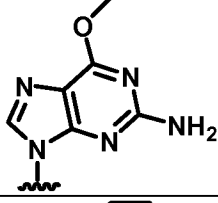
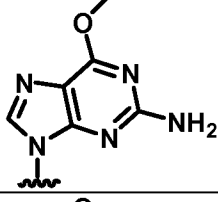
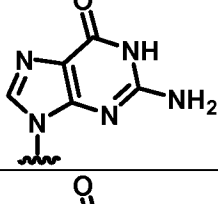
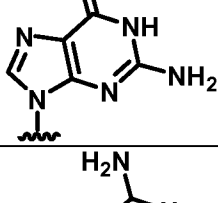
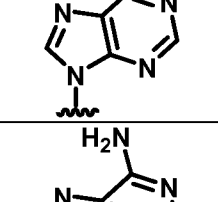
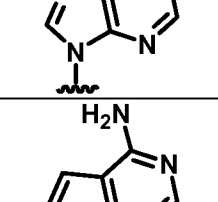
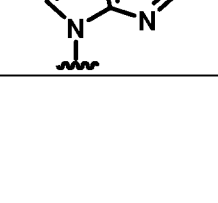
463	OH	1-Naphthyl	H	i-Pr	
464	F	1-Naphthyl	H	i-Pr	
465	OH	1-Naphthyl	H	i-Pr	
466	F	1-Naphthyl	H	i-Pr	
467	OH	1-Naphthyl	H	i-Pr	
468	F	1-Naphthyl	H	i-Pr	
469	OH	1-Naphthyl	H	i-Pr	
470	F	1-Naphthyl	H	i-Pr	
471	OH	1-Naphthyl	H	i-Pr	
472	F	1-Naphthyl	H	i-Pr	

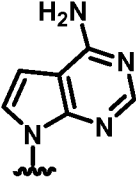
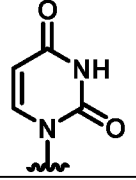
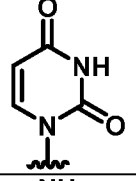
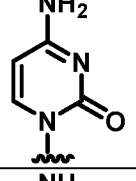
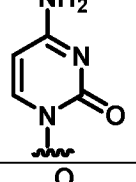
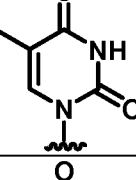
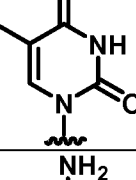
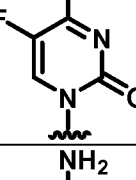
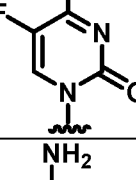
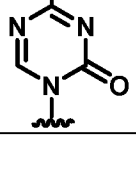
473	OH	1-Naphthyl	H	i-Pr	
474	F	1-Naphthyl	H	i-Pr	
475	OH	1-Naphthyl	H	i-Pr	
476	F	1-Naphthyl	H	i-Pr	
477	OH	1-Naphthyl	H	i-Pr	
478	F	1-Naphthyl	H	i-Pr	
479	OH	1-Naphthyl	H	i-Pr	
480	F	1-Naphthyl	H	i-Pr	
481	OH	Ph	Me	Benzyl	

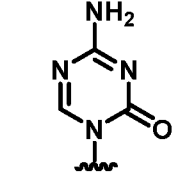
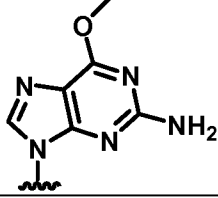
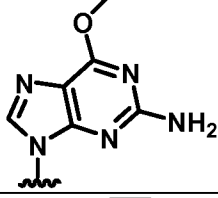
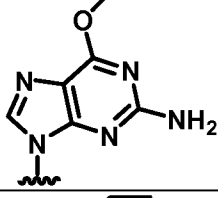
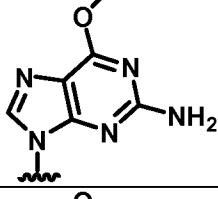
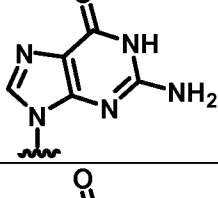
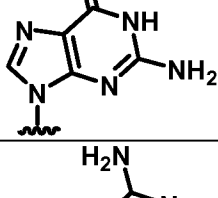
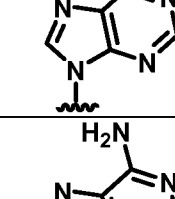
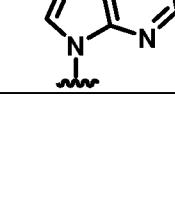
482	F	Ph	Me	Benzyl	
483	OH	Ph	Me	Benzyl	
484	F	Ph	Me	Benzyl	
485	OH	Ph	Me	Benzyl	
486	F	Ph	Me	Benzyl	
487	OH	Ph	Me	Benzyl	
488	F	Ph	Me	Benzyl	
489	OH	Ph	Me	Benzyl	
490	F	Ph	Me	Benzyl	
491	OH	Ph	Me	Benzyl	

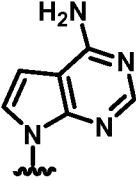
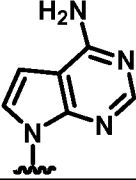
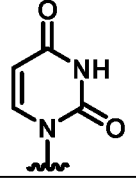
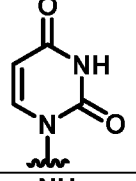
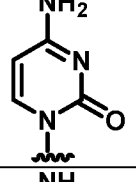
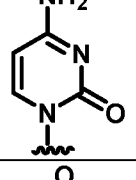
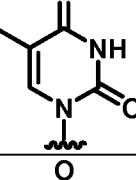
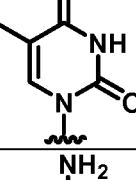
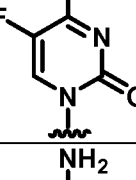
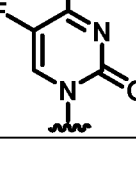
492	F	Ph	Me	Benzyl	
493	OH	Ph	Me	Benzyl	
494	F	Ph	Me	Benzyl	
495	OH	Ph	Me	Benzyl	
496	F	Ph	Me	Benzyl	
497	OH	Ph	Me	Benzyl	
498	F	Ph	Me	Benzyl	
499	OH	Ph	Me	Benzyl	
500	F	Ph	Me	Benzyl	

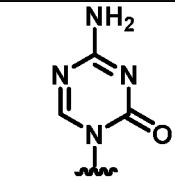
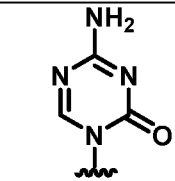
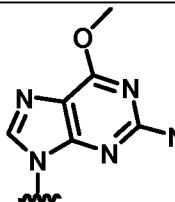
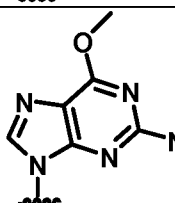
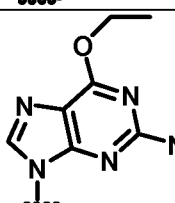
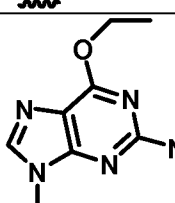
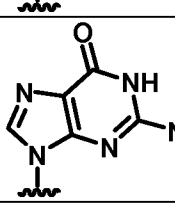
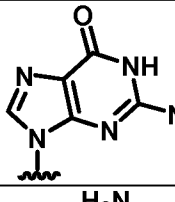
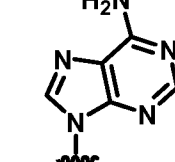
501	OH	1-Naphthyl	Me	Benzyl	
502	F	1-Naphthyl	Me	Benzyl	
503	OH	1-Naphthyl	Me	Benzyl	
504	F	1-Naphthyl	Me	Benzyl	
505	OH	1-Naphthyl	Me	Benzyl	
506	F	1-Naphthyl	Me	Benzyl	
507	OH	1-Naphthyl	Me	Benzyl	
508	F	1-Naphthyl	Me	Benzyl	
509	OH	1-Naphthyl	Me	Benzyl	
510	F	1-Naphthyl	Me	Benzyl	

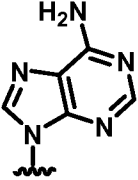
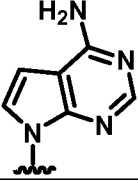
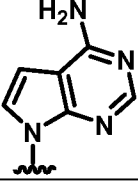
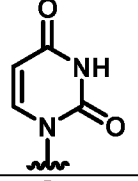
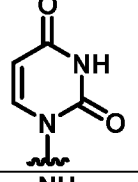
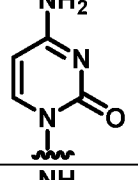
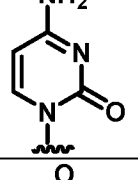
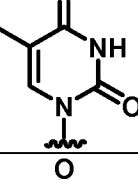
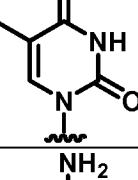
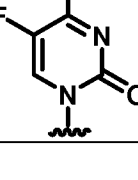
511	OH	1-Naphthyl	Me	Benzyl	
512	F	1-Naphthyl	Me	Benzyl	
513	OH	1-Naphthyl	Me	Benzyl	
514	F	1-Naphthyl	Me	Benzyl	
515	OH	1-Naphthyl	Me	Benzyl	
516	F	1-Naphthyl	Me	Benzyl	
517	OH	1-Naphthyl	Me	Benzyl	
518	F	1-Naphthyl	Me	Benzyl	
519	OH	1-Naphthyl	Me	Benzyl	

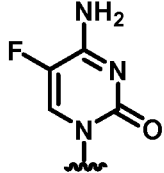
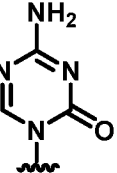
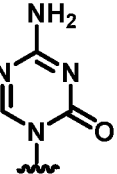
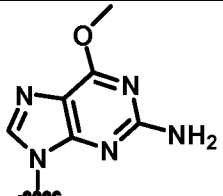
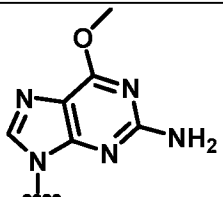
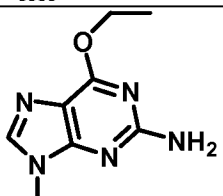
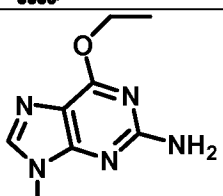
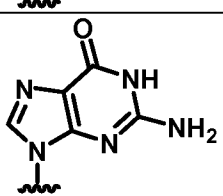
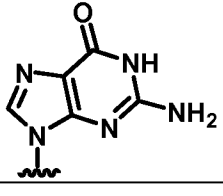
520	F	1-Naphthyl	Me	Benzyl	
521	OH	Ph	H	Benzyl	
522	F	Ph	H	Benzyl	
523	OH	Ph	H	Benzyl	
524	F	Ph	H	Benzyl	
525	OH	Ph	H	Benzyl	
526	F	Ph	H	Benzyl	
527	OH	Ph	H	Benzyl	
528	F	Ph	H	Benzyl	
529	OH	Ph	H	Benzyl	

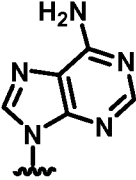
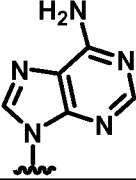
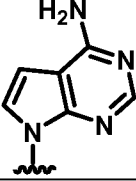
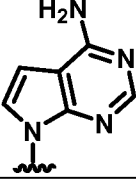
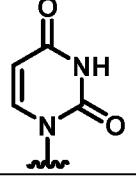
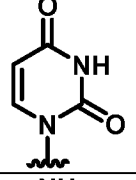
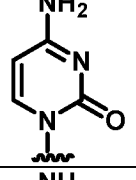
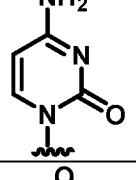
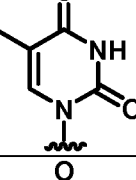
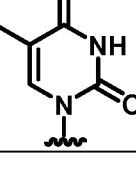
530	F	Ph	H	Benzyl	
531	OH	Ph	H	Benzyl	
532	F	Ph	H	Benzyl	
533	OH	Ph	H	Benzyl	
534	F	Ph	H	Benzyl	
535	OH	Ph	H	Benzyl	
536	F	Ph	H	Benzyl	
537	OH	Ph	H	Benzyl	
538	F	Ph	H	Benzyl	

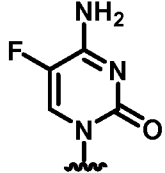
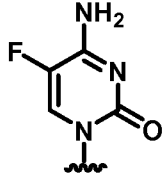
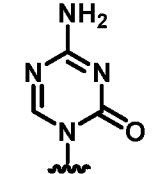
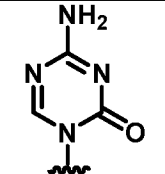
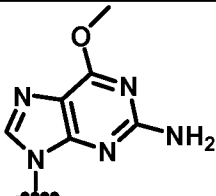
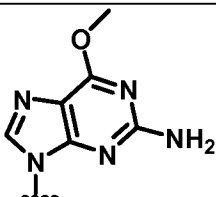
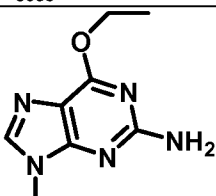
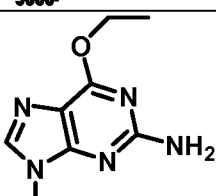
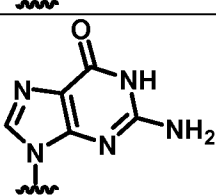
539	OH	Ph	H	Benzyl	
540	F	Ph	H	Benzyl	
541	OH	1-Naphthyl	H	Benzyl	
542	F	1-Naphthyl	H	Benzyl	
543	OH	1-Naphthyl	H	Benzyl	
544	F	1-Naphthyl	H	Benzyl	
545	OH	1-Naphthyl	H	Benzyl	
546	F	1-Naphthyl	H	Benzyl	
547	OH	1-Naphthyl	H	Benzyl	
548	F	1-Naphthyl	H	Benzyl	

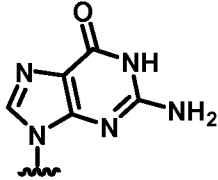
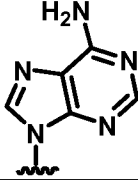
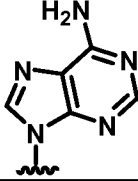
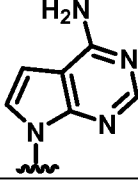
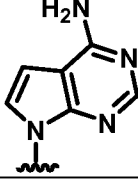
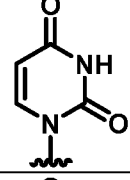
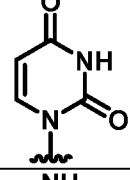
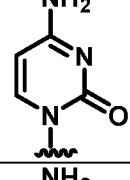
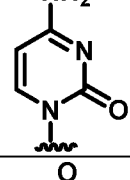
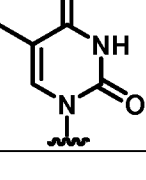
549	OH	1-Naphthyl	H	Benzyl	
550	F	1-Naphthyl	H	Benzyl	
551	OH	1-Naphthyl	H	Benzyl	
552	F	1-Naphthyl	H	Benzyl	
553	OH	1-Naphthyl	H	Benzyl	
554	F	1-Naphthyl	H	Benzyl	
555	OH	1-Naphthyl	H	Benzyl	
556	F	1-Naphthyl	H	Benzyl	
557	OH	1-Naphthyl	H	Benzyl	

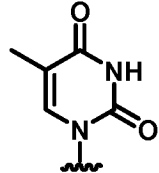
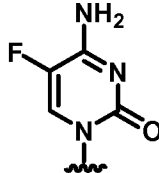
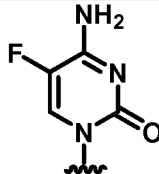
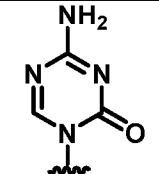
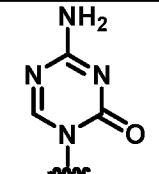
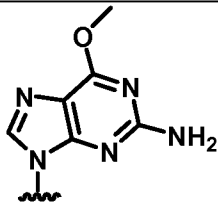
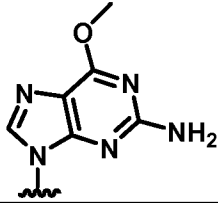
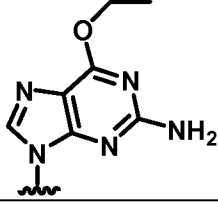
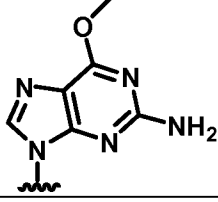
558	F	1-Naphthyl	H	Benzyl	
559	OH	1-Naphthyl	H	Benzyl	
560	F	1-Naphthyl	H	Benzyl	
561	OH	Ph	Me	t-BuCH ₂ -	
562	F	Ph	Me	t-BuCH ₂ -	
563	OH	Ph	Me	t-BuCH ₂ -	
564	F	Ph	Me	t-BuCH ₂ -	
565	OH	Ph	Me	t-BuCH ₂ -	
566	F	Ph	Me	t-BuCH ₂ -	
567	OH	Ph	Me	t-BuCH ₂ -	

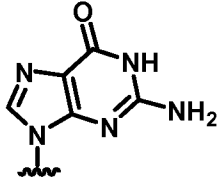
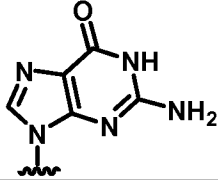
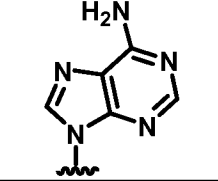
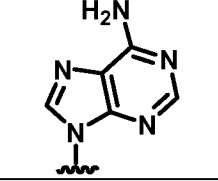
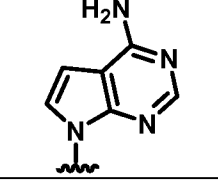
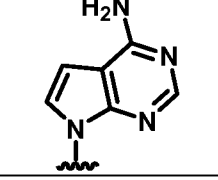
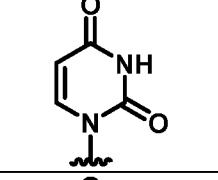
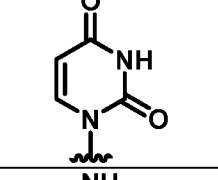
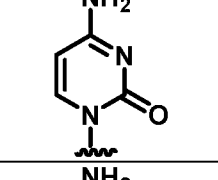
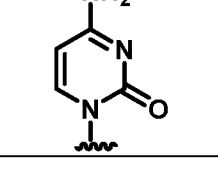
568	F	Ph	Me	t-BuCH ₂ -	
569	OH	Ph	Me	t-BuCH ₂ -	
570	F	Ph	Me	t-BuCH ₂ -	
571	OH	Ph	Me	t-BuCH ₂ -	
572	F	Ph	Me	t-BuCH ₂ -	
573	OH	Ph	Me	t-BuCH ₂ -	
574	F	Ph	Me	t-BuCH ₂ -	
575	OH	Ph	Me	t-BuCH ₂ -	
576	F	Ph	Me	t-BuCH ₂ -	

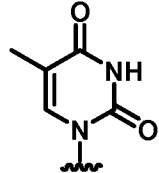
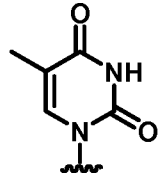
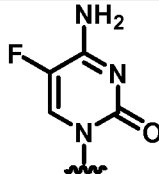
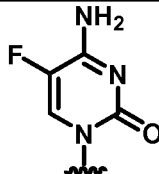
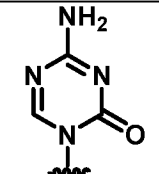
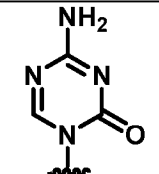
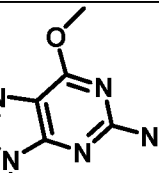
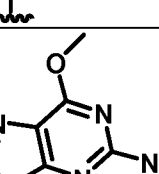
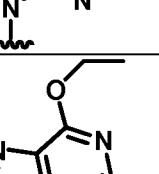
577	OH	Ph	Me	t-BuCH ₂ -	
578	F	Ph	Me	t-BuCH ₂ -	
579	OH	Ph	Me	t-BuCH ₂ -	
580	F	Ph	Me	t-BuCH ₂ -	
581	OH	1-Naphthyl	Me	t-BuCH ₂ -	
582	F	1-Naphthyl	Me	t-BuCH ₂ -	
583	OH	1-Naphthyl	Me	t-BuCH ₂ -	
584	F	1-Naphthyl	Me	t-BuCH ₂ -	
585	OH	1-Naphthyl	Me	t-BuCH ₂ -	
586	F	1-Naphthyl	Me	t-BuCH ₂ -	

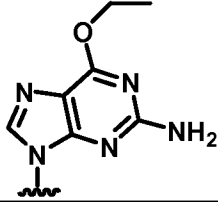
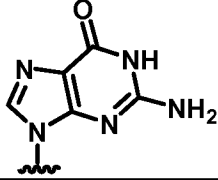
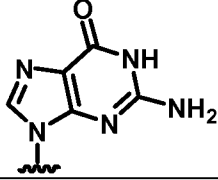
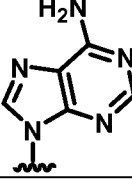
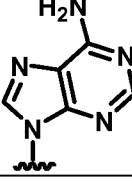
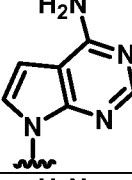
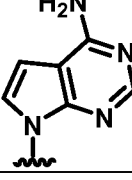
587	OH	1-Naphthyl	Me	t-BuCH ₂ -	
588	F	1-Naphthyl	Me	t-BuCH ₂ -	
589	OH	1-Naphthyl	Me	t-BuCH ₂ -	
590	F	1-Naphthyl	Me	t-BuCH ₂ -	
591	OH	1-Naphthyl	Me	t-BuCH ₂ -	
592	F	1-Naphthyl	Me	t-BuCH ₂ -	
593	OH	1-Naphthyl	Me	t-BuCH ₂ -	
594	F	1-Naphthyl	Me	t-BuCH ₂ -	
595	OH	1-Naphthyl	Me	t-BuCH ₂ -	

596	F	1-Naphthyl	Me	t-BuCH ₂ -	
597	OH	1-Naphthyl	Me	t-BuCH ₂ -	
598	F	1-Naphthyl	Me	t-BuCH ₂ -	
599	OH	1-Naphthyl	Me	t-BuCH ₂ -	
600	F	1-Naphthyl	Me	t-BuCH ₂ -	
601	OH	Ph	H	t-BuCH ₂ -	
602	F	Ph	H	t-BuCH ₂ -	
603	OH	Ph	H	t-BuCH ₂ -	
604	F	Ph	H	t-BuCH ₂ -	
605	OH	Ph	H	t-BuCH ₂ -	

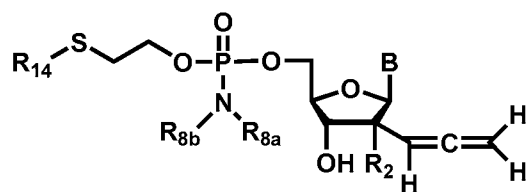
606	F	Ph	H	t-BuCH ₂ -	
607	OH	Ph	H	t-BuCH ₂ -	
608	F	Ph	H	t-BuCH ₂ -	
609	OH	Ph	H	t-BuCH ₂ -	
610	F	Ph	H	t-BuCH ₂ -	
611	OH	Ph	H	t-BuCH ₂ -	
612	F	Ph	H	t-BuCH ₂ -	
613	OH	Ph	H	t-BuCH ₂ -	
614	F	Ph	H	t-BuCH ₂ -	

615	OH	Ph	H	t-BuCH ₂ -	
616	F	Ph	H	t-BuCH ₂ -	
617	OH	Ph	H	t-BuCH ₂ -	
618	F	Ph	H	t-BuCH ₂ -	
619	OH	Ph	H	t-BuCH ₂ -	
620	F	Ph	H	t-BuCH ₂ -	
621	OH	1-Naphthyl	H	t-BuCH ₂ -	
622	F	1-Naphthyl	H	t-BuCH ₂ -	
623	OH	1-Naphthyl	H	t-BuCH ₂ -	
624	F	1-Naphthyl	H	t-BuCH ₂ -	

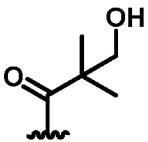
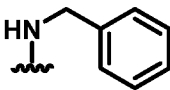
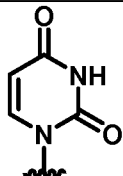
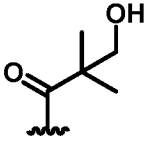
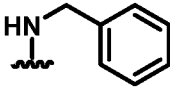
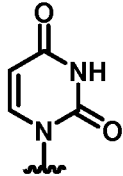
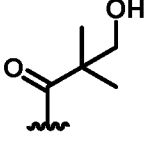
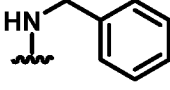
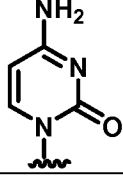
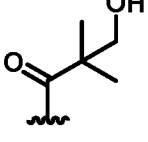
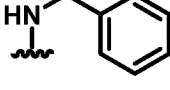
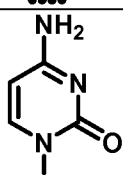
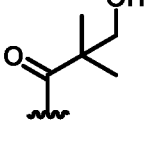
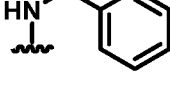
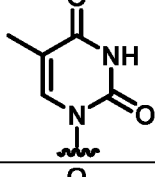
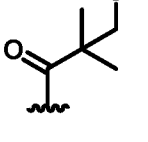
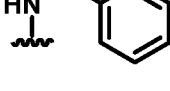
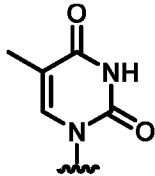
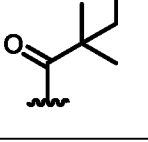
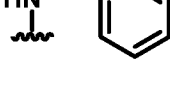
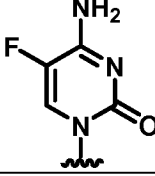
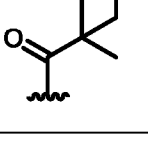
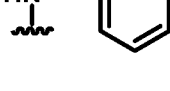
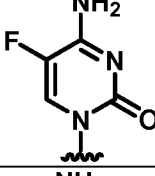
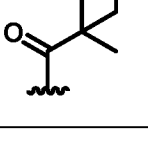
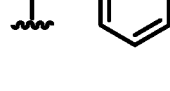
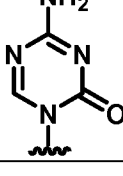
625	OH	1-Naphthyl	H	t-BuCH ₂ -	
626	F	1-Naphthyl	H	t-BuCH ₂ -	
627	OH	1-Naphthyl	H	t-BuCH ₂ -	
628	F	1-Naphthyl	H	t-BuCH ₂ -	
629	OH	1-Naphthyl	H	t-BuCH ₂ -	
630	F	1-Naphthyl	H	t-BuCH ₂ -	
631	OH	1-Naphthyl	H	t-BuCH ₂ -	
632	F	1-Naphthyl	H	t-BuCH ₂ -	
633	OH	1-Naphthyl	H	t-BuCH ₂ -	

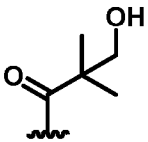
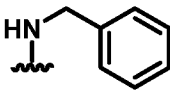
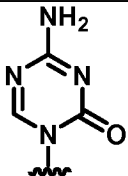
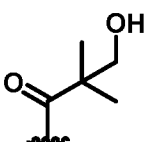
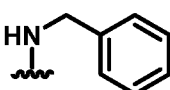
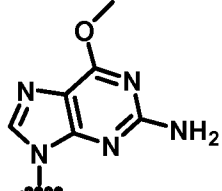
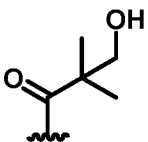
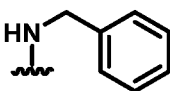
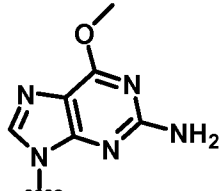
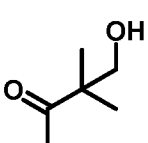
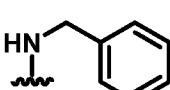
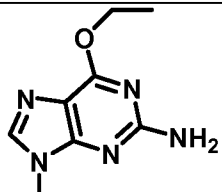
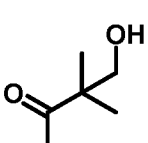
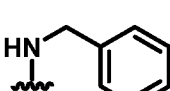
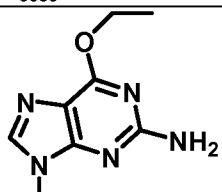
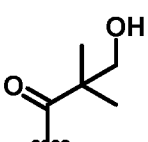
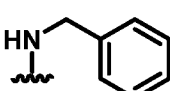
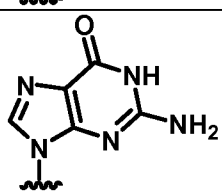
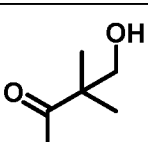
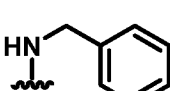
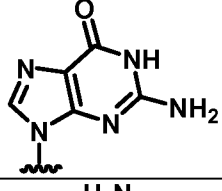
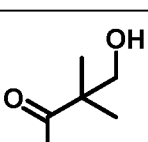
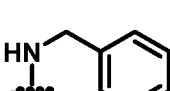
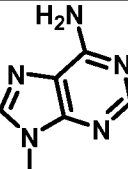
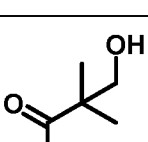
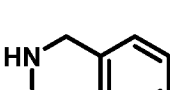
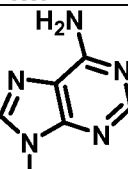
634	F	1-Naphthyl	H	t-BuCH ₂ -	
635	OH	1-Naphthyl	H	t-BuCH ₂ -	
636	F	1-Naphthyl	H	t-BuCH ₂ -	
637	OH	1-Naphthyl	H	t-BuCH ₂ -	
638	F	1-Naphthyl	H	t-BuCH ₂ -	
639	OH	1-Naphthyl	H	t-BuCH ₂ -	
640	F	1-Naphthyl	H	t-BuCH ₂ -	

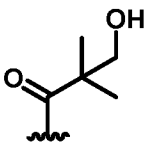
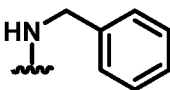
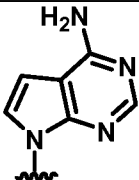
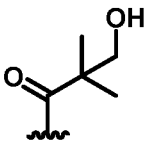
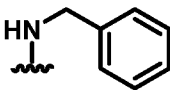
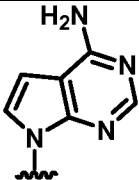
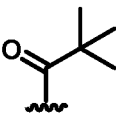
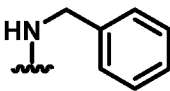
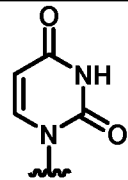
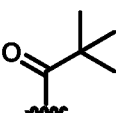
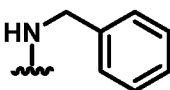
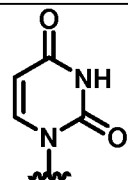
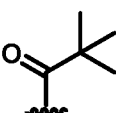
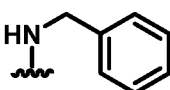
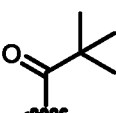
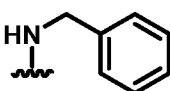
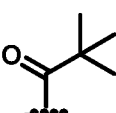
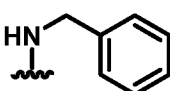
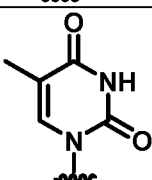
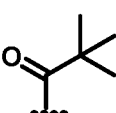
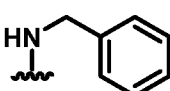
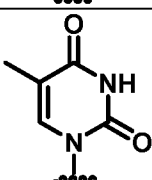
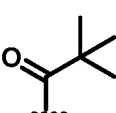
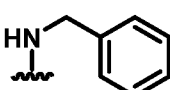
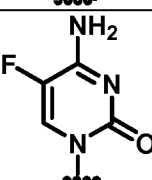
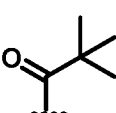
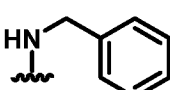
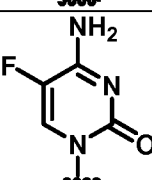
Compounds in Table 4 are represented by Formula (VI-1) wherein R₂, R_{8a}, R_{8b}, R₁₄, and B are delineated for each example in Table 4.

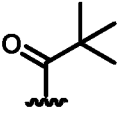
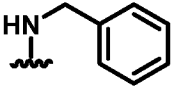
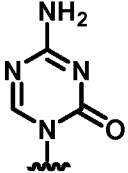
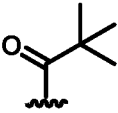
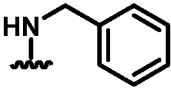
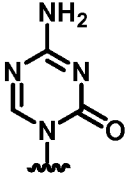
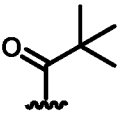
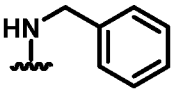
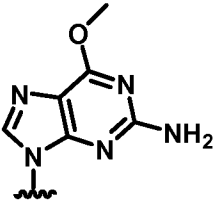
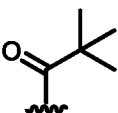
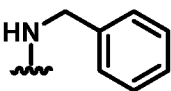
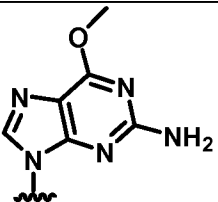
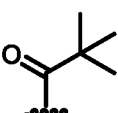
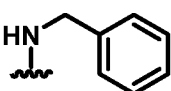
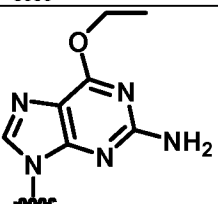
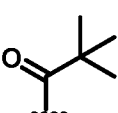
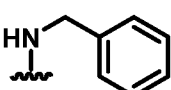
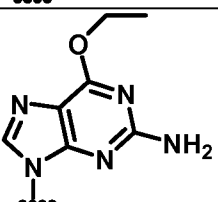
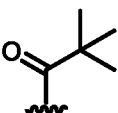
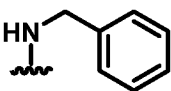
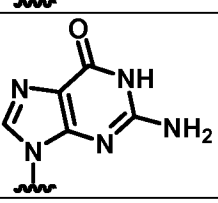
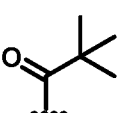
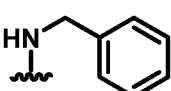
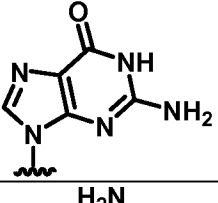
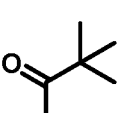
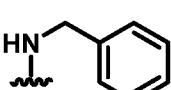
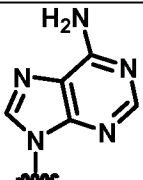


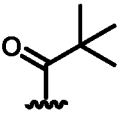
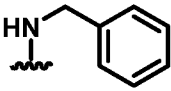
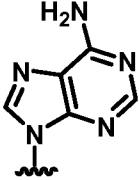
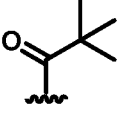
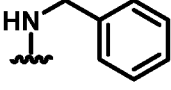
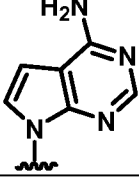
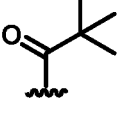
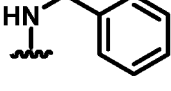
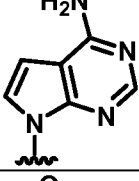
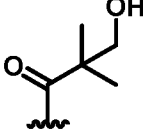
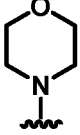
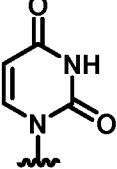
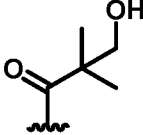
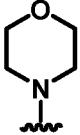
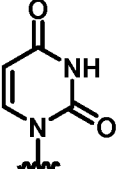
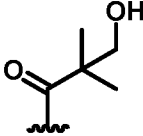
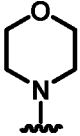
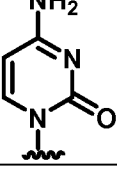
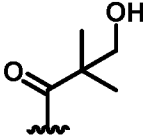
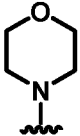
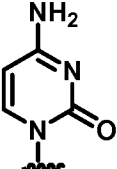
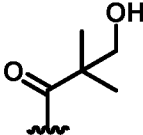
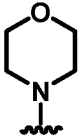
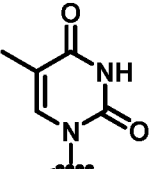
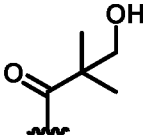
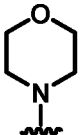
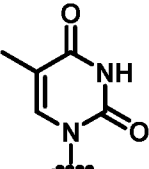
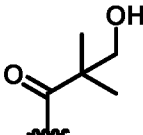
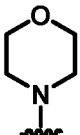
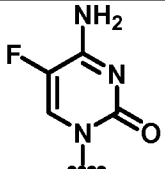
(VI-1)

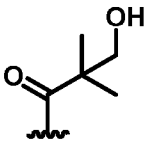
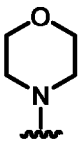
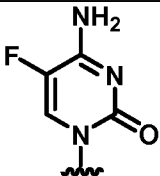
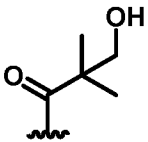
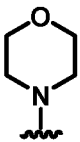
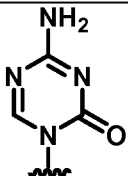
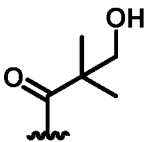
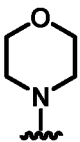
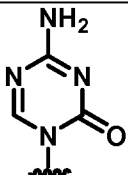
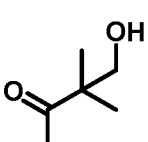
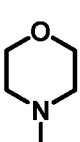
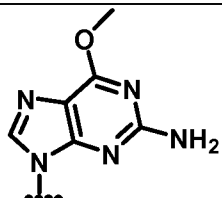
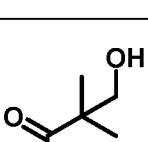
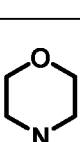
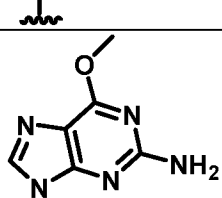
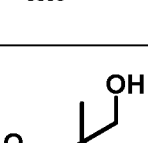
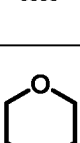
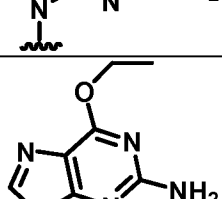
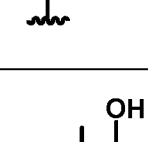
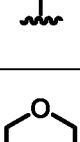
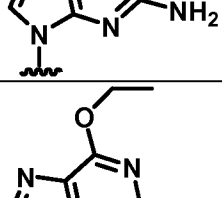
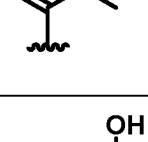
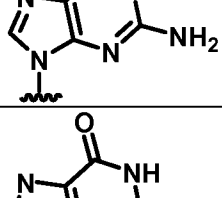
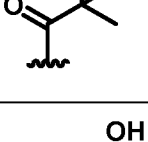
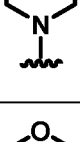
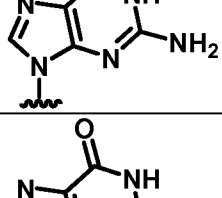
Example#	R ₂	R ₁₄	NR _{8a} R _{8b}	B
641	OH			
642	F			
643	OH			
644	F			
645	OH			
646	F			
647	OH			
648	F			
649	OH			

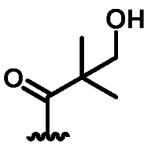
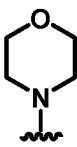
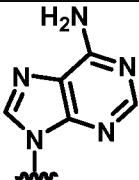
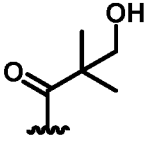
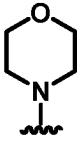
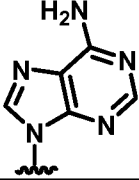
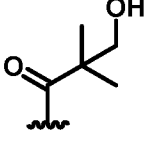
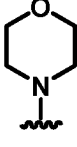
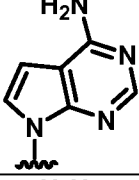
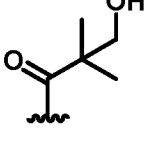
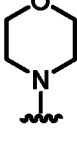
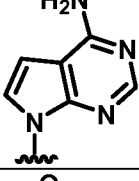
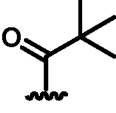
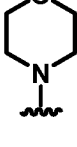
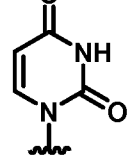
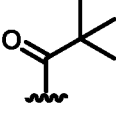
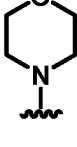
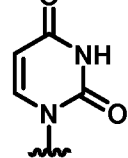
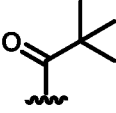
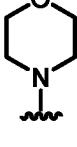
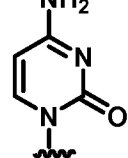
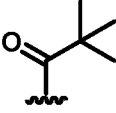
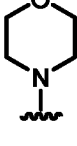
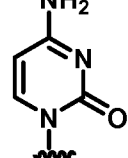
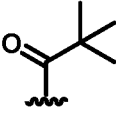
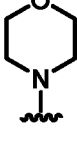
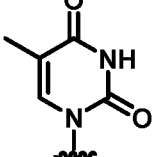
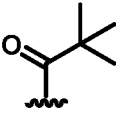
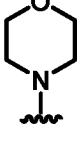
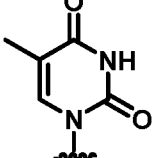
650	F			
651	OH			
652	F			
653	OH			
654	F			
655	OH			
656	F			
657	OH			
658	F			

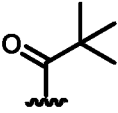
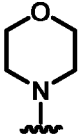
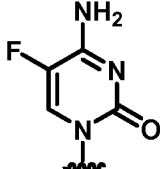
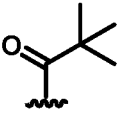
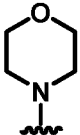
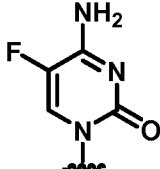
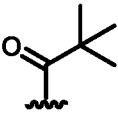
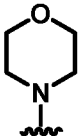
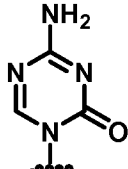
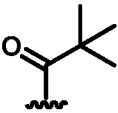
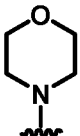
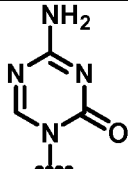
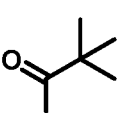
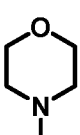
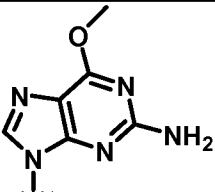
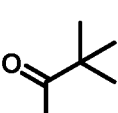
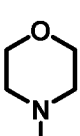
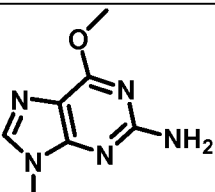
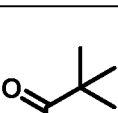
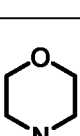
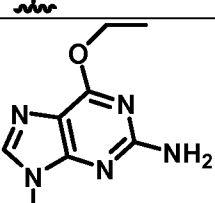
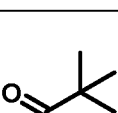
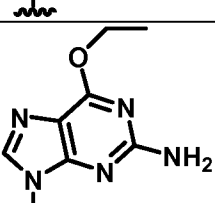
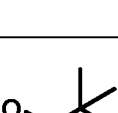
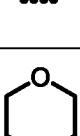
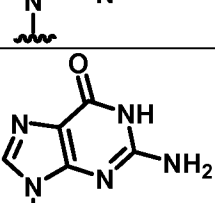
659	OH			
660	F			
661	OH			
662	F			
663	OH			
664	F			
665	OH			
666	F			
667	OH			
668	F			

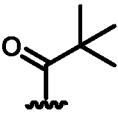
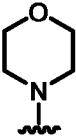
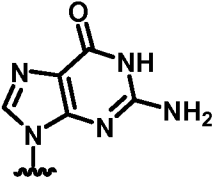
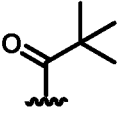
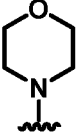
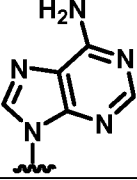
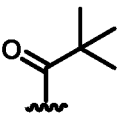
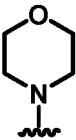
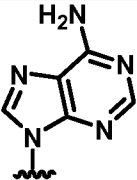
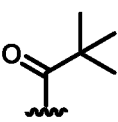
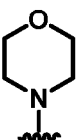
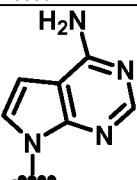
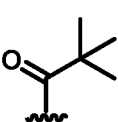
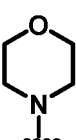
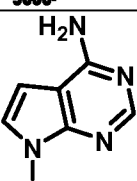
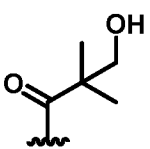
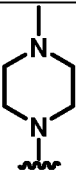
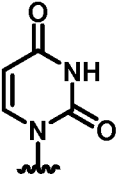
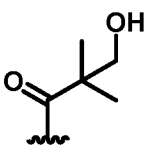
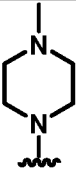
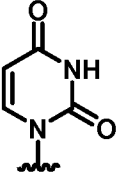
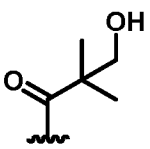
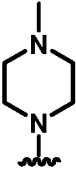
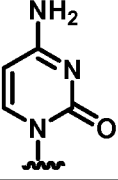
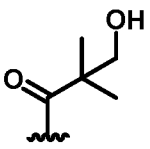
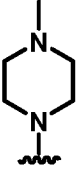
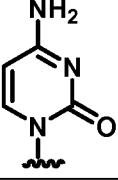
669	OH			
670	F			
671	OH			
672	F			
673	OH			
674	F			
675	OH			
676	F			
677	OH			

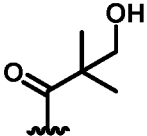
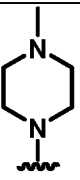
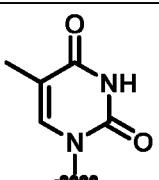
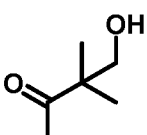
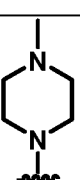
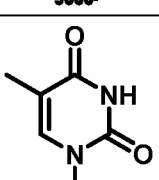
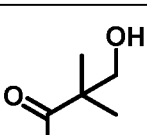
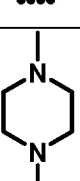
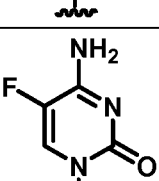
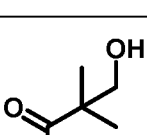
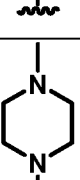
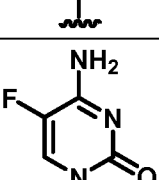
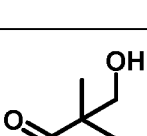
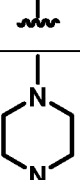
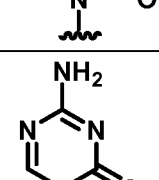
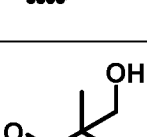
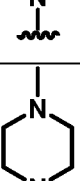
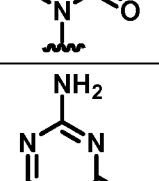
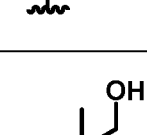
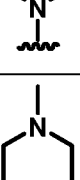
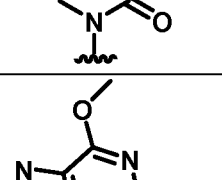
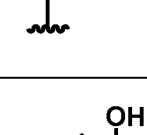
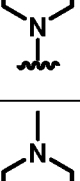
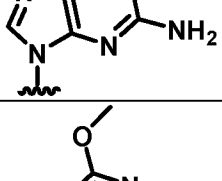
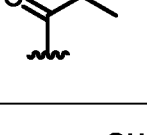
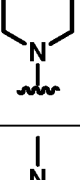
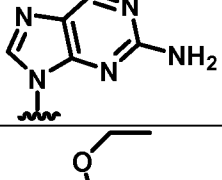
678	F			
679	OH			
680	F			
681	OH			
682	F			
683	OH			
684	F			
685	OH			
686	F			
687	OH			

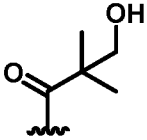
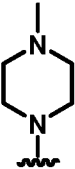
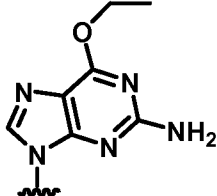
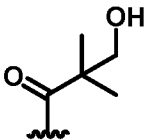
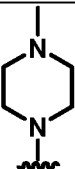
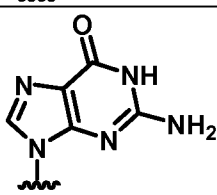
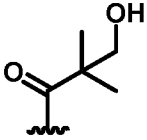
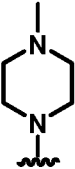
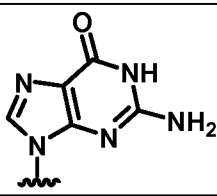
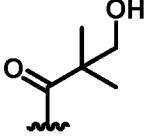
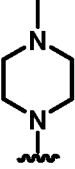
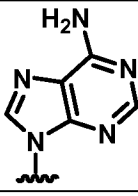
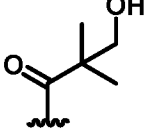
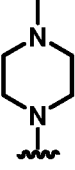
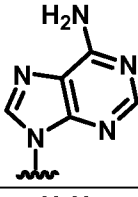
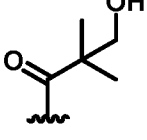
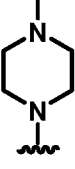
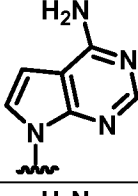
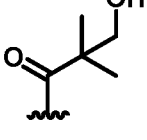
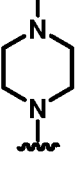
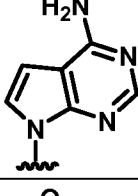
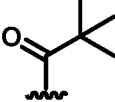
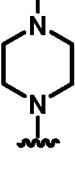
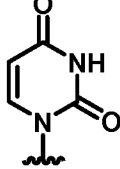
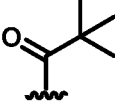
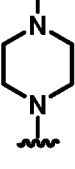
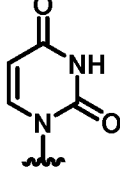
688	F			
689	OH			
690	F			
691	OH			
692	F			
693	OH			
694	F			
695	OH			
696	F			

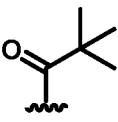
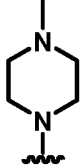
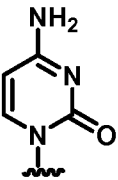
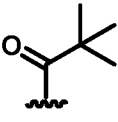
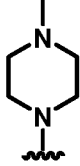
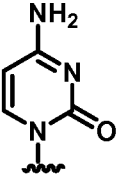
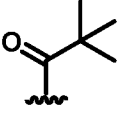
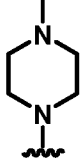
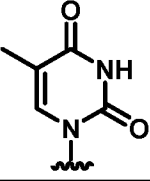
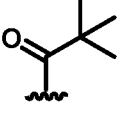
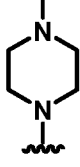
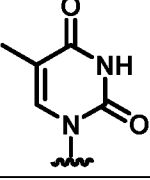
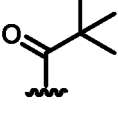
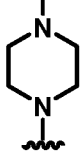
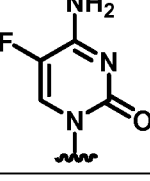
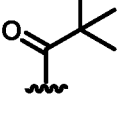
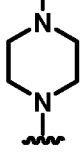
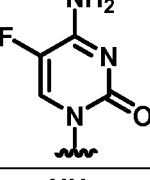
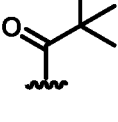
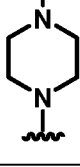
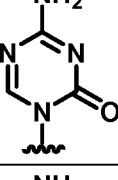
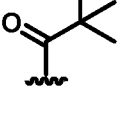
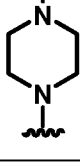
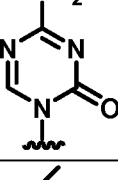
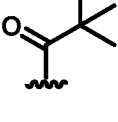
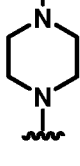
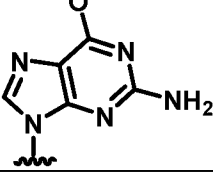
697	OH			
698	F			
699	OH			
700	F			
701	OH			
702	F			
703	OH			
704	F			
705	OH			
706	F			

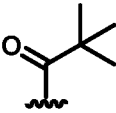
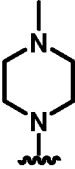
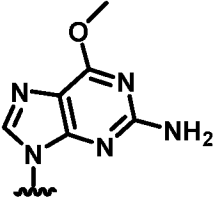
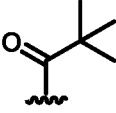
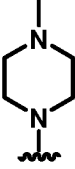
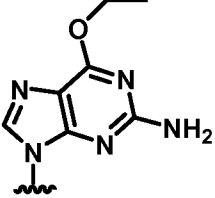
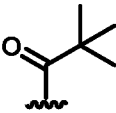
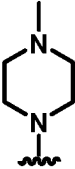
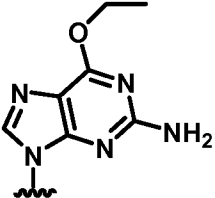
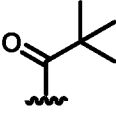
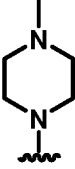
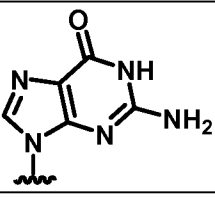
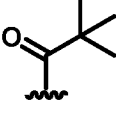
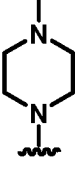
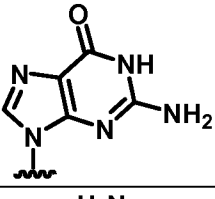
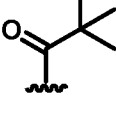
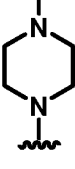
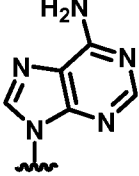
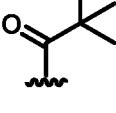
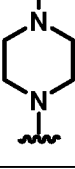
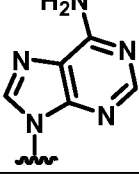
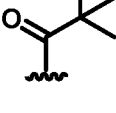
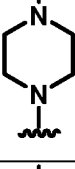
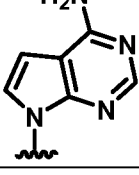
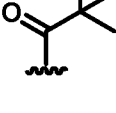
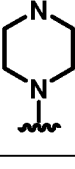
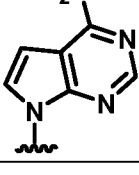
707	OH			
708	F			
709	OH			
710	F			
711	OH			
712	F			
713	OH			
714	F			
715	OH			

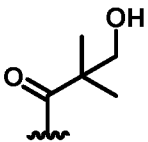
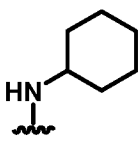
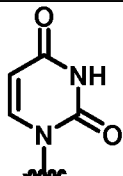
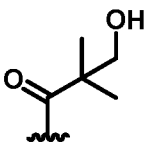
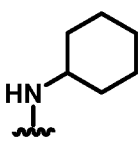
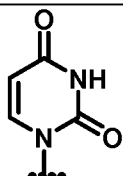
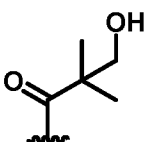
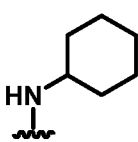
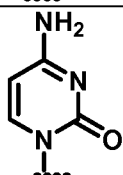
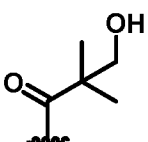
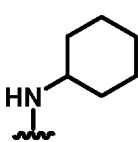
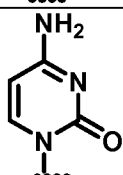
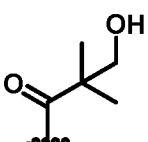
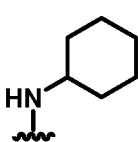
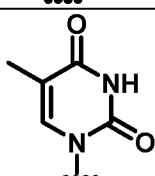
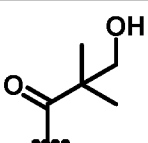
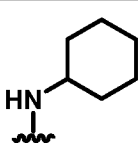
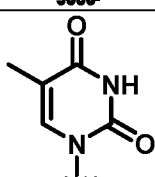
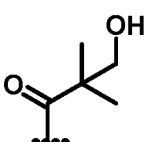
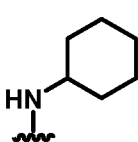
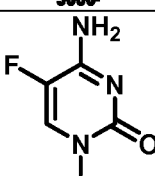
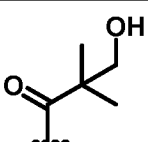
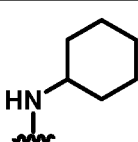
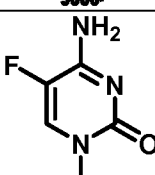
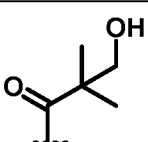
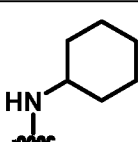
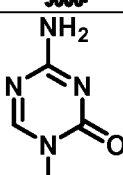
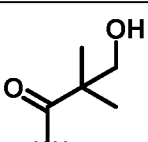
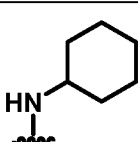
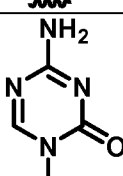
716	F			
717	OH			
718	F			
719	OH			
720	F			
721	OH			
722	F			
723	OH			
724	F			

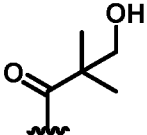
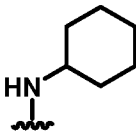
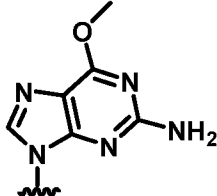
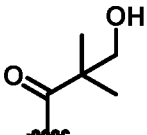
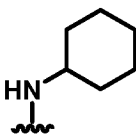
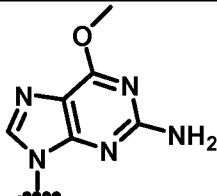
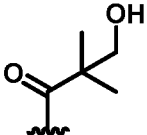
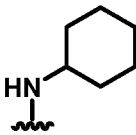
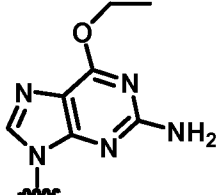
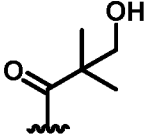
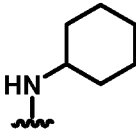
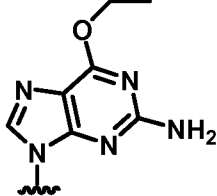
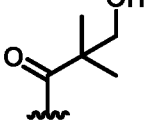
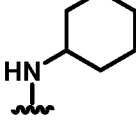
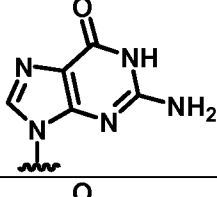
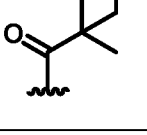
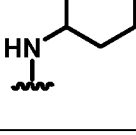
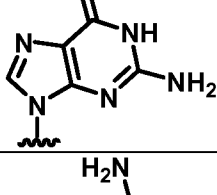
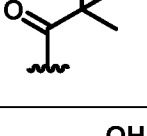
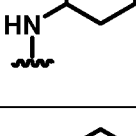
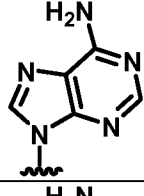
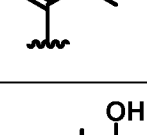
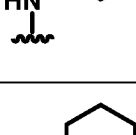
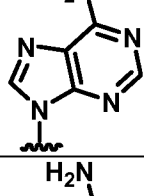
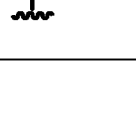
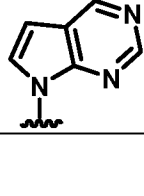
725	OH			
726	F			
727	OH			
728	F			
729	OH			
730	F			
731	OH			
732	F			
733	OH			

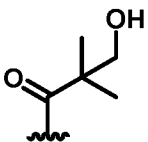
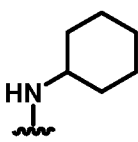
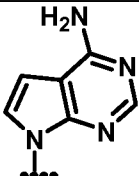
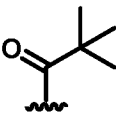
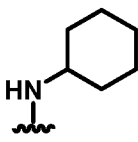
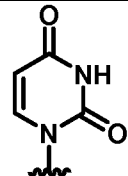
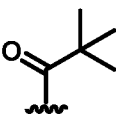
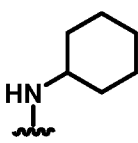
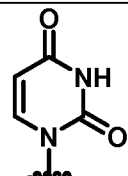
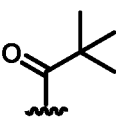
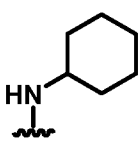
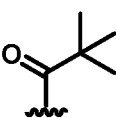
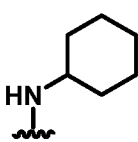
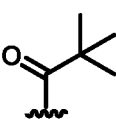
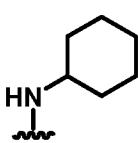
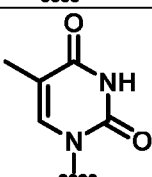
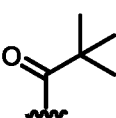
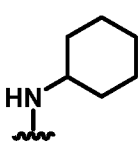
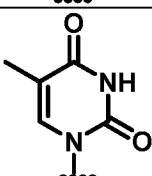
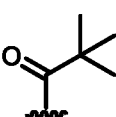
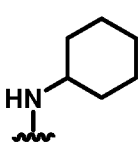
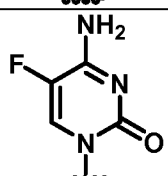
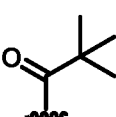
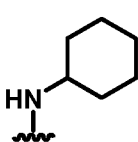
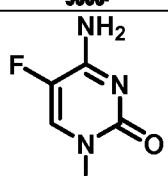
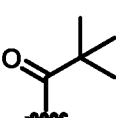
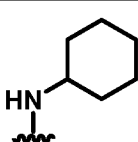
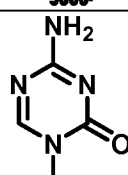
734	F			
735	OH			
736	F			
737	OH			
738	F			
739	OH			
740	F			
741	OH			
742	F			

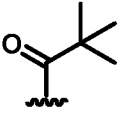
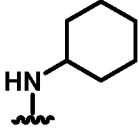
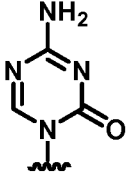
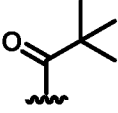
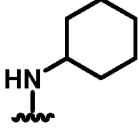
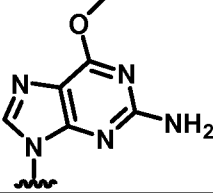
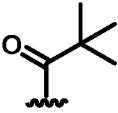
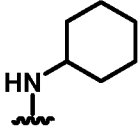
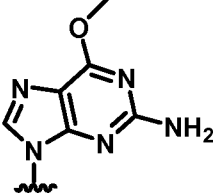
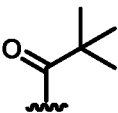
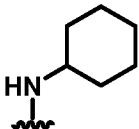
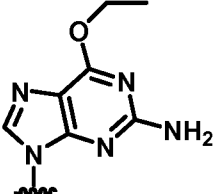
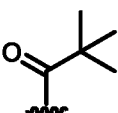
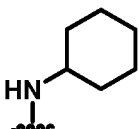
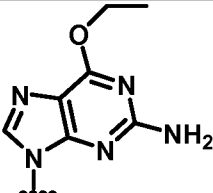
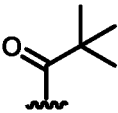
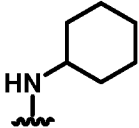
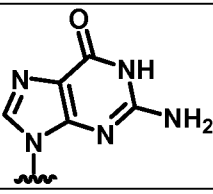
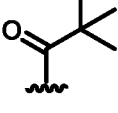
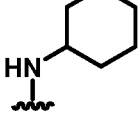
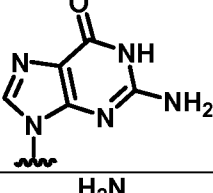
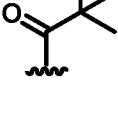
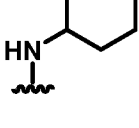
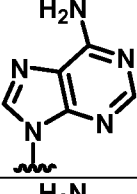
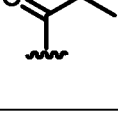
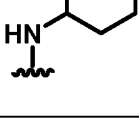
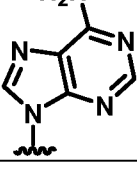
743	OH			
744	F			
745	OH			
746	F			
747	OH			
748	F			
749	OH			
750	F			
751	OH			

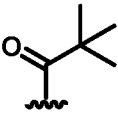
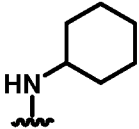
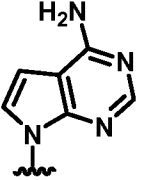
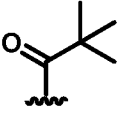
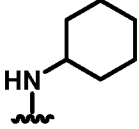
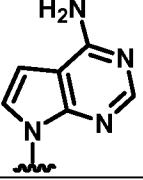
752	F			
753	OH			
754	F			
755	OH			
756	F			
757	OH			
758	F			
759	OH			
760	F			

761	OH			
762	F			
763	OH			
764	F			
765	OH			
766	F			
767	OH			
768	F			
769	OH			
770	F			

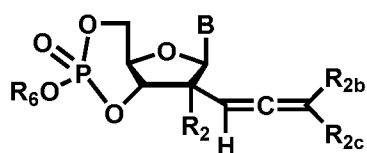
771	OH			
772	F			
773	OH			
774	F			
775	OH			
776	F			
777	OH			
778	F			
779	OH			

780	F			
781	OH			
782	F			
783	OH			
784	F			
785	OH			
786	F			
787	OH			
788	F			
789	OH			

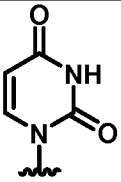
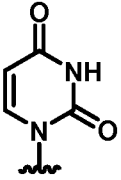
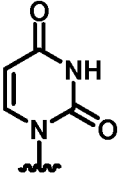
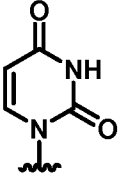
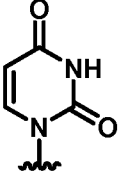
790	F			
791	OH			
792	F			
793	OH			
794	F			
795	OH			
796	F			
797	OH			
798	F			

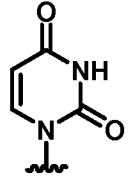
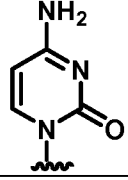
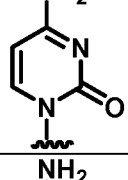
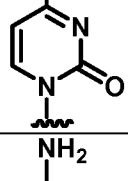
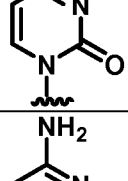
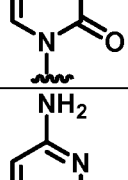
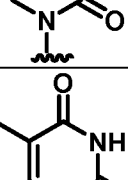
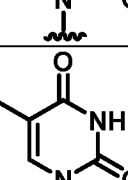
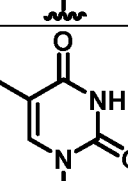
799	OH			
800	F			

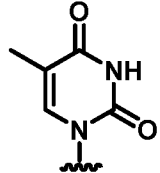
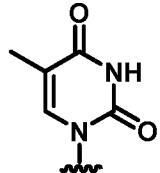
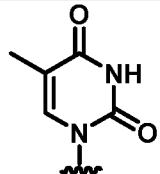
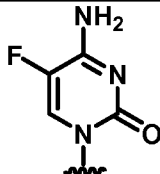
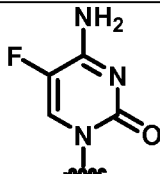
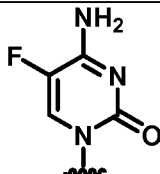
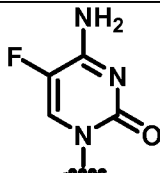
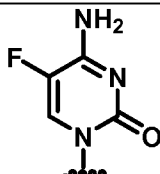
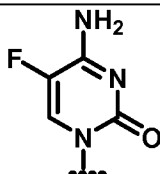
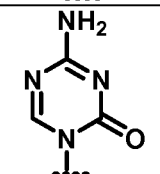
Compounds in Table 5 are represented by Formula (VII-1) wherein R_2 , R_{2b} , R_{2c} , R_6 , and B are delineated for each example in Table 5.

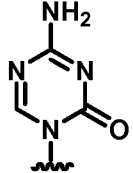
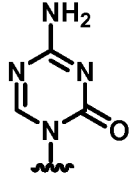
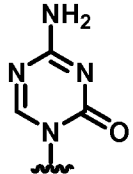
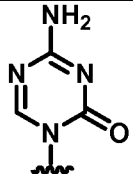
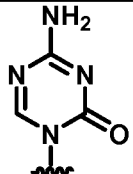
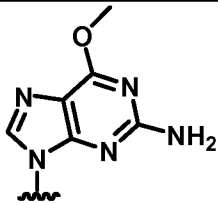
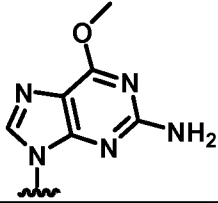
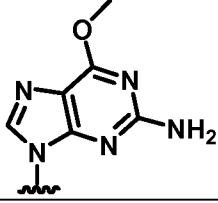
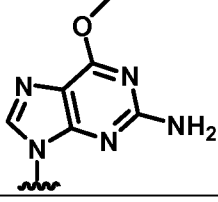


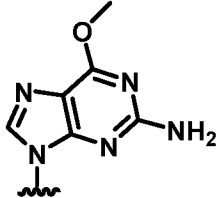
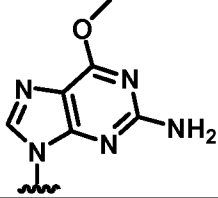
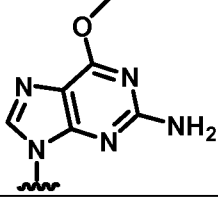
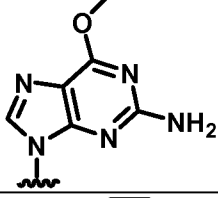
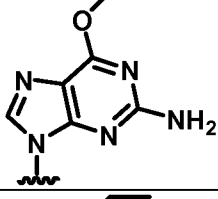
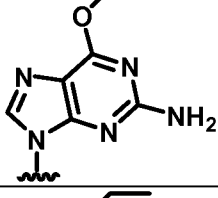
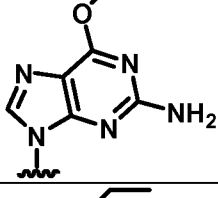
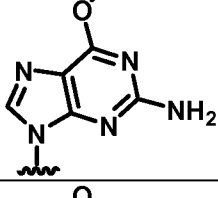
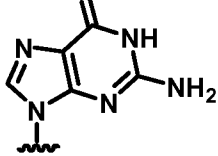
(VII-1)

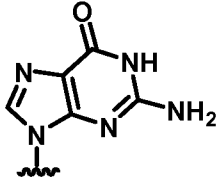
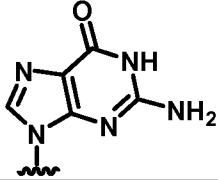
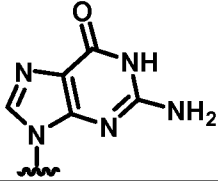
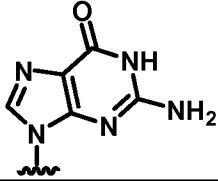
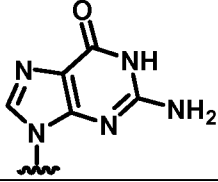
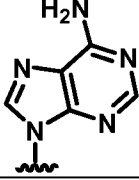
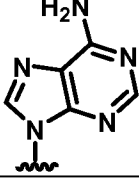
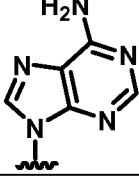
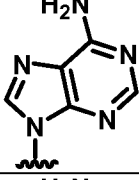
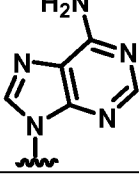
Example#	R_6	R_{2b}	R_{2c}	R_2	B
801	i-Pr	H	H	OH	
802	i-Pr	H	H	F	
803	i-Pr	Me	Me	OH	
804	i-Pr	Me	Me	F	
805	i-Pr	F	F	OH	

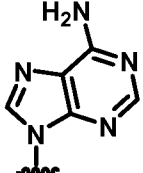
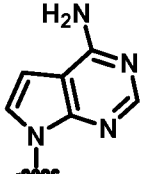
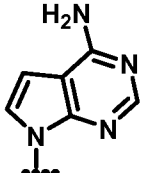
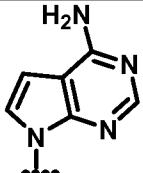
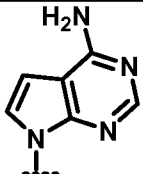
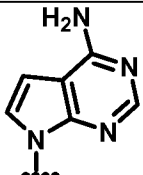
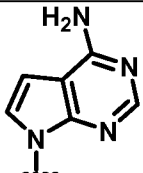
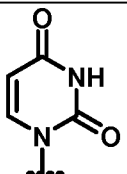
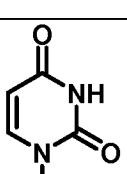
806	i-Pr	F	F	F	
807	i-Pr	H	H	OH	
808	i-Pr	H	H	F	
809	i-Pr	Me	Me	OH	
810	i-Pr	Me	Me	F	
811	i-Pr	F	F	OH	
812	i-Pr	F	F	F	
813	i-Pr	H	H	OH	
814	i-Pr	H	H	F	
815	i-Pr	Me	Me	OH	

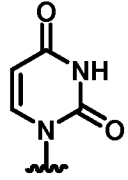
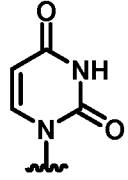
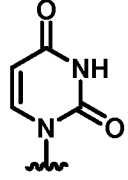
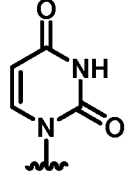
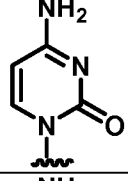
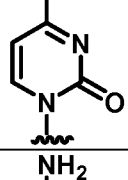
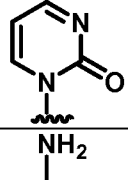
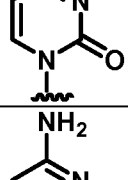
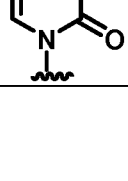
816	i-Pr	Me	Me	F	
817	i-Pr	F	F	OH	
818	i-Pr	F	F	F	
819	i-Pr	H	H	OH	
820	i-Pr	H	H	F	
821	i-Pr	Me	Me	OH	
822	i-Pr	Me	Me	F	
823	i-Pr	F	F	OH	
824	i-Pr	F	F	F	
825	i-Pr	H	H	OH	

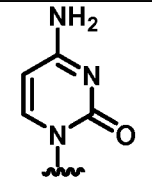
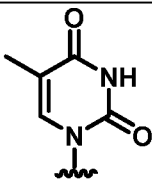
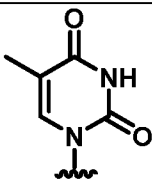
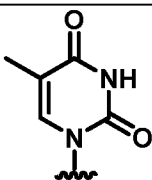
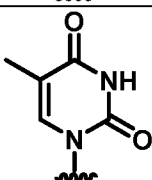
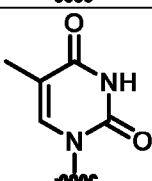
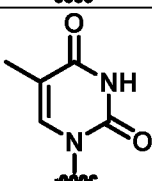
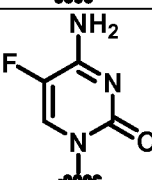
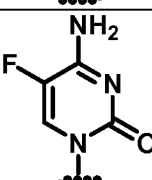
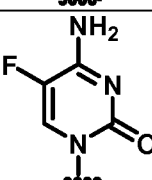
826	i-Pr	H	H	F	
827	i-Pr	Me	Me	OH	
828	i-Pr	Me	Me	F	
829	i-Pr	F	F	OH	
830	i-Pr	F	F	F	
831	i-Pr	H	H	OH	
832	i-Pr	H	H	F	
833	i-Pr	Me	Me	OH	
834	i-Pr	Me	Me	F	

835	i-Pr	F	F	OH	
836	i-Pr	F	F	F	
837	i-Pr	H	H	OH	
838	i-Pr	H	H	F	
839	i-Pr	Me	Me	OH	
840	i-Pr	Me	Me	F	
841	i-Pr	F	F	OH	
842	i-Pr	F	F	F	
843	i-Pr	H	H	OH	

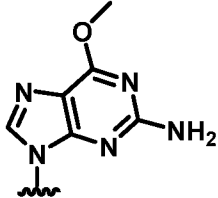
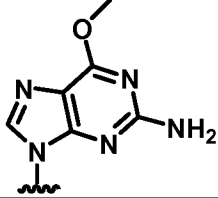
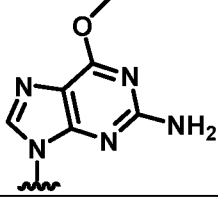
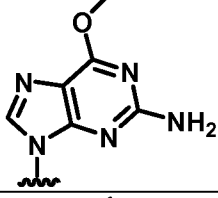
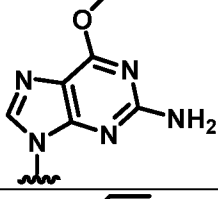
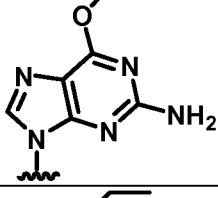
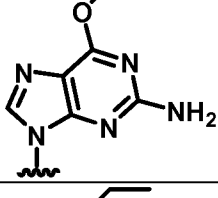
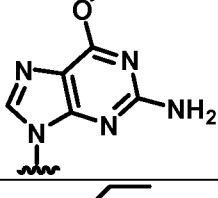
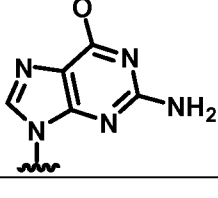
844	i-Pr	H	H	F	
845	i-Pr	Me	Me	OH	
846	i-Pr	Me	Me	F	
847	i-Pr	F	F	OH	
848	i-Pr	F	F	F	
849	i-Pr	H	H	OH	
850	i-Pr	H	H	F	
851	i-Pr	Me	Me	OH	
852	i-Pr	Me	Me	F	
853	i-Pr	F	F	OH	

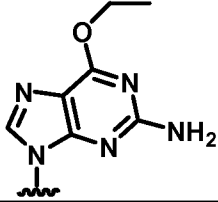
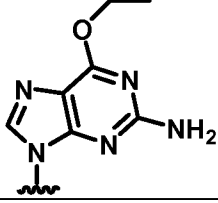
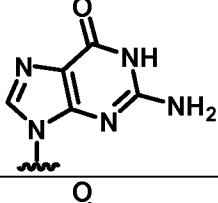
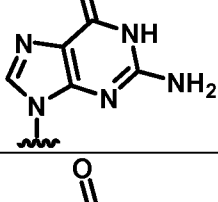
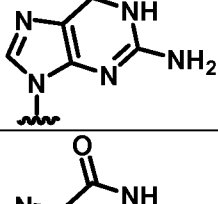
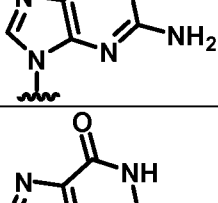
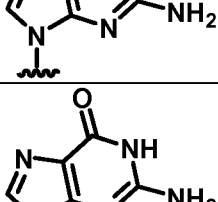
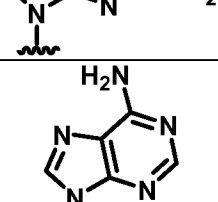
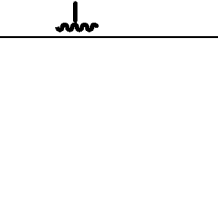
854	i-Pr	F	F	F	
855	i-Pr	H	H	OH	
856	i-Pr	H	H	F	
857	i-Pr	Me	Me	OH	
858	i-Pr	Me	Me	F	
859	i-Pr	F	F	OH	
860	i-Pr	F	F	F	
861	Et	H	H	OH	
862	Et	H	H	F	

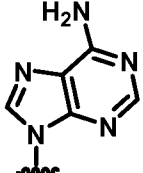
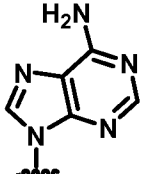
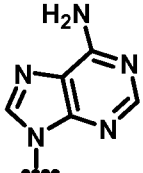
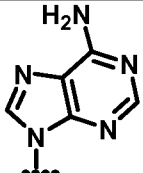
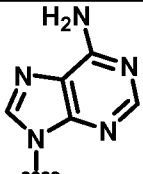
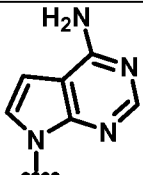
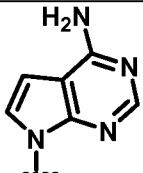
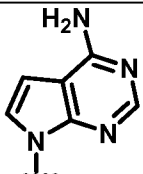
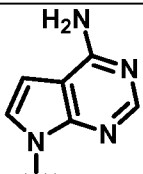
863	Et	Me	Me	OH	
864	Et	Me	Me	F	
865	Et	F	F	OH	
866	Et	F	F	F	
867	Et	H	H	OH	
868	Et	H	H	F	
869	Et	Me	Me	OH	
870	Et	Me	Me	F	
871	Et	F	F	OH	

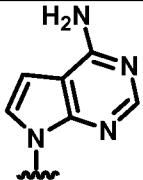
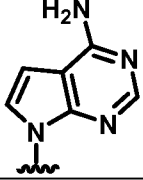
872	Et	F	F	F	
873	Et	H	H	OH	
874	Et	H	H	F	
875	Et	Me	Me	OH	
876	Et	Me	Me	F	
877	Et	F	F	OH	
878	Et	F	F	F	
879	Et	H	H	OH	
880	Et	H	H	F	
881	Et	Me	Me	OH	

882	Et	Me	Me	F	
883	Et	F	F	OH	
884	Et	F	F	F	
885	Et	H	H	OH	
886	Et	H	H	F	
887	Et	Me	Me	OH	
888	Et	Me	Me	F	
889	Et	F	F	OH	
890	Et	F	F	F	
891	Et	H	H	OH	

892	Et	H	H	F	
893	Et	Me	Me	OH	
894	Et	Me	Me	F	
895	Et	F	F	OH	
896	Et	F	F	F	
897	Et	H	H	OH	
898	Et	H	H	F	
899	Et	Me	Me	OH	
900	Et	Me	Me	F	

901	Et	F	F	OH	
902	Et	F	F	F	
903	Et	H	H	OH	
904	Et	H	H	F	
905	Et	Me	Me	OH	
906	Et	Me	Me	F	
907	Et	F	F	OH	
908	Et	F	F	F	
909	Et	H	H	OH	

910	Et	H	H	F	
911	Et	Me	Me	OH	
912	Et	Me	Me	F	
913	Et	F	F	OH	
914	Et	F	F	F	
915	Et	H	H	OH	
916	Et	H	H	F	
917	Et	Me	Me	OH	
918	Et	Me	Me	F	

919	Et	F	F	OH	
920	Et	F	F	F	

In one embodiment of the invention, the 2'-allene-substituted nucleoside derivatives of the invention are the isolated β -D or β -L isomer. In another embodiment of the invention, the nucleoside derivative is in an enantiomeric mixture in which the desired enantiomer is at least 95%, 98% or 99% free of its enantiomer. In a preferred embodiment, the nucleoside derivatives are enantiomerically enriched.

In one embodiment of the present invention, the compounds of the formula (I) are in the β -D configuration. In an alternate embodiment of the present invention, the compounds of formula (I) are in the β -L configuration.

The nucleoside derivatives depicted above are in the β -D configuration, however, it should be understood that the nucleoside derivatives can be either in the β -L or β -D configuration.

The nucleoside derivatives of the present invention are biologically active molecules that are useful in the treatment or prophylaxis of viral infections, and in particular human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV) infection. The compounds are also useful for the treatment of abnormal cellular proliferation, including tumors and cancer. In another embodiment of the present invention, any of the active compounds are useful in the treatment of HCV. One can easily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

For instance, in one embodiment the efficacy of the antiviral compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus in vitro, according to methods set forth more particularly herein, by 50% (i.e. the compound's EC_{50}). In preferred embodiments the compound exhibits an EC_{50} of less than 15 or preferably, less than 10 micromolar in vitro.

In another embodiment, for the treatment or prophylaxis of a viral infection, and in particular an HIV, HCV or HBV infection, in a host, the active compound or its derivative or salt can be administered in combination or alternation with another antiviral agent, such as an anti-HIV agent or anti-hepatitis agent, including those of the formula above. Alternatively, for the treatment of abnormal cellular proliferation, such as tumors and cancer, in a host, the active compound or its derivative or salt can be administered in combination or alternation with another antiproliferative agent, such as an anti-neoplastic agent, including those of the formula above. In general, in combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those skilled in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

The compounds of the present invention can also be used to treat equine infectious anemia virus (EIAV), feline immunodeficiency virus, and simian immunodeficiency virus. (Wang, S., et al, "Activity of nucleoside and non-nucleoside reverse transcriptase inhibitors (NNRTI) against equine infectious anemia virus (EIAV). *"First National Conference on Human Retroviruses and Related Infections*, Washington, D.C., Dec. 12-16, 1993; Sellon D. C., "Equine Infectious Anemia" *Vet. Clin. North Am. Equine Pract. United States*, 9: 321-336, 1993; Philpott, M. S., et al "Evaluation of 9-(2-phosphonylmethoxyethyl)adenine therapy for feline immunodeficiency virus using a quantitative polymerase chain reaction" *Vet. Immunol. Immunopathol.* 35:155166, 1992.

The present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human, comprising a therapeutically effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier.

The present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and

cancer, in a host, preferably a human, comprising a therapeutically effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier.

5 The present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human, comprising a therapeutically effective amount of an active compound of the present invention, in combination with one or more other effective antiviral agent, and in particular an anti-HBV, anti-HCV or anti-HIV agent, optionally in a pharmaceutically acceptable carrier.

10 The present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a host, preferably a human, comprising a therapeutically effective amount of an active compound of the present invention, in combination with one or more other effective antiproliferative agent, such as an antineoplastic agent, optionally in a pharmaceutically acceptable carrier.

15 The present invention also provides a method for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human, comprising administering to the host a therapeutically effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier.

20 The present invention also provides a method for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a host, preferably a human, comprising administering to the host a therapeutically effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier.

25 The present invention also provides a method for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human, comprising administering to the host a therapeutically effective amount of an active compound of the present invention, in combination and/or alternation with one or more other effective antiviral agent, and in particular an anti-HBV, anti-HCV or anti-HIV agent, optionally in a pharmaceutically acceptable carrier.

The present invention also provides a method for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a

host, preferably a human, comprising administering to the host a therapeutically effective amount of an active compound of the present invention, in combination and/or alternation with one or more other effective antiproliferative agent, such as an antineoplastic agent, optionally in a pharmaceutically acceptable carrier.

5 The present invention also provides a use of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human.

10 The present invention also provides a use of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a host, preferably a human.

15 The present invention also provides a use of an active compound of the present invention, in combination and/or alternation with one or more other effective antiviral agent, and in particular an anti-HBV, anti-HCV or anti-HIV agent, optionally in a pharmaceutically acceptable carrier, for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human.

20 The present invention also provides a use of an active compound of the present invention, in combination and/or alternation with one or more other effective antiproliferative agent, such as an antineoplastic agent, optionally in a pharmaceutically acceptable carrier, for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a host, preferably a human.

25 The present invention also provides a use of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human.

30 The present invention also provides a use of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and cancer, in a host, preferably a human.

 The present invention also provides a use of an active compound of the present invention, in combination and/or alternation with one or more other effective

antiviral agent, and in particular an anti-HBV, anti-HCV or anti-HIV agent, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment and/or prophylaxis of a viral infection, and in particular a HBV, HCV or HIV infection, in a host, preferably a human.

5 The present invention also provides an use of an active compound of the present invention, in combination and/or alternation with one or more other effective antiproliferative agent, such as an antineoplastic agent, optionally in a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment and/or prophylaxis of an abnormal cellular proliferation, such as tumors and
10 cancer, in a host, preferably a human.

The invention also provides synthetic methods useful for preparing the compounds of the invention, as well as intermediates disclosed herein that are useful in the preparation of the compounds of the present invention.

The invention as disclosed herein is method and composition for the treatment
15 of HIV, hepatitis B or C, or abnormal cellular proliferation, in humans or other host animals, that includes administering a therapeutically effective amount of a β -D- or β -L-nucleoside derivatives, a pharmaceutically acceptable derivative, including a compound which has been alkylated or acylated on sugar or phosphonate moiety, or on the purine or pyrimidine, or a pharmaceutically acceptable salt thereof, optionally
20 in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral (i.e., anti-HIV-1, anti-HIV-2, anti-hepatitis B/C virus) activity or antiproliferative activity, or are metabolized to a compound that exhibits such activity. The invention as disclosed herein also includes the process for the preparation of such β -D- or β -L-nucleoside derivatives.

25

Stereoisomerism and Polymorphism

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers or enantiomers, with all isomeric forms being included in the present invention. Compounds of the present
30 invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. The present invention encompasses racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein. Optically active forms of the compounds can be prepared using any

method known in the art, including but not limited to by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials; by chiral synthesis, or by chromatographic separation using a chiral stationary phase or by enzymatic resolution.

5

Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of

10

a larger group.

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl.

15

The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbons, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl.

20

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

25

The terms "C₁-C₈ alkyl," or "C₁-C₁₂ alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and eight, or one and twelve carbon atoms, respectively. Examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, heptyl and octyl radicals; and examples of C₁-C₁₂ alkyl radicals include, but are not limited to, ethyl, propyl, isopropyl, *n*-hexyl, octyl, decyl, dodecyl radicals.

30

The term "C₂-C₈ alkenyl," or "C₂-C₂₀ alkenyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight carbon atoms having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl, and the like.

The term "C₂-C₈ alkynyl," or "C₂-C₂₀ alkynyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight carbon atoms having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl, and the like.

The term "C₃-C₈-cycloalkyl", or "C₃-C₁₂-cycloalkyl," as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring compound. Examples of C₃-C₈-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The terms "C₂-C₈ alkylene," or "C₂-C₈ alkenylene," as used herein, refer to saturated or unsaturated respectively, straight- or branched-chain hydrocarbon diradicals containing between two and eight carbon atoms, while the diradical may reside at the same or different carbon atoms.

The term "C₃-C₈ cycloalkenyl", or "C₃-C₁₂ cycloalkenyl" as used herein, refers to monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond. Examples of C₃-C₈ cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂ cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

It is understood that any alkyl, alkenyl, alkynyl and cycloalkyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group. An "aliphatic" group is a non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted.

The term “alicyclic,” as used herein, denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such

5 alicyclic groups may be further substituted.

The terms “heterocyclic” or “heterocycloalkyl” can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) 10 the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (iv) any of the above rings may be fused to an aromatic ring, and (v) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocyclic groups include, but are not limited to, 1,3-dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, 15 imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted.

The term “substituted” refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, 20 but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -N₃, -CN, -NH₂, protected amino, oxo, thioxo, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₈-alkenyl, -NH-C₂-C₈-alkynyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₈-alkenyl, -O-C₂-C₈-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, - 25 C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₈-alkenyl, -C(O)-C₂-C₈-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₈-alkenyl, -CONH-C₂-C₈-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₈-alkenyl, -OCO₂-C₂-C₈-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, - 30 OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₈-alkenyl, -OCONH-C₂-C₈-alkynyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₈-alkenyl, -NHC(O)-C₂-C₈-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -

NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₈-alkenyl, -NHCO₂-C₂-C₈-alkynyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₈-alkenyl, -NHC(O)NH-C₂-C₈-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₈-alkenyl, -NHC(S)NH-C₂-C₈-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₈-alkenyl, -NHC(NH)NH-C₂-C₈-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₈-alkenyl, -NHC(NH)-C₂-C₈-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₈-alkenyl, -C(NH)NH-C₂-C₈-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₈-alkenyl, -S(O)-C₂-C₈-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₈-alkenyl, -SO₂NH-C₂-C₈-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₈-alkenyl, -NHSO₂-C₂-C₈-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₈-alkenyl, -S-C₂-C₈-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

The term "halogen," as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reactions. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

5 The term "hydroxy protecting group" or "thiol protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group or thiol against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic
10 Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl,
15 allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl- 3 -butenyl, allyl, benzyl, para-methoxybenzyldiphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, 2-
20 (trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxyl protecting groups for the present invention are acetyl (Ac or -C(O)CH₃), benzoyl (Bz or -C(O)C₆H₅), and trimethylsilyl (TMS or -Si(CH₃)₃).

25 The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "hydroxy prodrug group", as used herein, refers to a promoietty group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking
30 the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group in vivo. Hydroxy prodrug groups as known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery, (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992).

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protic solvent" as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those

skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of
5 protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

10 The term “hydrogen” includes deuterium. In general, the identification of an element embraces the isotopes of the element, as suitable for the preparation a pharmaceutical.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture
15 and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid
20 chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the Formula herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and
25 deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH (1999); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John
30 Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The term “subject” as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system),
5 increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for
10 amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some
15 combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include
20 both E and Z geometric isomers, or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. Tautomers may be in cyclic or acyclic. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond
25 depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,
30 irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by

reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended

use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of the invention.

Various forms of prodrugs are known in the art, for example, as discussed in

5 Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed).

"Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, *J. of Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975); Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002); and J. Rautio *et al.*, "Prodrugs: design and clinical applications", *Nature Review - Drug Discovery*, 7, 255-270 (2008).

15 The present invention also relates to solvates of the compounds of Formula (I), for example hydrates.

It is to be understood that when a variable appears two or more times in a formula set forth herein, each occurrence of the variable is independently selected from the identities set forth for that variable.

20 This invention also encompasses pharmaceutical compositions containing, and methods of treating viral infections through administering, pharmaceutically acceptable prodrugs of compounds of the invention. For example, compounds of the invention having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a

25 polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine,

30 demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates,

phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as

5 (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or

10 phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a

15 therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, excipient, encapsulating material or formulation auxiliary of any type. Some examples of

20 materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters

25 such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as

30 well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally,

vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with

5 pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

10 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl
15 acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and
20 suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally
25 acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In
30 addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders
5 which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be
10 accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is
15 accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include
20 poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-
25 irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal
30 administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as

sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof and j) coloring agents. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxybutylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets, may be, made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may

be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.*, and WO 98/43,650 by Montgomery, all of which are incorporated herein by reference). A discussion of pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The compounds and pharmaceutical compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutical

compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, the compound of the present invention may be administered concurrently with another anti-HCV agent), or they may achieve different effects (*e.g.*, control of any adverse effects).

The compounds of the invention may be administered intravenously, intramuscularly, intraperitoneally, subcutaneously, topically, orally, or by other acceptable means. The compounds may be used to treat mammals (*i.e.*, humans, livestock, and domestic animals), birds, lizards, and any other organism, which can tolerate the compounds.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

ANTIVIRAL ACTIVITY

According to the methods of treatment of the present invention, viral infections, and conditions are treated or prevented in a patient such as a human or another animal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (*i.e.*, measurable by some test or marker) or subjective (*i.e.*, subject gives an indication of or feels an effect). A therapeutically effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will

also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific

5 therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound

10 employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example,

15 from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or

20 multiple doses.

The compounds of the invention described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a

25 dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of a therapeutically effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of

30 this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically expipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical

preparation will contain from about 5% to about 95% active compound (w/w).
Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific
5 dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the
10 treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is
15 retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

When the compositions of this invention comprise a combination of a compound of the invention described herein and one or more additional therapeutic or
20 prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single
25 dosage form, mixed together with the compounds of this invention in a single composition.

The said "additional therapeutic or prophylactic agents" includes but not limited to, immune therapies (eg. interferon), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as
30 beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (eg ribavirin and amantidine).

The compositions according to the invention may also be used in combination with gene replacement therapy.

Pharmaceutically Acceptable Derivatives

5 The compound of the present invention can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound. Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the derivative and testing its antiviral and anti-proliferative activity according to the methods described herein, or other method
10 known to those skilled in the art.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable
15 anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate and α -glycerophosphate. Suitable inorganic salts may also be formed, including sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures
20 well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Any of the nucleosides described herein can be administered as a nucleotide
25 prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety
30 are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, *Antiviral Research*, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L. S. et al 1990. "Novel membrane interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." *AIDS Res. Hum. Retro Viruses*. 6:491-501; Piantadosi, C., J. et al 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." *J. Med. Chem.* 34:1408.1414; Hosteller, K. Y. et al 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3'-deoxythymidine." *Antimicrob. Agents Chemother.* 36:2025.2029; Hosetler, K. Y., et al 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." *J. Biol. Chem.* 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Pat. Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); 5,194,654 (Mar. 16, 1993, Hostetler et al., 5,223,263 (Jun. 29, 1993, Hostetler et al.); 5,256,641 (Oct. 26, 1993, Yatvin et al.); 5,411,947 (May 2, 1995, Hostetler et al.); 5,463,092 (Oct. 31, 1995, Hostetler et al.); 5,543,389 (Aug. 6, 1996, Yatvin et al.); 5,543,390 (Aug. 6, 1996, Yatvin et al.); 5,543,391 (Aug. 6, 1996, Yatvin et al.); and 5,554,728 (Sep. 10, 1996; Basava et al.), all of which are incorporated herein by reference. Foreign patent publications that disclose lipophilic substituents that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, WO 90/00555, WO 91/16920, WO 91/18914, WO 93/00910, WO 94/26273, WO 96/15132, EP 0 350 287, and WO 91/19721.

Nonlimiting examples of nucleotide prodrugs are described in the following references: J. K. Dickson, Jr. et al, "Orally active squalene synthetase inhibitors: bis((acyloxy)alkyl) prodrugs of the α -phosphonosulfonic acid moiety" *J. Med. Chem.* 1996, 39, 661-664; T. Kurz, et al, "Synthesis and antimalarial activity of chain substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098" *Bioorg. Med. Chem.* 2006, 14, 5121-5135; J. E. Starrett, Jr. et al, "Synthesis, oral bioavailability determination, and *in vitro* evaluation of prodrugs of the antiviral agent 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA)" *J. Med. Chem.* 1994, 37, 1857-1864; H. T. Serafinowska, et al, "Synthesis and *in vivo* evaluation of prodrugs of 9-[2-

(phosphonomethoxy)ethoxy]adenine" *J. Med. Chem.* 1995, 38, 1372-1379; S. Benzaria, *et al*, "Synthesis, *in vitro* antiviral evaluation, and stability studies of bis(*S*-acyl-2-thioethyl) ester derivatives of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as potential PMEA prodrugs with improved oral bioavailability" *J. Med. Chem.* 1996, 39, 4958-4965; M. S. Louie and H. Chapman, "An efficient process for the synthesis of cyclic HPMPC" *Nucleosides, Nucleotides Nucleic acid* 2001, 20, 1099-1102; J.-R. Choi *et al*, "A novel class of phosphonate nucleosides. 9-[(1-phosphonomethoxy)-cyclopropyl)methyl]guanine as a potent and selective anti-HBV agent" *J. Med. Chem.* 2004, 47, 2864-2869; M. Wu, *et al*, "Synthesis of 9-[1-(substituted)-3-(phosphonomethoxy)propyl]adenine derivatives as possible antiviral agents" *Nucleosides, Nucleotides Nucleic acid.* 2005, 24, 1543-1568; X. Fu, *et al*, "Design and synthesis of novel bis(L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) with improved anti-HBV activity" *Bioorg. Med. Chem. Lett.* 2007, 17, 465-470.

Similarly, the 5'-phosphonate can also be provided as various phosphonate prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the phosphonate. A number of phosphonate prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of one or more hydroxy on the phosphonate moiety can be used to achieve a desired effect.

Combination and Alternation Therapy for HIV, HBV or HCV

It has been recognized that drug-resistant variants of HIV, HBV and HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for a protein such as an enzyme used in viral replication, and most typically in the case of HIV, reverse transcriptase, protease, or DNA polymerase, and in the case of HBV, DNA polymerase, or in the case of HCV, RNA polymerase, protease, or helicase. Recently, it has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

The second antiviral agent for the treatment of HIV, in one embodiment, can be a reverse transcriptase inhibitor (a "RTI"), which can be either a synthetic nucleoside (a "NRTI") or a non-nucleoside compound (a "NNRTI"). In an alternative embodiment, in the case of HIV, the second (or third) antiviral agent can be a protease inhibitor. In other embodiments, the second (or third) compound can be a pyrophosphate analog, or a fusion binding inhibitor. A list compiling resistance data collected *in vitro* and *in vivo* for a number of antiviral compounds is found in Schinazi, et al, Mutations in retroviral genes associated with drug resistance, *International Antiviral News*, 1997.

Preferred compounds for combination or alternation therapy for the treatment of HBV include 3TC, FTC, L-FMAU, interferon, adefovir dipivoxil, entecavir, telbivudine (L-dT), valtorcitabine (3'-valinyl L-dC), β -D-dioxolanyl-guanine (DXG), β -D-dioxolanyl-2,6-diaminopurine (DAPD), and β -D-dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, lobucavir, ganciclovir, and ribavirin.

Preferred examples of antiviral agents that can be used in combination or alternation with the compounds disclosed herein for HIV therapy include cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); ziagen (abacavir), emtriva, viread (tenofovir DF), carbovir, acyclovir, foscarnet, interferon, AZT, DDI, D4T, CS-87 (3'-azido-2',3'-dideoxyuridine), and β -D-dioxolane nucleosides such as β -D-dioxolanyl-guanine (DXG), β -D-dioxolanyl-2,6-diaminopurine (DAPD), and β -D-dioxolanyl-6-chloropurine (ACP), and integrase inhibitors such as MK-0518.

Preferred protease inhibitors (PIs) include crixivan (indinavir), viracept (nelfinavir), norvir (ritonavir), invirase (saquinavir), aptivus (tipranavir), kaletra, lexiva (fosamprenavir), reyataz (atazanavir) and TMC-114.

Preferred Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) include rescripton (delavirdine), sustiva (efavirenz), viramune (nevirapine) and TMC-125.

Preferred Entry inhibitors include fuzeon (T-20), PRO-542, TNX-355, vicriviroc, aplaviroc and maraviroc.

A more comprehensive list of compounds that can be administered in combination or alternation with any of the disclosed nucleosides include (1S,4R)-4-[2-amino-6-cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate ("1592", a carbovir analog; GlaxoWellcome); 3TC: (-)- β -L-2',3'-dideoxy-3'-thiacytidine (GlaxoWellcome); a-APA R18893: a-nitro-anilino-phenylacetamide; A-

- 77003; C2 symmetry-based protease inhibitor (Abbott); A-75925: C2 symmetry-based protease inhibitor (Abbott); AAP-BHAP: bishetero-aryl piperazine analog (Upjohn); ABT-538: C2-symmetry-based protease inhibitor (Abbott); AzddU: 3'-azido-2',3'-dideoxyuridine; AZT: 3'-azido-3'-deoxythymidine (GlaxoWellcome);
- 5 AZT-p-ddI: 3'-azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxyinosinic acid (Ivax); BHAP: bisheteroaryl-piperazine; BILA 1906: N-{1S-[[[3-[2S-{(1,1-dimethylethyl)amino]carbonyl}-4R]-3-pyridinylmethyl]thio]-1-piperidinyl]-2R-hydroxy-1S-(phenylmethyl)-propyl]amino]-carbonyl]-2-methylpropyl}-2-quinolinecarboxamide (Bio Mega/Boehringer-Ingelheim); BILA 2185: N-(1,1-
- 10 dimethylethyl)-1-[2S-[[2-2,6-dimethylphenoxy)-1-oxethyl]amino]-2R-hydroxy-4-phenylbutyl]-4R-pyridinylthio)-2-piperidinecarboxamide (BioMega/Boehringer-Ingelheim); BMS 186,318: aminodiol derivative HIV-1 protease inhibitor (Bristol-Myers-Squibb); d4API: 9-[2,5-d]hydro-5-(phosphonomethoxy)-2-furanyl adenine (Gilead); d4C: 2',3'-didehydro-2',3'-dideoxycytidine; d4T: 2',3'-didehydro-3'-
- 15 deoxythymidine (Bristol-Myers-Squibb); ddC: 2',3'-dideoxycytidine (Roche); ddI: 2',3'-dideoxyinosine (Bristol-Myers-Squibb); DMP-266: a 1,4-dihydro-2H-3,1-benzoxazin-2-one; DMP-450: {[4R-(4-a,5-a,6-b,7-b)]-hexahydro-5,6-bis(hydroxy)-1,3-bis(3-amino)phenyl]-methyl)-4,7-bis-(phenylmethyl)-2H-1,3-diazepin-2-one}-bismesylate (Gilead); DXG: (-)-β-D-dioxolane-guanosine (Gilead); EBU-dM: 5-ethyl-
- 20 1-ethoxymethyl-6-(3,5-dimethylbenzyl)-uracil; E-EBU: 5-ethyl-1-ethoxymethyl-6-benzyluracil; DS: dextran sulfate; E-EPSeU: 1-(ethoxymethyl)-(6-phenylselenyl)-5-ethyluracil; E-EPU: 1-(ethoxymethyl)-(6-phenylthio)-5-ethyluracil; FTC: β-2',3'-dideoxy-5-fluoro-3'-thiacytidine (Gilead); HBY097: S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1H)-thione; HEPT: 1-[(2-
- 25 hydroxyethoxy)methyl]-6-(phenylthio)thymine; HIV-1: human immunodeficiency virus type 1; JM2763: 1,1'-(1,3-propanediyl)-bis-1,4,8,11-tetraaza-cyclotetradecane (Johnson Matthey); JM3100: 1,1'-[1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane (Johnson Matthey); KNI-272: (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid-containing tripeptide; L-697,593: 5-ethyl-6-methyl-3-(2-
- 30 phthalimido-ethyl)pyridin-2(1H)-one; L-735,524: hydroxy-amino-pentane amide HIV-1 protease inhibitor (Merck); L-697,661: 3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one; L-FDDC: (-)-β-L-5-fluoro-2',3'-dideoxycytidine; L-FDOC: (-)-β-L-5-fluoro-dioxolane cytosine; MKC442: 6-benzyl-1-ethoxymethyl-5-isopropyluracil (1-EBU; Mitsubishi); Nevirapine: 11-

- cyclopropyl-5,1 l-dihydro-4-methyl-6H-dipyridol-[3,2-b:2',3'-e]-diazepin-6-one (Boehringer-Ingelheim); NSC648400: 1-benzyloxymethyl-5-ethyl-6-(alpha-pyridylthio)uracil (E-BPTU); P9941: [2-pyridylacetyl-IlePheAla-y(CHOH)]₂ (Dupont Merck); PFA: phosphonoformate (foscarnet; Astra); PMEA: 9-(2-phosphonylmethoxyethyl)adenine (Gilead); PMPA: (R)-9-(2-phosphonylmethoxypropyl)adenine (Gilead); Ro 31-8959: hydroxyethylamine derivative HIV-1 protease inhibitor (Roche); RPI-312: peptidyl protease inhibitor, 1-[(3S)-3-(n-alpha-benzyloxycarbonyl)-1-asparginyl]-amino-2-hydroxy-4-phenylbutyryl]-n-tert-1-proline amide; 2720: 6-chloro-3,3-dimethyl-4-(isopropenyloxycarbonyl)-3,4-dihydro-quinoxalin-2-(1H)-thione; SC-52151: hydroxy-ethylurea isostere protease inhibitor (Searle); SC-55389A: hydroxyethyl-urea isostere protease inhibitor (Searle); TIBO R82150: (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-jk]-[1,4]benzodiazepin-2(1H)-thione (Janssen); TIBO 82913: (+)-(5s)-4, 5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,ljk]-[1,4]benzo-diazepin-2(1H)-thione (Janssen); TSAO-m3T: [2',5'-bis-O-(tert-butyl-dimethylsilyl)-3'-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide)]-β-D-pento-furanosyl-N3-methylthymine; U90152: 1-[3-[(1-methylethyl)-amino]-2-pyridinyl]-4-[[5-[(methylsulphonyl)-amino]-1H-indol-2-yl]carbonyl]piperazine; UC: thiocarboxanilide derivatives (Uniroyal); UC-781: N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide; UC-82: N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-thiophenecarbothioamide; VB 11,328: hydroxyethyl-sulphonamide protease inhibitor (Vertex); VX-478: hydroxyethylsulphonamide protease inhibitor (Vertex); XM 323: cyclic urea protease inhibitor (Dupont Merck).

- 25 The active compound can also be administered in combination or alternation with ribavarin, interferon, interleukin or a stabilized prodrug of any of them. More broadly described, the compound can be administered in combination or alternation with any of the anti-HCV drugs listed below in Table 6.

Table 6: Table of anti-Hepatitis C Compounds in Current Clinical Development		
Drug name	Drug category	Pharmaceutical Company
PEGASYS pegylated interferon alfa-2a	Long acting interferon	Roche
INFERGEN	Long acting interferon	InterMune

interferon alfacon-1		
OMNIFERON natural interferon	Long acting interferon	Viragen
ALBUFERON	Long acting interferon	Human Genome Sciences
REBIF interferon beta-la	Interferon	Ares-Serono
Omega Interferon	Interferon	BioMedicine
Oral Interferon alpha	Oral Interferon	Amarillo Biosciences
Interferon gamma-lb	Anti-fibrotic	InterMune
IP-501	Anti-fibrotic	InterMune
Merimebodib VX-497	IMPDH inhibitor (inosine monophosphate dehydrogenase)	Vertex
AMANTADINE (Symmetrel)	Broad Antiviral Agent	Endo Labs Solvay
IDN-6556	Apoptosis regulation	Idun Pharma.
XTL-002	Monoclonal Antibody	XTL
HCV/MF59	Vaccine	Chiron
CIVACIR	Polyclonal Antibody Therapeutic vaccine	NABI Innogenetics
VIRAMIDINE	Nucleoside Analogue	ICN
ZADAXIN (thymosin alfa-1)	Immunomodulator	Sci Clone
CEPLENE (histamine)	Immunomodulator	Maxim
VX 950/LY 570310	Protease inhibitor	Vertex/Eli Lilly
ISIS 14803	Antisense	Isis Pharmaceutical/Elan
IDN-6556	Caspase inhibitor	Idun Pharmaceuticals
JTK 003	Polymerase Inhibitor	AKROS Pharma
Tarvacin	Anti-Phospholipid Therapy	Peregrine
HCV-796	Polymerase Inhibitor	ViroPharma/Wyeth
CH-6	Protease inhibitor	Schering
ANA971	Isatoribine	ANADYS
ANA245	Isatoribine	ANADYS
CPG 10101 (Actilon)	Immunomodulator	Coley
Rituximab (Rituxam)	Anti-CD20 Monoclonal Antibody	Genetech/IDEC
NM283 (Valopicitabine)	Polymerase Inhibitor	Idenix Pharmaceuticals
HepX TM -C	Monoclonal Antibody	XTL
IC41	Therapeutic Vaccine	Intercell
Medusa Interferon	Longer acting interferon	Flamel Technology
E-1	Therapeutic Vaccine	Innogenetics
Multiferon	Long Acting Interferon	Viragen
BILN 2061	Protease inhibitor	Boehringer-Ingelheim
TMC435350	Protease inhibitor	Tibotec/Medivir
Telaprevir (VX-950)	Protease inhibitor	Vertex
Boceprevir (SCH 503034)	Protease inhibitor	Schering-Plough
ACH-1625	Protease inhibitor	Achillion
ABT-450	Protease inhibitor	Abbott/Enanta
BI-201335	Protease inhibitor	Boehringer-Ingelheim
PHX-1766	Protease inhibitor	Phenomix
VX-500	Protease inhibitor	Vertex
MK-7009	protease inhibitor	Merck
R7227 (ITMN-191)	protease inhibitor	InterMune
Narlaprevir (SCH 900518)	Protease inhibitor	Schering/Merck
Alinia (nitazoxanide)	To be determined	Romark
ABT-072	Polymerase Inhibitor	Abbott
ABT-333	Polymerase Inhibitor	Abbott
Filibuvir (PF-00868554)	Polymerase Inhibitor	Pfizer
VCH-916	Polymerase Inhibitor	Vertex

R7128 (PSI6130)	Polymerase Inhibitor	Roche/Pharmasset
IDX184	Polymerase Inhibitor	Idenix
R1626	Polymerase inhibitor	Roche
MK-3281	Polymerase inhibitor	Merck
PSI-7851	Polymerase inhibitor	Pharmasset
ANA598	Polymerase inhibitor	Anadys Pharmaceuticals
BI-207127	Polymerase inhibitor	Boehringer-Ingelheim
GS-9190	Polymerase inhibitor	Gilead
VCH-759	Polymerase Inhibitor	Vertex
Clemizole	NS4B inhibitor	Eiger Biopharmaceuticals
A-832	NS5A inhibitor	ArrowTherapeutics
BMS-790052	NS5A inhibitor	Bristol-Myers-Squibb
ITX5061	Entry inhibitor	iTherx
GS-9450	Caspase inhibitor	Gilead
ANA773	TLR agonist	Anadys
CYT107	Immunomodulator	Cytheris
SPC3649 (LNA-antimiR TM -122)	microRNA	Santaris Pharma
Debio 025	Cyclophilin inhibitor	Debiopharm
SCY-635	Cyclophilin inhibitor	Scynexis

Combination Therapy for the Treatment of Proliferative Conditions

- In another embodiment, the compounds, when used as an antiproliferative, can be administered in combination with another compound that increases the effectiveness of the therapy, including but not limited to an antifolate, a 5-fluoropyrimidine (including 5-fluorouracil), a cytidine analogue such as β -L-1,3-dioxolanyl cytidine or β -L-1,3-dioxolanyl 5-fluorocytidine, antimetabolites (including purine antimetabolites, cytarabine, fudarabine, floxuridine, 6-mercaptopurine, methotrexate, and 6-thioguanine), hydroxyurea, mitotic inhibitors (including CPT-11, Etoposide (VP-21), taxol, and vinca alkaloids such as vincristine and vinblastine, an alkylating agent (including but not limited to busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and thiotepa), nonclassical alkylating agents, platinum containing compounds, bleomycin, an anti-tumor antibiotic, an anthracycline such as doxorubicin and daunomycin, an anthracenedione, topoisomerase II inhibitors, hormonal agents (including but not limited to corticosteroids (dexamethasone, prednisone, and methylprednisone), androgens such as fluoxymesterone and methyltestosterone, estrogens such as diethylstilbesterol, antiestrogens such as tamoxifen, LHRH analogues such as leuprolide, antiandrogens such as flutamide, aminoglutethimide, megestrol acetate, and medroxyprogesterone), asparaginase, carmustine, lomustine, hexamethylmelamine, dacarbazine, mitotane, streptozocin, cisplatin, carboplatin, levamasole, and leucovorin. The compounds of the present invention can also be used in combination

with enzyme therapy agents and immune system modulators such as an interferon, interleukin, tumor necrosis factor, macrophage colony-stimulating factor and colony stimulating factor.

Unless otherwise defined, all technical and scientific terms used herein are
5 accorded the meaning commonly known to one of ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

Although the invention has been described with respect to various preferred
10 embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

Abbreviations

Abbreviations which may be used in the descriptions of the scheme and the
15 examples that follow are: Ac for acetyl; AcOH for acetic acid; AIBN for azobisisobutyronitrile; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc₂O for di-*tert*-butyl-dicarbonate; Boc for *t*-butoxycarbonyl; Bpoc for 1-methyl-1-(4-biphenyl)ethyl carbonyl; Bz for benzoyl; Bn for benzyl; BocNHOH for *tert*-butyl N-hydroxycarbamate; *t*-BuOK for potassium *tert*-butoxide; Bu₃SnH for tributyltin
20 hydride; BOP for (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium Hexafluorophosphate; Brine for sodium chloride solution in water; CDI for carbonyldiimidazole; CH₂Cl₂ for dichloromethane; CH₃ for methyl; CH₃CN for acetonitrile; Cs₂CO₃ for cesium carbonate; CuCl for copper (I) chloride; CuI for copper (I) iodide; dba for dibenzylidene acetone; dppb for diphenylphosphino butane;
25 DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC for N,N'-dicyclohexylcarbodiimide; DEAD for diethylazodicarboxylate; DIAD for diisopropyl azodicarboxylate; DIPEA or (i-Pr)₂EtN for N,N,-diisopropylethyl amine; Dess-Martin periodinane for 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; DMAP for 4-dimethylaminopyridine; DME for 1,2-dimethoxyethane; DMF for N,N-
30 dimethylformamide; DMSO for dimethyl sulfoxide; DMT for di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl; DPPA for diphenylphosphoryl azide; EDC for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide; EDC HCl for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; EtOAc for ethyl acetate; EtOH for ethanol; Et₂O for diethyl ether; HATU for O-(7-azabenzotriazol-1-

yl)-N,N,N',N',-tetramethyluronium Hexafluorophosphate; HCl for hydrogen chloride; HOBT for 1-hydroxybenzotriazole; K₂CO₃ for potassium carbonate; *n*-BuLi for *n*-butyl lithium; *i*-BuLi for *i*-butyl lithium; *t*-BuLi for *t*-butyl lithium; PhLi for phenyl lithium; LDA for lithium diisopropylamide; LiTMP for lithium 2,2,6,6-tetramethylpiperidinate; MeOH for methanol; Mg for magnesium; MOM for methoxymethyl; Ms for mesyl or -SO₂-CH₃; Ms₂O for methanesulfonic anhydride or mesyl-anhydride; NaN(TMS)₂ for sodium bis(trimethylsilyl)amide; NaCl for sodium chloride; NaH for sodium hydride; NaHCO₃ for sodium bicarbonate or sodium hydrogen carbonate; Na₂CO₃ sodium carbonate; NaOH for sodium hydroxide;

10 Na₂SO₄ for sodium sulfate; NaHSO₃ for sodium bisulfite or sodium hydrogen sulfite; Na₂S₂O₃ for sodium thiosulfate; NH₂NH₂ for hydrazine; NH₄HCO₃ for ammonium bicarbonate; NH₄Cl for ammonium chloride; NMMO for N-methylmorpholine N-oxide; NaIO₄ for sodium periodate; Ni for nickel; OH for hydroxyl; OsO₄ for osmium tetroxide; TBAF for tetrabutylammonium fluoride; TEA or Et₃N for triethylamine;

15 TFA for trifluoroacetic acid; THF for tetrahydrofuran; TMEDA for N,N,N',N'-tetramethylethylenediamine; TPP or PPh₃ for triphenyl-phosphine; Troc for 2,2,2-trichloroethyl carbonyl; Ts for tosyl or -SO₂-C₆H₄CH₃; Ts₂O for tolylsulfonic anhydride or tosyl-anhydride; TsOH for p-tolylsulfonic acid; Pd for palladium; Ph for phenyl; POPd for dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(II);

20 Pd₂(dba)₃ for tris(dibenzylideneacetone) dipalladium (0); Pd(PPh₃)₄ for tetrakis(triphenylphosphine)palladium (0); PdCl₂(PPh₃)₂ for for trans-dichlorobis-(triphenylphosphine)palladium (II); Pt for platinum; Rh for rhodium; Ru for ruthenium; TBS for *tert*-butyl dimethylsilyl; TMS for trimethylsilyl; or TMSCl for trimethylsilyl chloride.

25

Synthetic Methods

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. These schemes

30 are of illustrative purpose, and are not meant to limit the scope of the invention. Equivalent, similar, or suitable solvents, reagents or reaction conditions may be substituted for those particular solvents, reagents, or reaction conditions described herein without departing from the general scope of the method of synthesis.

- The syntheses of various nucleoside analogs have been well documented in the literature, the following reviews are incorporated hereinwith by references: D. M. Huryn and M. Okabe, *Chem. Rev.* 1992, 92, 1745; K. W. Pankiewicz, *Carbohydrate Research*, 2000, 327, 87-105; G. Gumina *et al*, *Antiviral Nucleosides: Chiral*
- 5 *Synthesis and Chemotherapy*, C. K. Chu (Ed.), Elsevier, 2003, pages 1-76 and 77-189; nucleoside analogs used as antimetabolites have been summarized: M. M. Mader and J. R. Henry, *Comprehensive Medicinal Chemistry II*, Elsevier, 2007, Vol 7, pages 55-79; nucleoside analogs used as antiviral agents have been summarized:
- 10 *Comprehensive Medicinal Chemistry II*, Elsevier, 2007, Vol 7, pages 295-327 by E. Littler and X-X Zhou; and pages 338-343 by T. A. Lyle; and pages 398-400 by U. Schmitz *et al*. The synthesis of each of these individual analog can be found in the literatures cited therein. Nonlimiting examples of process are also incorporated hereinwith by reference: Clark *et al*, *J. Med. Chem.* 2005, 48, 5504; Clark *et al*, *Bioorg. Med. Chem. Lett.* 2006, 16, 1712; Clark *et al*, *J. Carbohydr. Chem.* 2006, 25,
- 15 461; Seela *et al*, *Org. Biomol. Chem.* 2008, 6, 596; Pan *et al*, *J. Org. Chem.* 1999, 94, 4; Shi *et al*, *Bioorg. Med. Chem.* 2005, 13, 1641; He *et al*, *J. Org. Chem.* 2003, 68, 5519; Gudmundsson *et al*, *J. Med. Chem.* 2000, 43, 2473; Jean-Baptiste *et al*, *Synlett* 2008, 817; Wilson *et al*, *Synthesis* 1995, 1465; Lin *et al*, *J. Med. Chem.* 1991, 34, 2607; Matsuda *et al*, *J. Med. Chem.* 1991, 34, 812; Robins *et al*, *J. Med. Chem.* 1992,
- 20 35, 2283; Serafinowski *et al*, *Tetrahedron* 1996, 52, 7929; Serafinowski *et al*, *Tetrahedron* 2000, 56, 333; Houlton *et al*, *Tetrahedron* 1993, 49, 8087; Serafinowski *et al*, *Synthesis* 1997, 225; McCarthy *et al*, *Tetrahedron* 1996, 52, 45; Schmit, *Synlett* 1994, 241; Hirota *et al*, *ChemComm* 1999, 1827; Babu *et al*, *Org. Biomol. Chem.* 2003, 1, 3514; Samano *et al*, *J. Am. Chem. Soc.* 1992, 114, 4007; Beard *et al*,
- 25 *Carbohydrate Res.* 1990, 87; Wigerinck *et al*, *J. Med. Chem.* 1991, 34, 2383; Ye *et al*, *J. Org. Chem.* 2005, 70, 7902; Eldrup *et al*, *J. Med. Chem.* 2004, 47, 2283 and 5284; Tang *et al*, *J. Org. Chem.* 1999, 64, 747; Jeannot *et al*, *Org. Biomol. Chem.* 2003, 1, 2096; Li *et al*, *Org. Lett.* 2001, 3, 1025; Marcotte *et al*, *Synthesis* 2001, 929; Dai *et al*, *Org. Lett.* 2001, 3, 807; Yoshimura *et al*, *Bioorg. Med. Chem. Lett.* 1994, 4, 721;
- 30 Ohtawa *et al*, *J. Med. Chem.* 2007, 50, 2007; McGee *et al*, *J. Org. Chem.* 1996, 61, 781; Ogamino *et al*, *J. Org. Chem.* 2005, 70, 1684; Ichikawa *et al*, *Org. Biomol. Chem.* 2006, 4, 1284; Pan *et al*, *J. Org. Chem.* 1999, 64, 4; Huang *et al*, *J. Med. Chem.* 1991, 34, 1640; Kodama *et al*, *Tetrahedron* 2006, 62, 10011; He *et al*, *J. Org.*

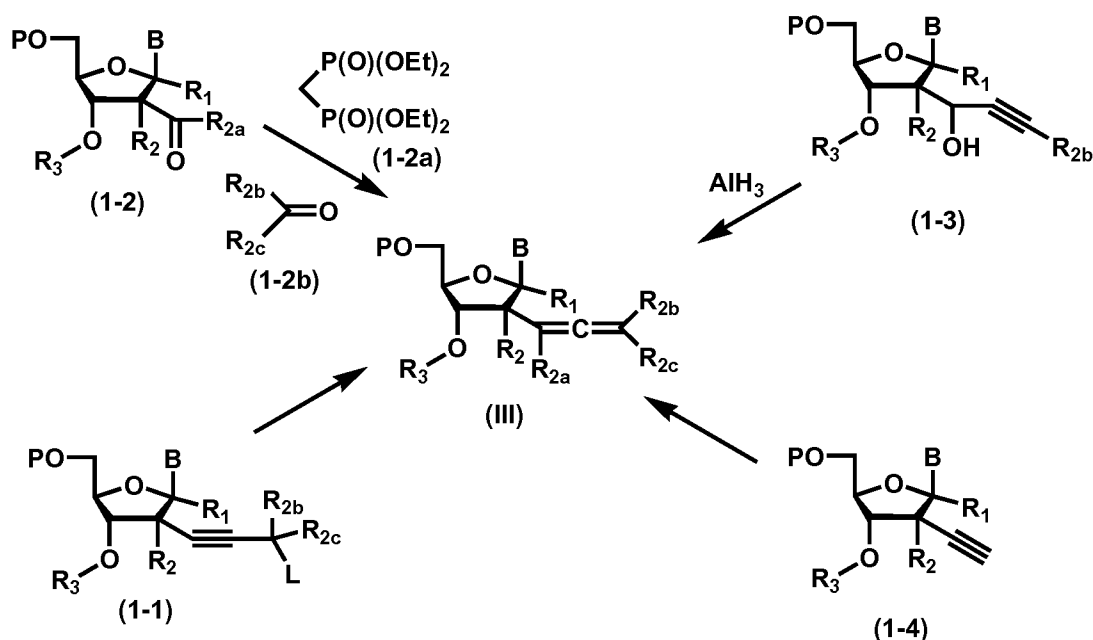
Chem. 2003, 68, 5519; Kumamoto *et al*, *J. Med. Chem.* 2006, 49, 7861; and Haraguchi *et al*, *Org. Lett.* 2004, 6, 2645.

One of the general procedures to synthesize the 2'-allenic nucleosides (**III**) of the present invention is shown in Scheme 1, in which 2'-substituents containing an alkyne group or a carbonyl group can be transformed and/or isomerized to an allenic moiety under a variety of conditions, wherein unless otherwise defined, R₁, R₂, R₃, R_{2a}, R_{2b}, R_{2c}, and B are as previously defined; P is a hydroxy protecting group; and L is a leaving group such as halide, OAc, OMe, OTMS, OTHP, the like.

The alkyne moiety of compound (1-1) can be transformed to an allenic moiety via a hydroxyl directed aluminum hydride reduction while R₂ is OH. The reaction conditions and the choice of leaving group L are well documented in the literature, see references cited in accounts by Cowie, J.S.; Landor, P.D.; Landor, S.R. *J Chem. Soc., Perkin Trans. 1*, **1973**, 720. Claesson, A; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, 101, 7302. Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T.V. *J. Org. Chem.* **2004**, 69, 7157. Yoshida, M.; Komatsuzaki, Y.; Nemoto, H.; Ihara, M. *Org. Biomol. Chem.* **2004**, 2, 3099. VanBrunt, M.P.; Standaert, R.F. *Org. Lett.* **2000**, 2, 705. Cao, H.; Flippen-Anderson, J.; Cook, J. *J. Am. Chem. Soc.* **2003**, 125, 3230. Bungard, C.J.; Morris, J. *J. Org. chem.* **2002**, 67, 2361.

Horner-Wadsworth-Emmons (HWE) reaction of compound (1-2) with methylenebisphosphonate (1-2a), followed by another HWE reaction with aldehyde or ketone (1-2b) to give a 2'-allenic nucleosides (**III**). The bases used in this reaction can be, but not limited to, such as alkyl lithium (MeLi or n-BuLi or the like), LDA, NaH, t-BuOK, KOH, the like. The solvent can be, but not limited to, such as THF, DMF.

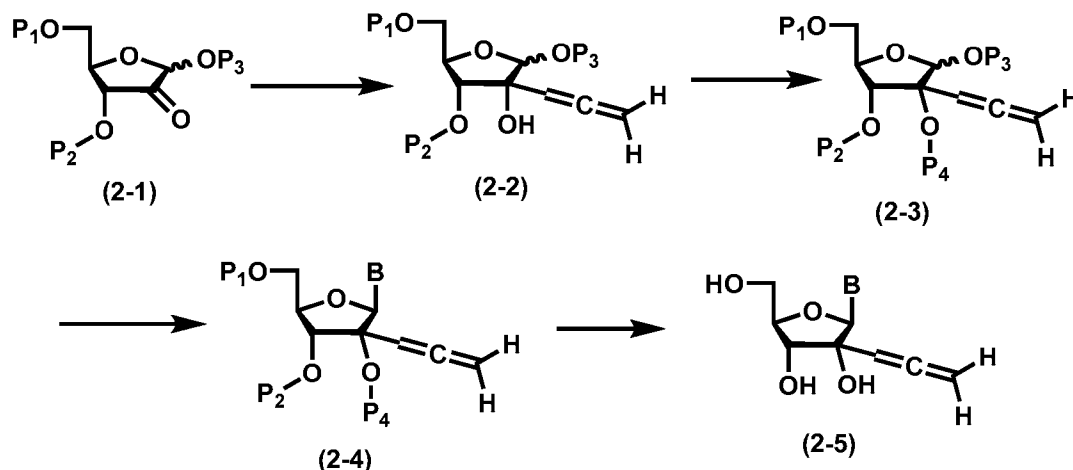
Scheme 1



The propargyl alcohol of compound (1-3) can be converted into allenic compound (III) with AlH₃. The terminal acetylene of compound (1-4) can be transformed to allene by Crabbe homologation reaction. These transformations are well documented in the literature, see references cited in accounts by Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Uang, B.-J. *J. Org. Chem.* **2002**, 67, 1308. Crabbe, P.; Andre, D.; Fillion, H. *Tetrahedron Lett.* **1979**, 20, 893. Crabbe, P.; Fillion, H.; Andre, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.*, **1979**, 859. Crabbe, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* 1985, 63, 203.

Another general procedure to prepare 2'-allenyl nucleoside of present invention is depicted in scheme 2. The ketone compound (2-1), herein P₁, P₂ and P₃ are hydroxyl protecting group, such as but not limited to, benzoyl, acetyl, TMS, TIPS, was treated with propargyl bromide in the presence of combination metal halides such as, but not limited to, SnCl₂, LiI in aprotic solvent such as THF, DME, DMF, toluene to give the allenyl compound (2-2) in good yield. The reaction temperature was from room temperature ~150°C.

Scheme 2



The 2'-hydroxyl group was protected with hydroxyl protecting group P₄, such as but not limited to, benzoyl, acetyl, TMS, TIPS to give the compound (2-3). A more thorough discussion of the procedures, reagents and conditions for protecting hydroxyl group is described in literature, for example, by T.W. Greene and P.G.M. Wuts in *"Protective Groups in Organic Synthesis"* 3rded., John Wiley & Son, Inc., 1999.

Further glycosylation of the nucleobase with compound (2-3) was accomplished by treatment of the compound (2-3) with the appropriate persilylated nucleobase in the presence of a Lewis acid such as, but not limited to, SnCl₄, TiCl₄, TMSOTf, HgO or HgBr₂ in an aprotic solvent such as, but not limited to, toluene, acetonitrile, benzene, THF, DME, or a mixture of any or all of these solvents. The reaction temperature was from room temperature to 150°C. The optional protecting groups in the protected nucleosides or the compound formula (2-4) can be cleaved following established deprotection methodologies. A more thorough discussion of the procedures, reagents and conditions for deprotection is described in literature, for example, by T.W. Greene and P.G.M. Wuts in *"Protective Groups in Organic Synthesis"* 3rded., John Wiley & Son, Inc., 1999. The synthesis of nucleoside 5'-monophosphate prodrugs have also been well documented in the literature, see references cited in accounts by Cahard *et al*, *Mini-Reviews Med. Chem.* 2004, 4, 371; Meier *et al*, *Mini-Reviews Med. Chem.* 2004, 4, 383; Peyrottes *et al*, *Mini-Reviews Med. Chem.* 2004, 4, 395; Drontle *et al*, *Mini-Reviews Med. Chem.* 2004, 4, 409; and nonlimiting examples of recent process: Gisch *et al*, *J. Med. Chem.* 2007, 50, 1658;

Boyer *et al*, *J. Med. Chem.* 2006, 49, 7711; Khamnei *et al*, *J. Med. Chem.* 1996, 39, 4109; Li *et al*, *Synlett* 2004, 2600; Perrone *et al*, *J. Med. Chem.* 2007, 50, 5463; Gisch *et al*, *J. Med. Chem.* 2007, 50, 1658 and 1840; Hecker *et al*, *J. Med. Chem.* 2007, 50, 3891; Prakash *et al*, *J. Med. Chem.* 2005, 48, 1199; and Gunic *et al*, *Bioorg. Med.*

5 *Chem. Lett.* 2007, 17, 2452 (for 3',5'-cyclic monophosphate prodrug).

The synthesis of nucleoside phosphonates and/or their prodrugs have also been well documented in the literature, see references cited in accounts by Hecker *et al*, *J. Med. Chem.* 2008, 51, 2328; Krise *et al*, *Adv. Drug Deliv. Rev.* 1996, 19, 287; Berkowitz *et al*, *J. Fluorine Chem.* 2001, 112, 13; Romanenko *et al*, *Chem. Rev.* 2006, 106, 3868; De Clercq, *Antiviral Res.* 2007, 75, 1; De Clercq *et al*, *Nat. Rev.- Drug*
10 *Disc.* 2005, 4, 928; and nonlimiting examples of recent process: Mackman *et al*, *Bioorg. Med. Chem.* 2007, 15, 5519; Dang *et al*, *Bioorg. Med. Chem. Lett.* 2007, 17, 3412; Meier *et al*, *J. Med. Chem.* 2005, 48, 8079; Wu *et al*, *Nucleosides Nucleotides Nucl. Acids* 2005, 24, 1543; Choi *et al*, *J. Med. Chem.* 2004, 47, 2864; Sekiya *et al*,
15 *J. Med. Chem.* 2002, 45, 3138; Louie *et al*, *Nucleosides Nucleotides Nucl. Acids* 2001, 20, 1099; Serafinowska *et al*, *J. Med. Chem.* 1995, 38, 1372; Koh *et al*, *J. Med. Chem.* 2005, 48, 2867; Mackman *et al*, *Bioorg. Med. Chem.* 2007, 15, 5519; Wang *et al*, *Nucleosides Nucleotides Nucl. Acids* 2004, 23, 317; Dyatkina *et al*, *Tetrahedron* 1995, 51, 761; Reddy *et al*, *J. Med. Chem.* 2008, 51, 666; Krecmerova *et al*, *J. Med.*
20 *Chem.* 2007, 50, 5765.

It will be appreciated that, with appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W
25 Greene and P G M Wuts "Protective Groups in Organic Synthesis", 3rd Ed (1999), J Wiley and Sons.

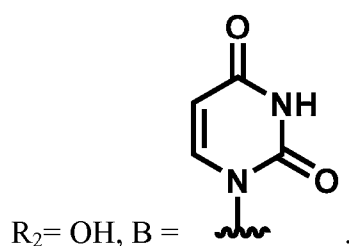
All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises,
30 internet web sites, databases, patents, and patent publications.

Examples

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an

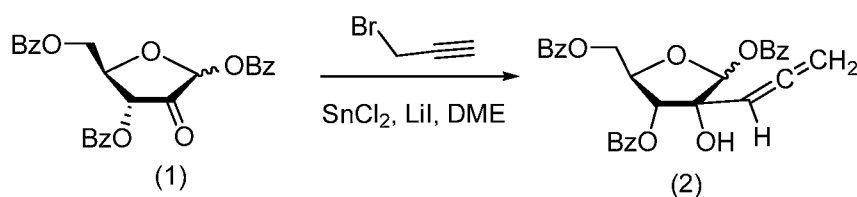
illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. Compound of Formula (I), wherein $R_1 = R_3 = R_5 = R_{2a} = R_{2b} = R_{2c} = H$,



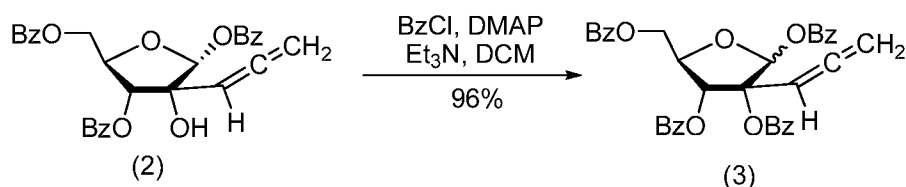
10

Step 1a:



To a mixture of ketone (1) (830 mg, 1.802 mmol), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (611 mg, 2.708 mmol), and $\text{LiI} \cdot 3\text{H}_2\text{O}$ (678 mg, 3.605 mmol) in dimethoxyethane (18 mL) was added propargyl bromide and the resulted yellow suspension was heated up in 85 °C oil bath for 60 mins. The solvent was removed under *vacuo* and the residue was purified by CombiFlash (eluted with hexane to 25% ethyl acetate in Hexane) to afford the allenyl compound (2) (650 mg, 72%). ^1H NMR (500 MHz, CDCl_3) δ 8.03-8.17 (m, 6H), 7.53-7.68 (m, 3H), 7.35-7.53 (m, 6H), 6.53 (s, 1H), 5.64 (t, $J = 6.7$ Hz, 1H), 5.47 (d, $J = 3.2$ Hz, 1H), 5.16 (d, $J = 6.6$ Hz, 2H), 4.8-4.83 (m, 1H), 4.65 (dd, $J = 12, 6.5$ Hz, 1H), 4.63 (dd, $J = 11.8, 6.4$ Hz, 1H).

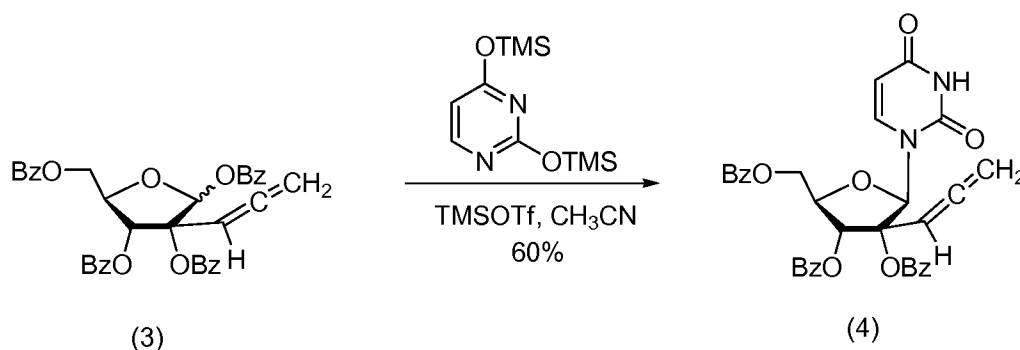
Step 1b:



To the allenyl compound (2) (650 mg, 1.299 mmol), which was from step 1a in DCM (15 mL) was added BzCl (0.30 mL, 2.598 mmol) and DMAP (159 mg, 1.299 mmol) and Et₃N (1.5 mL) and the resulted solution was stirred at RT for 4h. The

- 5 solvent was removed under *vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N HCl, water, NaHCO₃ solution, water, brine, dried (Na₂SO₄) and concentrated. The residue was purified by CombiFlash (eluted with hexane to 30% ethyl acetate in Hexane) to afford the full protected allenyl compound (3) (750 mg, 96%). ¹H NMR (500 MHz, CDCl₃) δ 8.10 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H). 7.52-7.60 (m, 3H), 7.34-7.47 (m, 7H), 7.10 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 6.16 (d, J = 7.5 Hz, 1H), 5.94 (dt, J = 7.0, 1.0 Hz, 1H), 4.66-4.8 (m, 4H), 4.46 (dd, J = 13.5, 6.5 Hz, 1H).
- 10

Step 1c



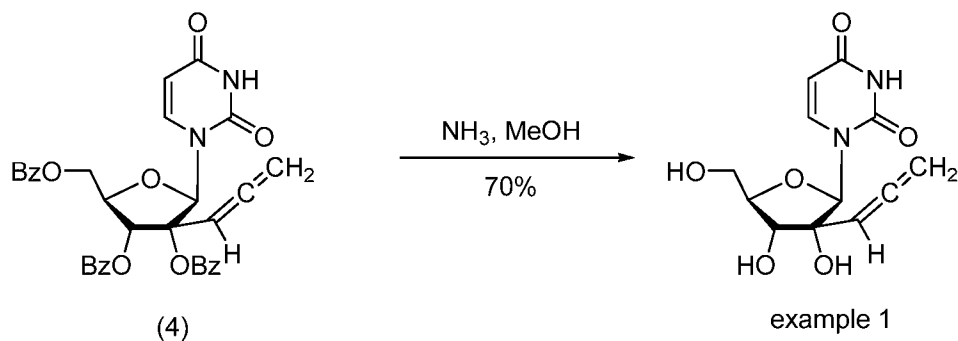
15

To a solution of the allenyl compound (3) (41 mg, 0.0678 mmol), which was from step 1b, in acetonitrile (1 mL) was added 2,4-bis(trimethylsilyloxy)-pyrimidine (52 mg, 0.203 mmol) and TMSOTf (50 uL, 0.271) at 0 °C. The resulted solution was warmed up to RT and stirred for 14h, then heated up to 85 °C for 6h. The mixture was

20 diluted with ethyl acetate, washed with NaHCO₃ solution, water, brine, dried (Na₂SO₄) and concentrated. The residue was purified by CombiFlash (eluted with hexane to 80% ethyl acetate in Hexane) to afford the compound (4) (24 mg, 60%).

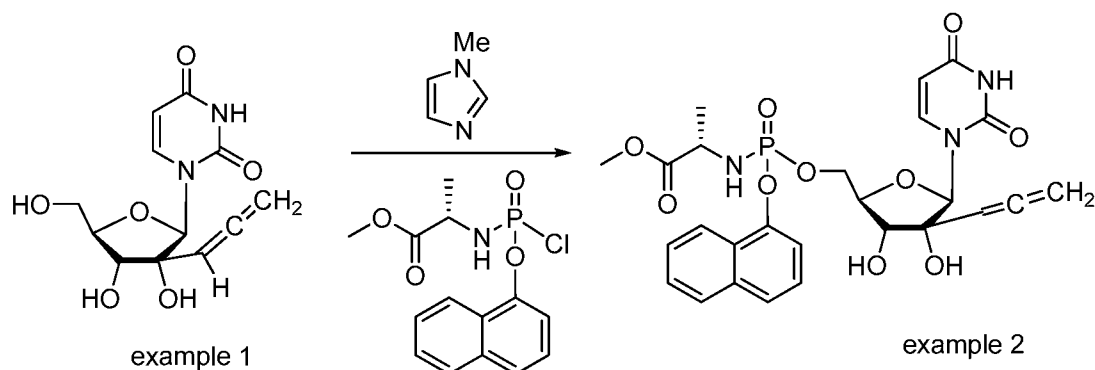
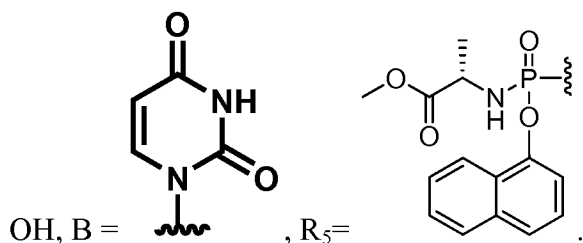
- MS-ESI m/z 617.17 (M+Na)⁺. ¹H NMR (500 MHz, CDCl₃) δ 8.91 (s, 1H), 8.05-8.12 (m, 4H), 7.86 (d, J = 8.0 Hz, 2H), 7.6 (t, J = 7.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.44-7.52 (m, 5H), 7.27 (t, J = 8.5 Hz, 2H), 6.7 (s, 1H), 6.01 (d, J = 3.8 Hz, 1H), 5.51 (t, J = 6.5 Hz, 1H), 5.05-5.14 (m, 2H), 4.81-4.91 (m, 2H), 4.60-4.65 (m, 1H).
- 25

Step 1d:



To the compound (4) (24 mg, 0.0404 mmol), which was from step 1c, was added NH_3 (7N in MeOH) and the resulted mixture was stirred at RT for 40 h. The solvent was removed under *vacuo* and the residue was purified by CombiFlash (eluted with hexane to 20% MeOH in DCM) to afford the compound of example 1 (8 mg, 70%). MS-ESI m/z 305.12 ($\text{M}+\text{Na}$)⁺. ^1H NMR (500 MHz, CD_3OD) δ 8.13 (d, J = 8 Hz, 1H), 5.97 (s, 1H), 5.66 (d, J = 8 Hz, 1H), 5.15 (t, J = 7 Hz, 1H), 4.94 (dd, J = 11.5, 7 Hz, 1H), 4.78 (dd, J = 11.5, 7 Hz, 1H), 4.23 (d, J = 10 Hz, 1H), 3.99 (m, 2H), 3.80 (d, J = 12 Hz, 1H).

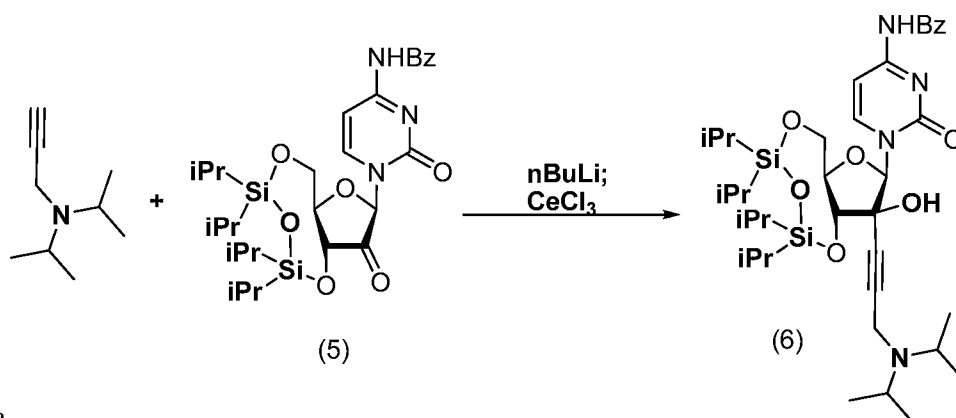
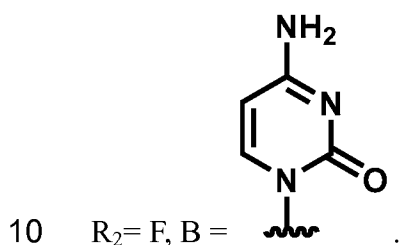
Example 2. Compound of Formula (I), wherein $\text{R}_1 = \text{R}_3 = \text{R}_{2a} = \text{R}_{2b} = \text{R}_{2c} = \text{H}$, $\text{R}_2 =$



To the compound of example 1 (27 mg, 0.0956 mmol) in THF (2 mL) was added (2S)-methyl 2-(chloro(naphthalen-1-yloxy)phosphorylamino)propanoate (125.4

mg, 0.383 mmol) and N-methyl imidazole (38 μ L, 1.478 mmol). The resulted suspension was stirred at RT for 14 h and then diluted with ethyl acetate. The organic layer was washed with 1N HCl, water, NaHCO₃ solution, water, brine, dried (Na₂SO₄) and concentrated. The residue was purified by CombiFlash (eluted with DCM to 20% MeOH in DCM) to afford the product which was further purified by HPLC to give the compound of example 2 as white solid (24 mg, 44%, ~1:1 diastereomers on Phosphorous atom). MS-ESI m/z 574.15 (M+H)⁺.

Example 3. Compound of Formula (I), wherein $R_1 = R_3 = R_5 = R_{2a} = R_{2b} = R_{2c} = H$,



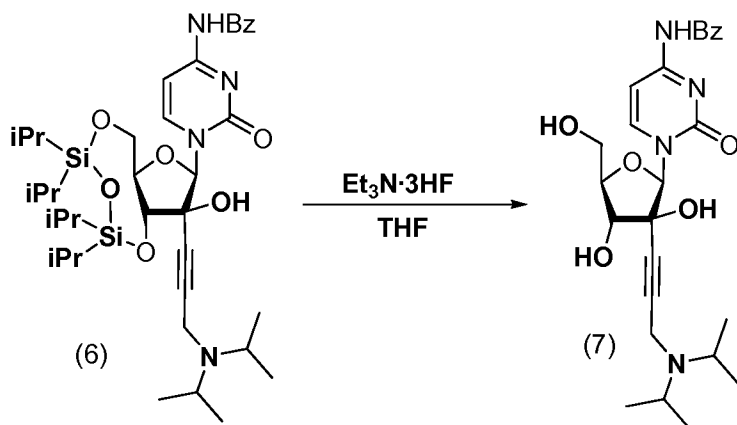
Step 3a

To the N,N-diisopropylprop-2-yn-1-amine (1.04 g, 7.48 mmol) in THF (20 mL) at -78 °C was added nBuLi (2.9 mL, 7.31 mmol, 2.5 M in Hexane) and the resulted solution was transferred via cannula at -78 °C into a suspension of CeCl₃ (freshly dried from 2.85 g CeCl₃·7H₂O) in THF (10 mL). After stirring at -78 °C for 1h, the compound (5), which was prepared from Cytidine, (1.0 g, 1.7 mmol) in THF (10 mL) at -78 °C was transferred to this suspension via cannula. The resulted mixture was stirred at -78 °C for 2h then slowly warmed up to 0 °C and quenched with saturated NH₄Cl solution and diluted with EtOAc. The suspension was filtered through celite, and the aqueous layer was extracted with EtOAc after separation. The organic layer was combined, washed with water, brine, dried (Na₂SO₄) and concentrated under *vacuo*. The residue was purified by CombiFlash (eluted with DCM to 10%

MeOH in DCM) to afford the compound (6) (758 mg) as yellow foam. MS-ESI m/z 727.20 ($M+H$)⁺.

Step 3b

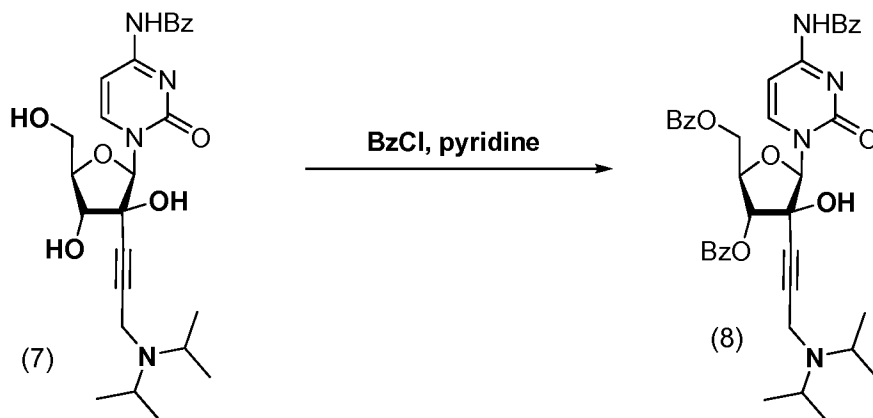
5



To the solution of the compound (6) (520 mg, 0.716 mmol), which was from step 3a, in THF (15 mL) was added Et_3N (0.8 mL) and $\text{Et}_3\text{N} \cdot \text{HF}$ sequentially. The mixture was stirred for 14 hr and solvent was removed under *vacuo*. The residue was purified by CombiFlash (eluted with DCM to 15% MeOH in DCM) to afford the compound (7) (340 mg) as yellow foam. MS-ESI m/z 485.16 ($M+H$)⁺.

10

Step 3c

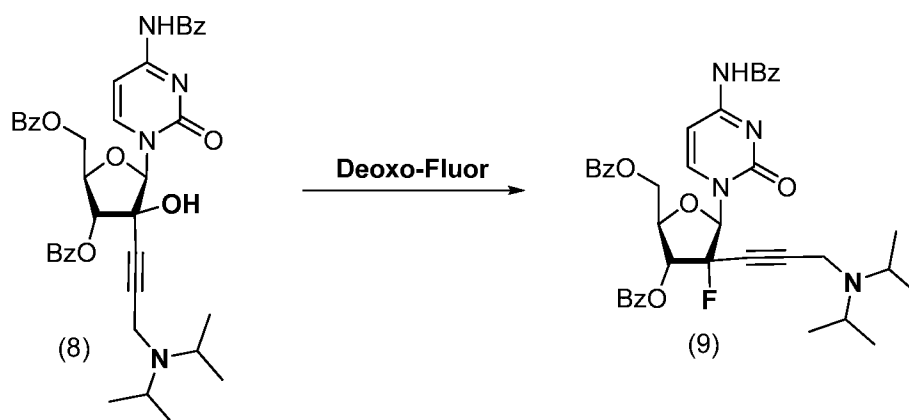


15

To the solution of the compound (7) (340 mg, 0.702 mmol), which was from step 3b, in pyridine (10 mL) was added Benzoyl chloride (0.25 mL, 2.148 mmol) and the resulted solution was stirred for 1.5 hr. The mixture was quenched with MeOH and solvent was removed under *vacuo*. The residue was purified by CombiFlash (eluted with DCM to 15% MeOH in DCM) to afford the compound (8) (350 mg) as yellow foam. MS-ESI m/z 693.26 ($M+H$)⁺.

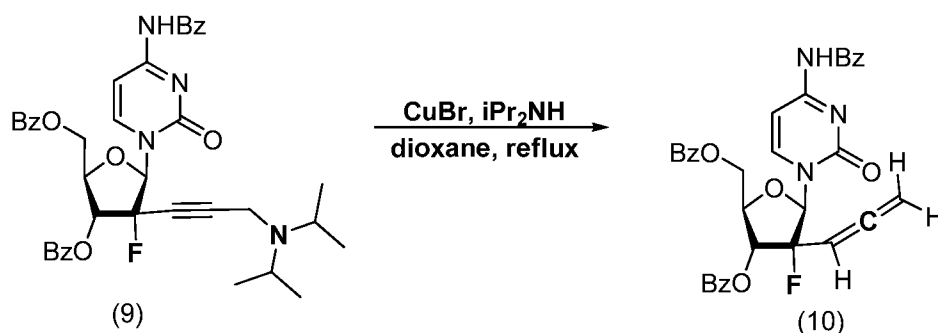
20

Step 3d



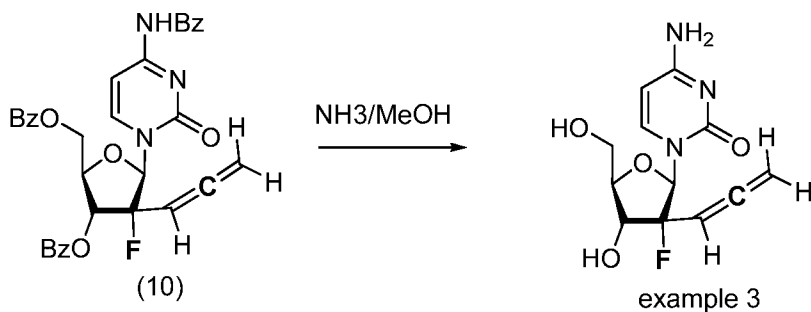
To the suspension of the compound (8) (70 mg), which was from step 3c, in toluene (4.5 mL) was added Deoxo-Fluor (67.1 mg, 0.303 mmol) and the resulted mixture was stirred for 1.5 hr. The mixture was poured into EtOAc/ NaHCO_3 , and after separation the organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated under *vacuo*. The residue was purified by CombiFlash (eluted with DCM to 10% MeOH in DCM) to afford the compound (9). MS-ESI m/z 695.31 ($\text{M}+\text{H}$)⁺.

10 Step 3e

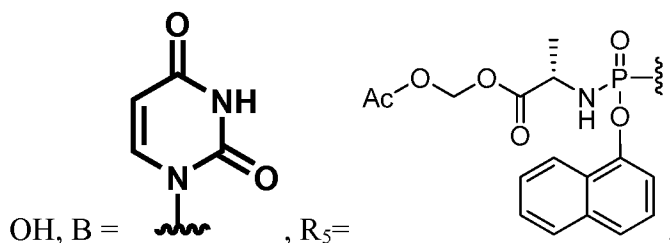


To the compound (9) (6 mg), which was from step 3d, in dioxane in sealed tube was added CuBr (1.5 mg) and $i\text{-Pr}_2\text{NH}$ (2.8 μL) and the resulted mixture was heated up to reflux for 16 hr. The mixture was diluted with EtOAc, washed with NH_4Cl (3X), water and brine, dried (Na_2SO_4) and concentrated under *vacuo*. The residue was purified by preparative TLC to afford the compound (10). MS-ESI m/z 596.18 ($\text{M}+\text{H}$)⁺.

20 Step 3f



Example 4. Compound of Formula (I), wherein $R_1 = R_3 = R_{2a} = R_{2b} = R_{2c} = H$, $R_2 =$



5 The compound of example 4 was prepared by using similar procedure in the preparation of compound of example 2; MS-ESI m/z 632.18 ($M+H$)⁺.

To the compound (10) which was from step 3e, is added NH₃ (7N in MeOH) and the resulted mixture is stirred at RT for 40 h. The solvent is removed under *vacuo* and the residue is purified by CombiFlash to afford the compound of example 3.

10 While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

BIOLOGICAL ACTIVITY

15 1. HCV Replicon Cell Lines

HCV replicon cell lines (kindly provided by R. Bartenschlager) isolated from colonies as described by Lohman et al. (Lohman et al. (1999) Science 285: 110-113, expressly incorporated by reference in its entirety) and used for all experiments. One of the HCV replicon cell lines (strain Con1, genotype 1b) has the nucleic acid

20 sequence set forth in EMBL Accession No.: AJ242651, the coding sequence of which is from nucleotides 1801 to 8406. Another replicon cell line (strain H77, genotype 1a) was constructed as described by Yi et. al. (Yi et. al. (2004) Journal of Virology 78(15):7904-15). The coding sequences of the published HCV replicons were

synthesized and subsequently assembled in plasmids using standard molecular biology techniques.

One replicon cell line (“SGR 11-7”) stably expresses HCV replicon RNA, genotype 1b, which consists of (i) the HCV 5’UTR fused to the first 12 amino acids of the capsid protein, (ii) the neomycin phosphotransferase gene (neo), (iii) the IRES from encephalomyocarditis virus (EMCV) and (iv) HCV NS2 to NS5B genes and the HCV 3’UTR. Another replicon cell line (“Huh-1a7”) described by Yi et. al. (Yi et. al. (2004) Journal of Virology 78(15):7904-15, expressly incorporated by reference in its entirety) stably expresses HCV replicon RNA, genotype 1a, which consists of (i) the HCV 5’UTR fused to the first 12 amino acids of the capsid protein, (ii) the HIV tat protein, (iii) the neomycin phosphotransferase gene (neo), (iv) the IRES from encephalomyocarditis virus (EMCV) and (vi) HCV NS3 to NS5B genes that harbor cell culture adaptive mutations (Q1067R, K1691R, S2204I) and the HCV 3’UTR.

These cell lines are maintained at 37°C, 5% CO₂, 100% relative humidity in DMEM (Cat# 11965-084, Invitrogen), with 10% fetal calf serum (“FCS”, Invitrogen), 1% non-essential amino acids (Invitrogen), 1% of Glutamax (Invitrogen), 1% of 100X penicillin/streptomycin (Cat# 15140-122, Invitrogen) and Geneticin (Cat# 10131-027, Invitrogen) at 0.75 mg/ml or 0.25 mg/ml for 11-7 and Huh-1a7 cells, respectively.

2. HCV Replicon Assay – qRT-PCR

EC₅₀ values of single agent compounds were determined by HCV RNA detection using quantitative RT-PCR, according to the manufacturer’s instructions, with a TAQMAN® One-Step RT-PCR Master Mix Reagents Kit (Cat# AB 4309169, Applied Biosystems) on an ABI Model 7500 thermocycler. EC₅₀ values of combinations are similarly determined by HCV RNA detection using quantitative RT-PCR. The TAQMAN primers to use for detecting and quantifying HCV RNA obtained from Integrated DNA Technologies. HCV RNA is normalized to GAPDH RNA levels in drug-treated cells, which is detected and quantified using the Human GAPDH Endogenous Control Mix (Applied Biosystems, AB 4310884E). Total cellular RNA is purified from 96-well plates using the RNAqueous 96 kit (Ambion, Cat# AM1812). Chemical agent cytotoxicity is evaluated using an MTS assay according to the manufacturer’s directions (Promega).

The compounds of the present invention can be effective against the HCV 1a and 1b genotypes. It should also be understood that the compounds of the present invention can inhibit multiple genotypes of HCV. In one embodiment, compounds of

the present invention are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. Table 7 shows the EC₅₀ values of representative compounds of the present invention against the HCV 1a and 1b genotypes from the above described qRT-PCR. EC₅₀ ranges against HCV 1a or 1b are as follows: A >10 µM; B 1-10 µM; C < 1 µM.

5

Table 7: Genotype-1a or 1b replicon EC₅₀

Example	1a EC ₅₀	1b EC ₅₀
1	A	A
2	B	B
3	A	A
4	C	C

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

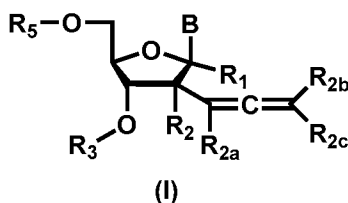
10

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):

5



or its β -L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof, wherein:

R₁ at each occurrence is independently selected from the group consisting of:

10

- 1) hydrogen;
- 2) -CN;
- 3) halogen;
- 4) -N₃; and
- 5) Substituted or unsubstituted -C₁-C₈ alkyl;

15

R_{2a}, R_{2b} and R_{2c} at each occurrence are independently selected from the group consisting of: hydrogen, halogen, and substituted or unsubstituted -C₁-C₈ alkyl;

R₂ at each occurrence is selected from the group consisting of:

20

- 1) halogen;
- 2) -CN;
- 3) -N₃; and
- 4) OR₆; where R₆ selected from the group consisting of: hydroxy protecting group, -C(O)R₇, -C(O)OR₇, and -C(O)NR_{8a}R_{8b}; wherein R₇ at

25

each occurrence is independently selected from the group consisting of: substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, substituted or unsubstituted -C₂-C₈ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{8a}; and R_{8b} at each occurrence is independently selected from the group consisting of: hydrogen and R₇; or alternatively R_{8a}

30

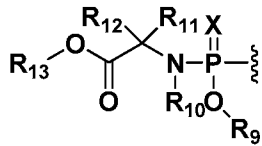
and R_{8b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;

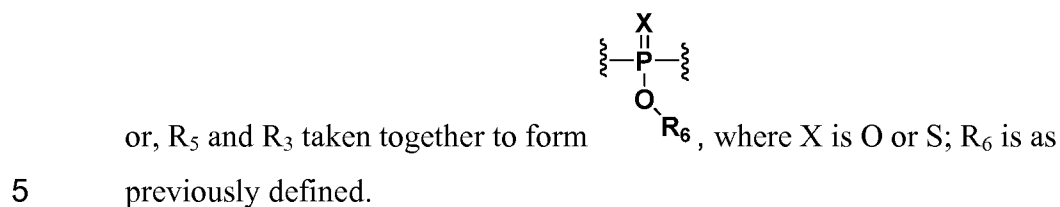
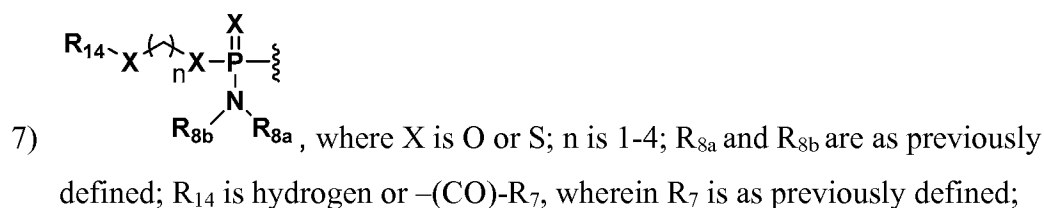
- R₃ is R₆; or alternatively R₂ is -OR₆ and R₃ and R₆ taken together form a group
 5 selected from: -C(Me)₂-, -C(CH₂)₄-, -CH(Ph)-, -CH(OMe)- and -P(O)(OH)-;

- B at each occurrence is each independently selected from a group consisting of:
 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and
 substituted or unsubstituted heterocyclic; preferably a heterocycle containing at least
 10 one nitrogen;

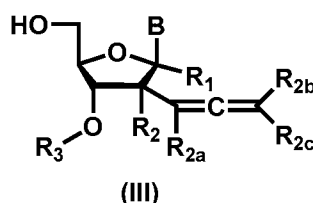
R₅ is at each occurrence is each independently selected from a group consisting of:

- 1) hydrogen;
- 2) R₆;
- 15 3) -P(O)(OR_{7a})(OR_{7b}); wherein R_{7a} and R_{7b} are each independently selected from the group consisting of a) hydrogen; b) unsubstituted or substituted -C₁-C₈ alkyl;
- 4) -P(O)(OR_{7a})-O-P(O)(OR_{7b})(OR_{7c}); wherein R_{7a} and R_{7b} are previously defined; R_{7c} is selected from the group consisting of a) hydrogen; b)
 20 unsubstituted or substituted -C₁-C₈ alkyl; and
- 5) -P(O)(OR_{7a})-O-P(O)(OR_{7b})-O-P(O)(OR_{7c})(OR_{7d}); wherein R_{7a}, R_{7b} and R_{7c} are previously defined; R_{7d} is selected from the group consisting of a) hydrogen;
 b) unsubstituted or substituted -C₁-C₈ alkyl;

- 25 6) ; where X is O or S; R₉ is R₇ wherein R₇ is previously defined; R₁₀, R₁₁ and R₁₂ are each independently selected from the group consisting of : a) hydrogen; b) unsubstituted or substituted -C₁-C₈ alkyl; c) R₁₁ is hydrogen, R₁₂ and R₁₀ taken together with the nitrogen which R₁₀ is attached to form a heterocyclic ring; d) R₁₁ and R₁₂ taken together with the carbon
 30 which they are attached form a ring; R₁₃ is hydrogen or R₇, wherein R₇ is previously defined;

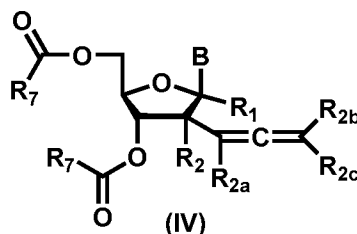


2. A compound of claim 1 represented by Formula (III):



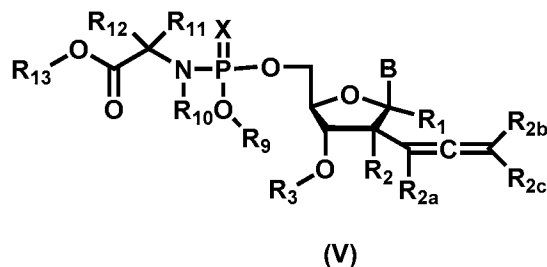
- 10 or its β-L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof.

3. A compound of claim 1 represented by Formula (IV):



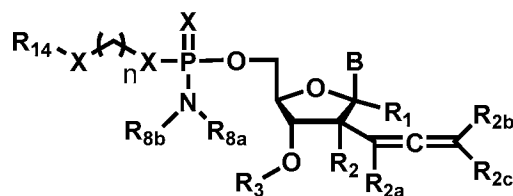
- 15 or its β-L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof.

4. A compound of claim 1 represented by Formula (V):



or its β -L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof.

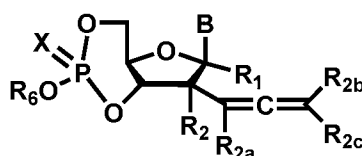
5. A compound of claim 1 represented by Formula (VI):



(VI)

or its β -L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof.

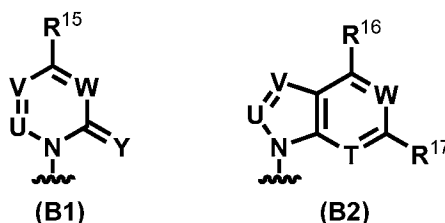
6. A compound of claim 1 represented by Formula (VII):



(VII)

or its β -L enantiomer, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, prodrug, or combination thereof.

7. A compound of claim 1, wherein B at each occurrence is an optionally substituted pyrimidinyl, purinyl group or the like of the general formula of (B1)-(B2):



wherein:

Y at each occurrence is independently selected from a group consisting of: O, S, NR_{8a}, NC(O)R₇, NC(O)OR₇ and NC(O)NR_{8a}R_{8b};

T, U, V and W at each occurrence are each independently N or CR₁₈; wherein R₁₈ is selected from a group consisting of: hydrogen, halogen, -CN, -C(O)R₇, -C(O)NR_{8a}R_{8b}, -NO₂, -N₃, -OR₇, -SR₇, -NR_{8a}R_{8b}, -OC(O)R₇, -OC(O)OR₇, -NHC(O)R₇, -NHC(O)OR₇ and -NHC(O)NR_{8a}R_{8b}, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic, substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, substituted or unsubstituted $-C_2-C_8$ alkynyl;

- 5 R_{15} , R_{16} and R_{17} at each occurrence are each independently selected from a group consisting of: hydrogen, halogen, $-CN$, $-C(O)R_7$, $-C(O)NR_{8a}R_{8b}$, $-NO_2$, $-N_3$, $-OR_7$, $-SR_7$, $-NR_{8a}R_{8b}$, $-OC(O)R_7$, $-OC(O)OR_7$, $-NHC(O)R_7$, $-NHC(O)OR_7$ and $-NHC(O)NR_{8a}R_{8b}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic, substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, substituted or unsubstituted $-C_2-C_8$ alkynyl.

8. A compound according to claim 1 as set forth in any of Tables 1 ~ Table 5 which is selected from compounds of Formula III-1 ~ Formula VII-1;

- 15 Compounds in Table 1 were illustrated according to Formula (III-1) wherein R_2 , R_{2a} , R_{2b} , R_{2c} , and B are delineated for each example in Table 1;

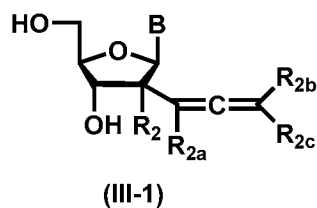
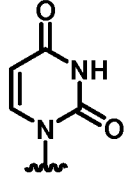
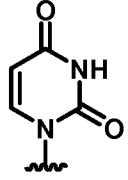
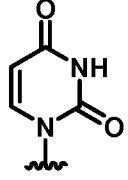
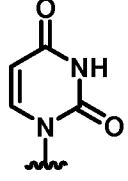
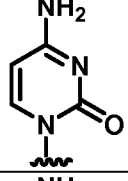
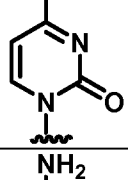
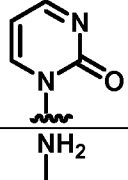
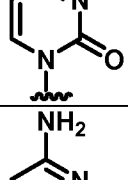
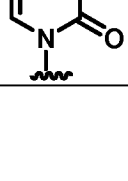
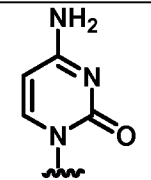
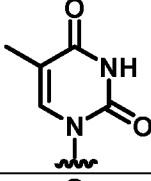
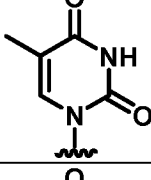
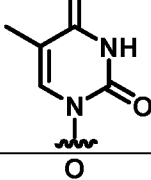
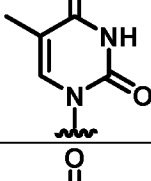
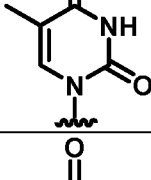
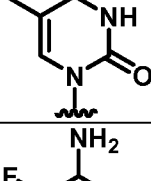
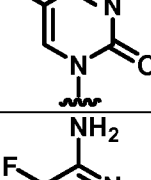
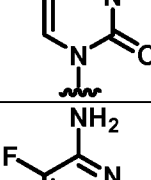
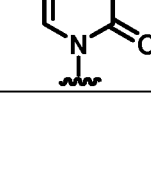
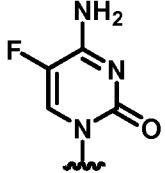
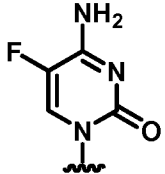
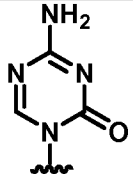
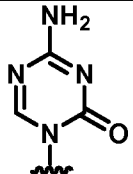
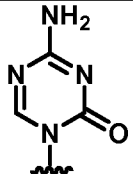
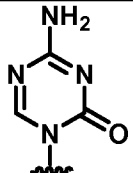
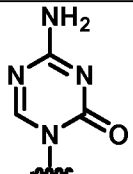
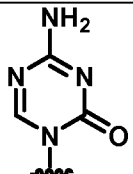
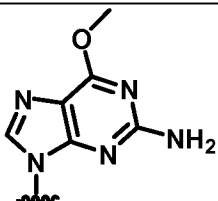


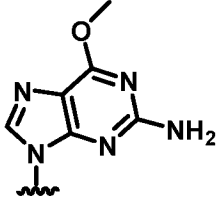
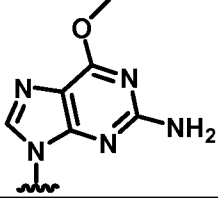
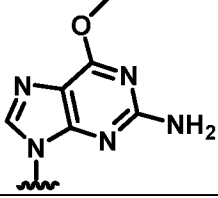
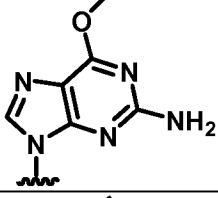
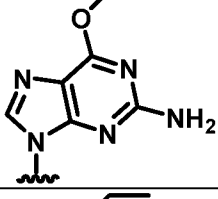
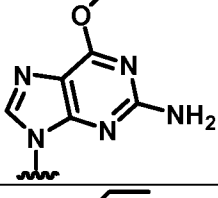
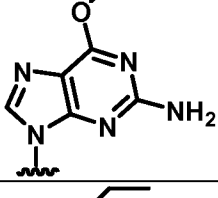
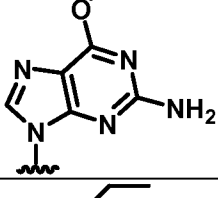
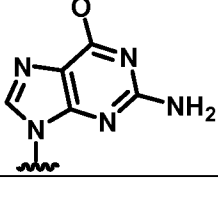
TABLE 1

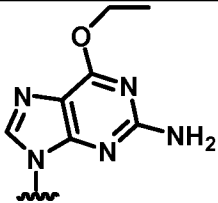
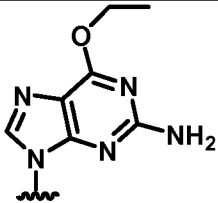
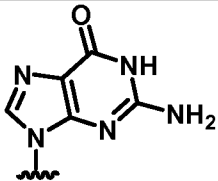
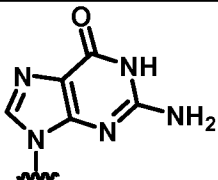
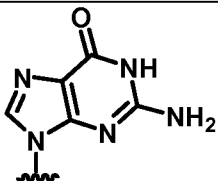
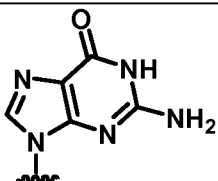
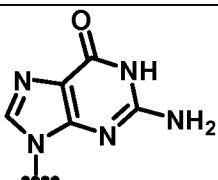
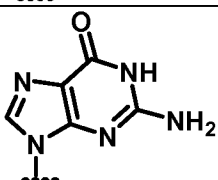
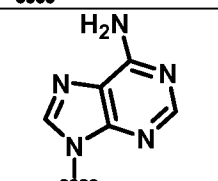
Example#	R_{2a}	R_{2b}	R_{2c}	R_2	B
1	H	H	H	OH	
2	H	H	H	F	

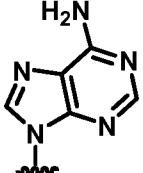
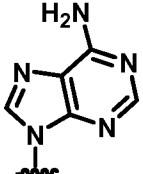
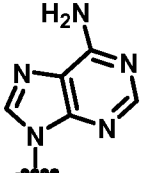
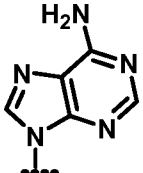
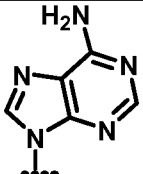
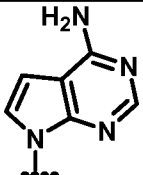
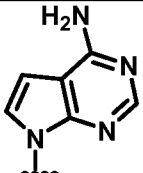
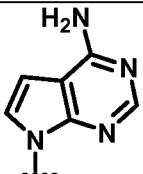
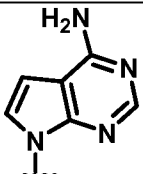
3	H	Me	Me	OH	
4	H	Me	Me	F	
5	H	F	F	OH	
6	H	F	F	F	
7	H	H	H	OH	
8	H	H	H	F	
9	H	Me	Me	OH	
10	H	Me	Me	F	
11	H	F	F	OH	

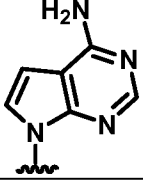
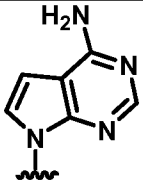
12	H	F	F	F	
13	H	H	H	OH	
14	H	H	H	F	
15	H	Me	Me	OH	
16	H	Me	Me	F	
17	H	F	F	OH	
18	H	F	F	F	
19	H	H	H	OH	
20	H	H	H	F	
21	H	Me	Me	OH	

22	H	Me	Me	F	
23	H	F	F	OH	
24	H	F	F	F	
25	H	H	H	OH	
26	H	H	H	F	
27	H	Me	Me	OH	
28	H	Me	Me	F	
29	H	F	F	OH	
30	H	F	F	F	
31	H	H	H	OH	

32	H	H	H	F	
33	H	Me	Me	OH	
34	H	Me	Me	F	
35	H	F	F	OH	
36	H	F	F	F	
37	H	H	H	OH	
38	H	H	H	F	
39	H	Me	Me	OH	
40	H	Me	Me	F	

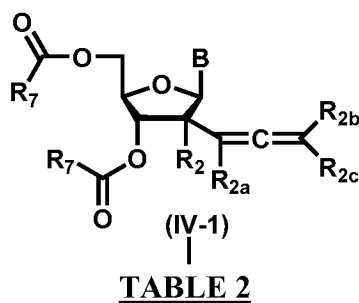
41	H	F	F	OH	
42	H	F	F	F	
43	H	H	H	OH	
44	H	H	H	F	
45	H	Me	Me	OH	
46	H	Me	Me	F	
47	H	F	F	OH	
48	H	F	F	F	
49	H	H	H	OH	

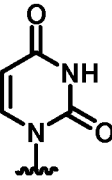
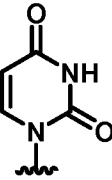
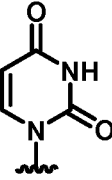
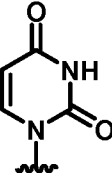
50	H	H	H	F	
51	H	Me	Me	OH	
52	H	Me	Me	F	
53	H	F	F	OH	
54	H	F	F	F	
55	H	H	H	OH	
56	H	H	H	F	
57	H	Me	Me	OH	
58	H	Me	Me	F	

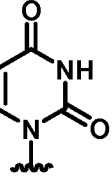
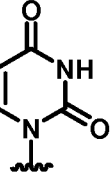
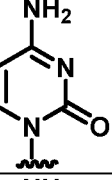
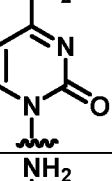
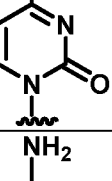
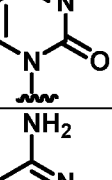
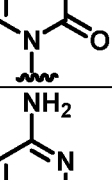
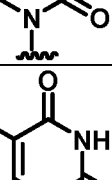
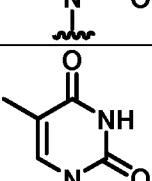
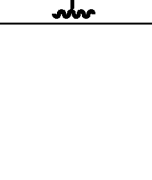
59	H	F	F	OH	
60	H	F	F	F	

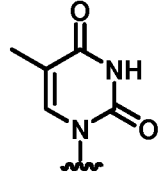
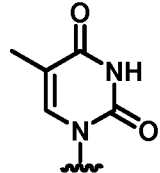
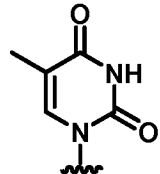
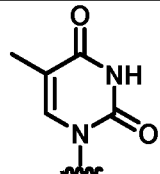
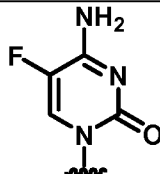
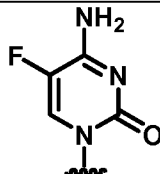
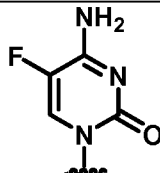
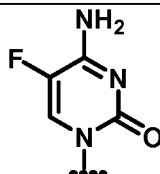
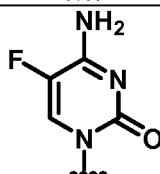
Compounds in Table 2 were illustrated according to Formula (IV-1) wherein R_2 , R_7 , R_{2a} , R_{2b} , R_{2c} , and B are delineated for each example in Table 2

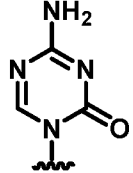
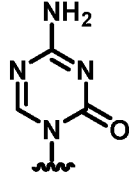
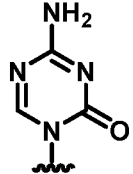
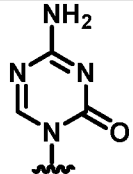
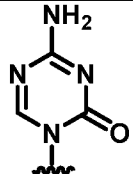
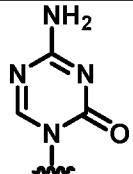
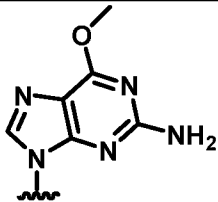
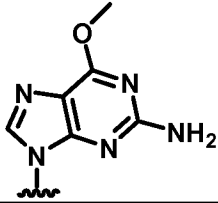
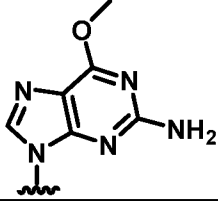
5

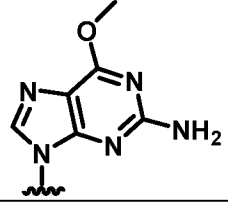
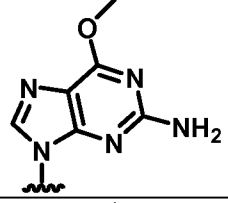
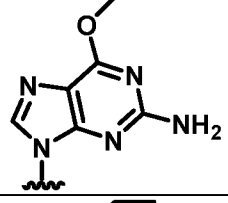
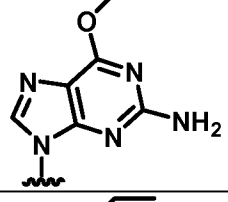
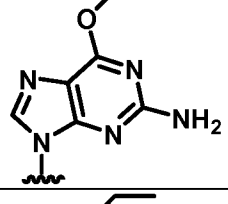
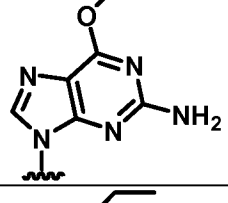
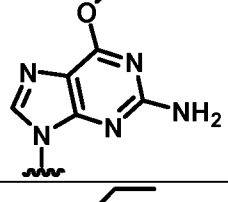
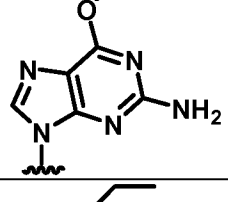
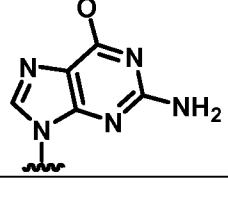


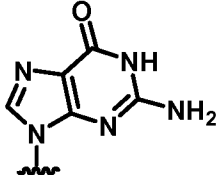
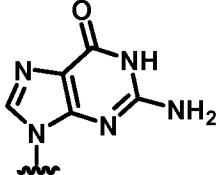
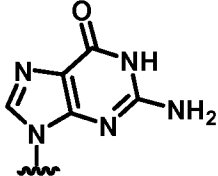
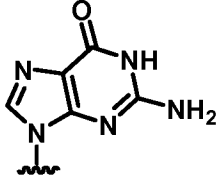
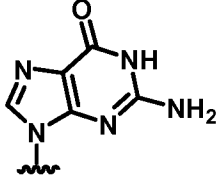
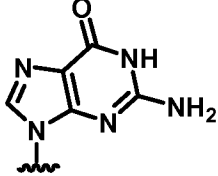
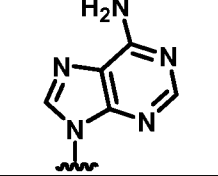
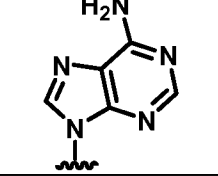
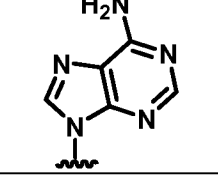
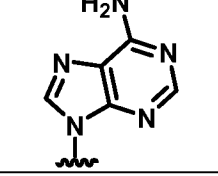
Example#	R_{2a}	R_{2b}	R_{2c}	R_2	R_7	B
61	H	H	H	OH	i-Pr	
62	H	H	H	F	i-Pr	
63	H	Me	Me	OH	i-Pr	
64	H	Me	Me	F	i-Pr	

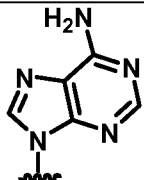
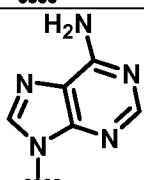
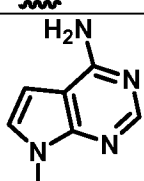
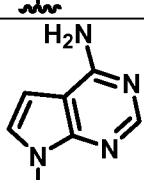
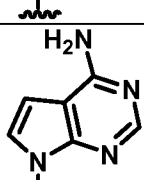
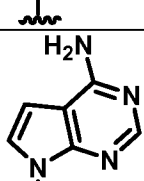
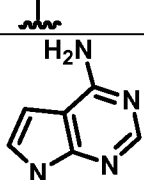
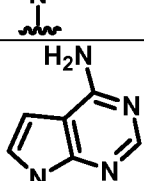
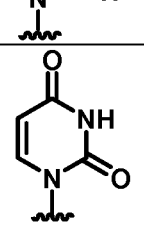
65	H	F	F	OH	i-Pr	
66	H	F	F	F	i-Pr	
67	H	H	H	OH	i-Pr	
68	H	H	H	F	i-Pr	
69	H	Me	Me	OH	i-Pr	
70	H	Me	Me	F	i-Pr	
71	H	F	F	OH	i-Pr	
72	H	F	F	F	i-Pr	
73	H	H	H	OH	i-Pr	
74	H	H	H	F	i-Pr	

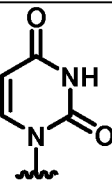
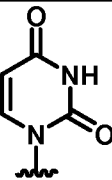
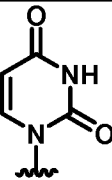
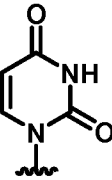
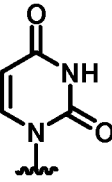
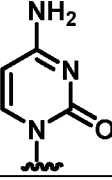
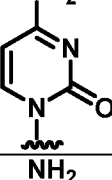
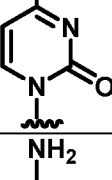
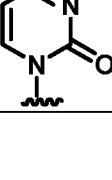
75	H	Me	Me	OH	i-Pr	
76	H	Me	Me	F	i-Pr	
77	H	F	F	OH	i-Pr	
78	H	F	F	F	i-Pr	
79	H	H	H	OH	i-Pr	
80	H	H	H	F	i-Pr	
81	H	Me	Me	OH	i-Pr	
82	H	Me	Me	F	i-Pr	
83	H	F	F	OH	i-Pr	
84	H	F	F	F	i-Pr	

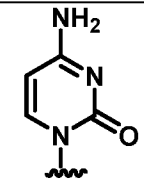
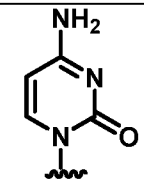
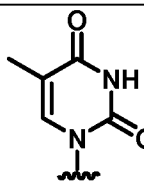
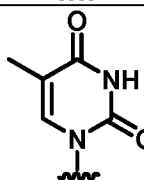
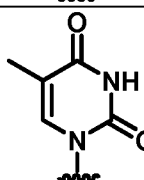
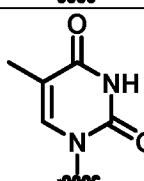
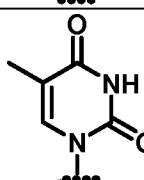
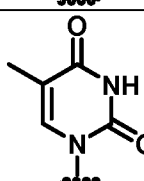
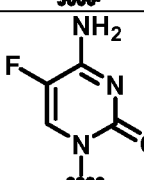
85	H	H	H	OH	i-Pr	
86	H	H	H	F	i-Pr	
87	H	Me	Me	OH	i-Pr	
88	H	Me	Me	F	i-Pr	
89	H	F	F	OH	i-Pr	
90	H	F	F	F	i-Pr	
91	H	H	H	OH	i-Pr	
92	H	H	H	F	i-Pr	
93	H	Me	Me	OH	i-Pr	

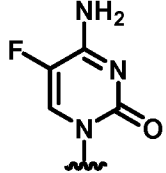
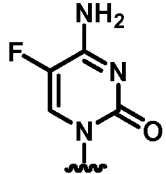
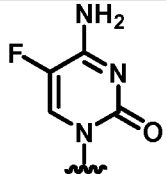
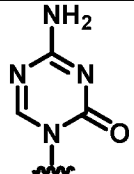
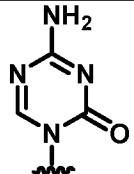
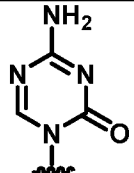
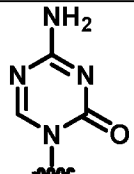
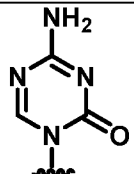
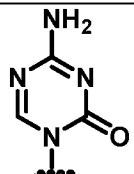
94	H	Me	Me	F	i-Pr	
95	H	F	F	OH	i-Pr	
96	H	F	F	F	i-Pr	
97	H	H	H	OH	i-Pr	
98	H	H	H	F	i-Pr	
99	H	Me	Me	OH	i-Pr	
100	H	Me	Me	F	i-Pr	
101	H	F	F	OH	i-Pr	
102	H	F	F	F	i-Pr	

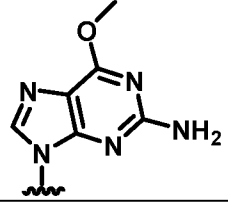
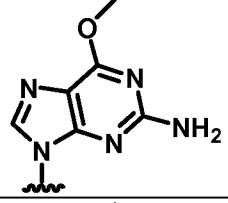
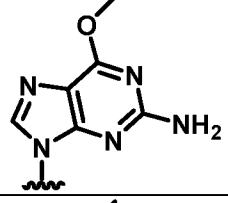
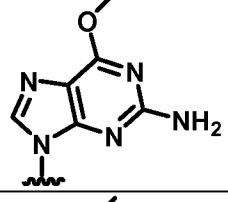
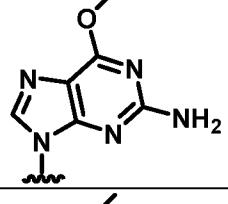
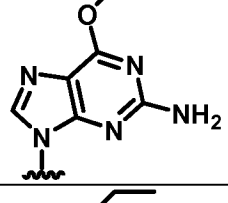
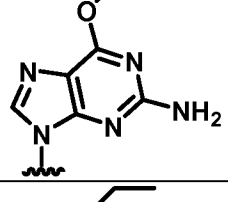
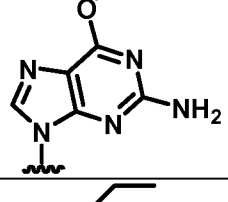
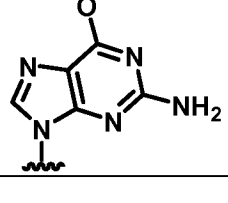
103	H	H	H	OH	i-Pr	
104	H	H	H	F	i-Pr	
105	H	Me	Me	OH	i-Pr	
106	H	Me	Me	F	i-Pr	
107	H	F	F	OH	i-Pr	
108	H	F	F	F	i-Pr	
109	H	H	H	OH	i-Pr	
110	H	H	H	F	i-Pr	
111	H	Me	Me	OH	i-Pr	
112	H	Me	Me	F	i-Pr	

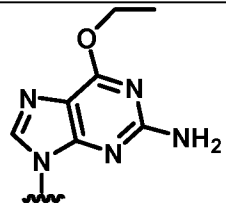
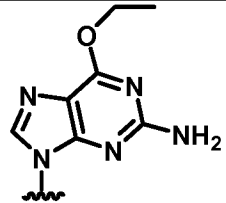
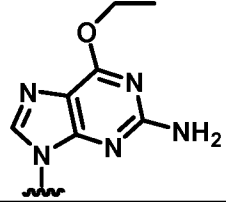
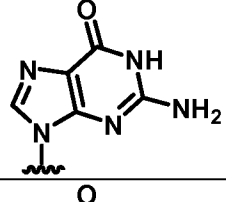
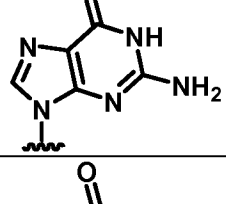
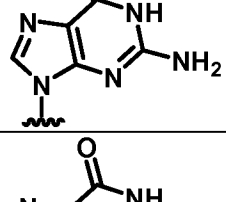
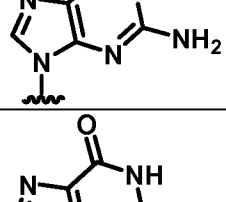
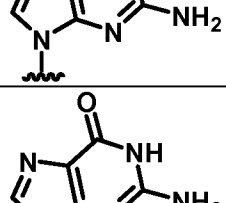
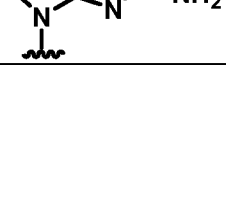
113	H	F	F	OH	i-Pr	
114	H	F	F	F	i-Pr	
115	H	H	H	OH	i-Pr	
116	H	H	H	F	i-Pr	
117	H	Me	Me	OH	i-Pr	
118	H	Me	Me	F	i-Pr	
119	H	F	F	OH	i-Pr	
120	H	F	F	F	i-Pr	
121	H	H	H	OH	Et	

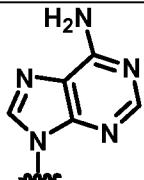
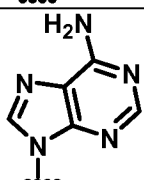
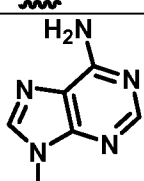
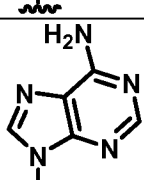
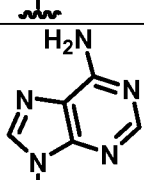
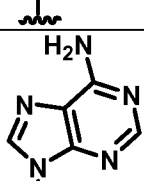
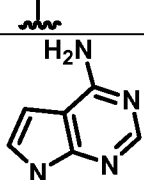
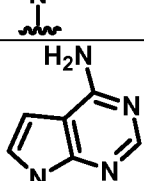
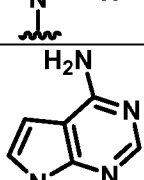
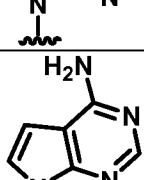
122	H	H	H	F	Et	
123	H	Me	Me	OH	Et	
124	H	Me	Me	F	Et	
125	H	F	F	OH	Et	
126	H	F	F	F	Et	
127	H	H	H	OH	Et	
128	H	H	H	F	Et	
129	H	Me	Me	OH	Et	
130	H	Me	Me	F	Et	

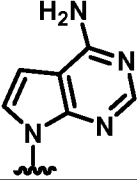
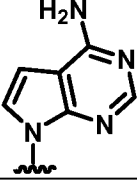
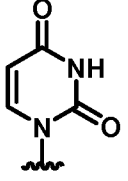
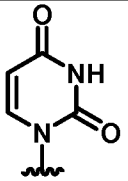
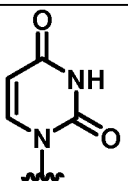
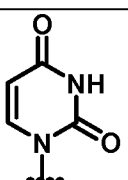
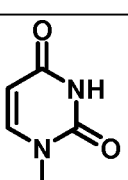
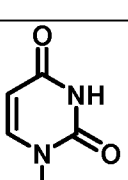
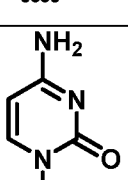
131	H	F	F	OH	Et	
132	H	F	F	F	Et	
133	H	H	H	OH	Et	
134	H	H	H	F	Et	
135	H	Me	Me	OH	Et	
136	H	Me	Me	F	Et	
137	H	F	F	OH	Et	
138	H	F	F	F	Et	
139	H	H	H	OH	Et	
140	H	H	H	F	Et	

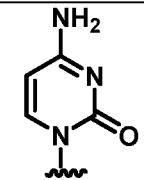
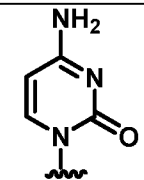
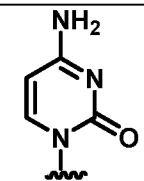
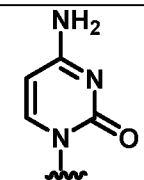
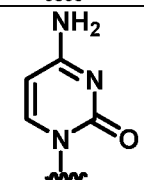
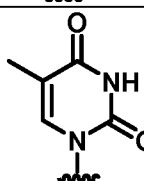
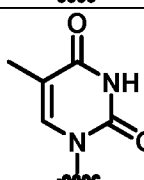
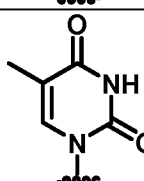
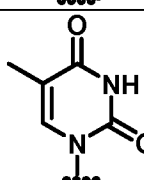
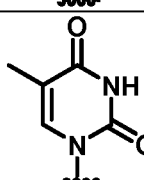
141	H	Me	Me	OH	Et	
142	H	Me	Me	F	Et	
143	H	F	F	OH	Et	
144	H	F	F	F	Et	
145	H	H	H	OH	Et	
146	H	H	H	F	Et	
147	H	Me	Me	OH	Et	
148	H	Me	Me	F	Et	
149	H	F	F	OH	Et	
150	H	F	F	F	Et	

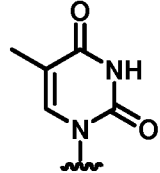
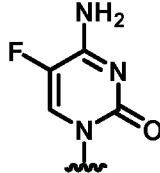
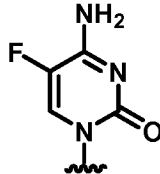
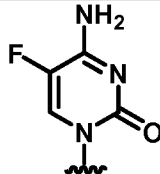
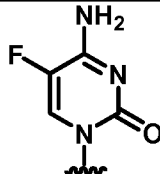
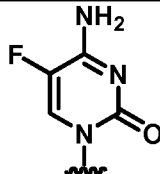
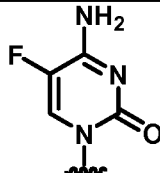
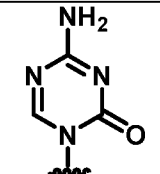
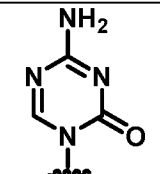
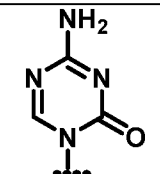
151	H	H	H	OH	Et	
152	H	H	H	F	Et	
153	H	Me	Me	OH	Et	
154	H	Me	Me	F	Et	
155	H	F	F	OH	Et	
156	H	F	F	F	Et	
157	H	H	H	OH	Et	
158	H	H	H	F	Et	
159	H	Me	Me	OH	Et	

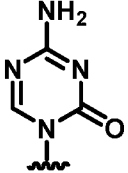
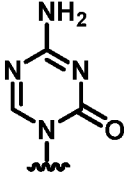
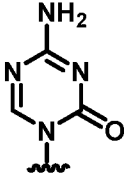
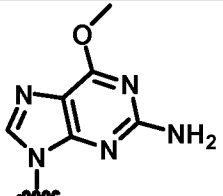
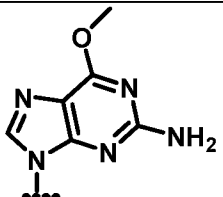
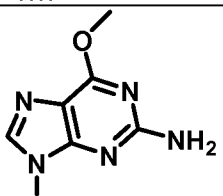
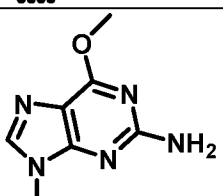
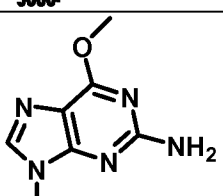
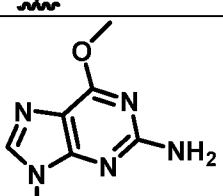
160	H	Me	Me	F	Et	
161	H	F	F	OH	Et	
162	H	F	F	F	Et	
163	H	H	H	OH	Et	
164	H	H	H	F	Et	
165	H	Me	Me	OH	Et	
166	H	Me	Me	F	Et	
167	H	F	F	OH	Et	
168	H	F	F	F	Et	

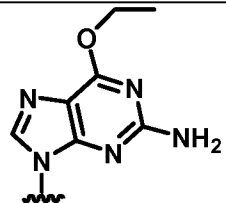
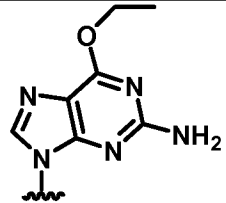
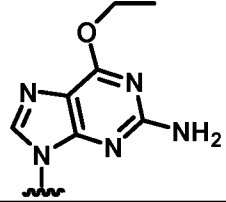
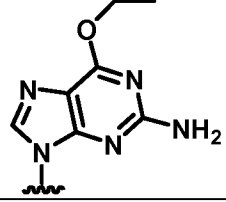
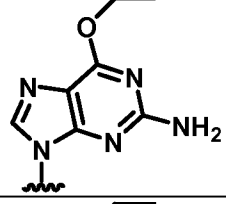
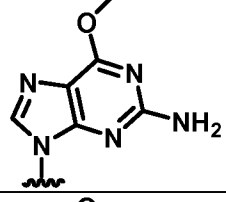
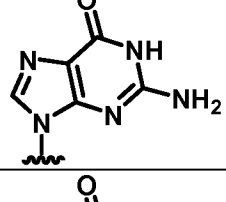
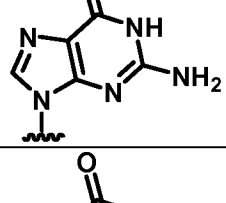
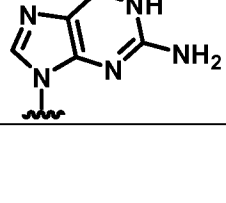
169	H	H	H	OH	Et	
170	H	H	H	F	Et	
171	H	Me	Me	OH	Et	
152	H	Me	Me	F	Et	
173	H	F	F	OH	Et	
174	H	F	F	F	Et	
175	H	H	H	OH	Et	
176	H	H	H	F	Et	
177	H	Me	Me	OH	Et	
178	H	Me	Me	F	Et	

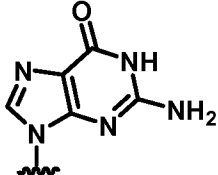
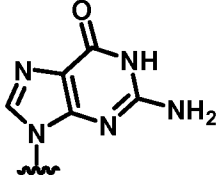
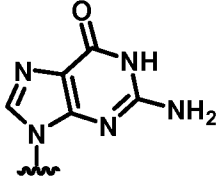
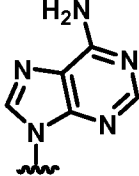
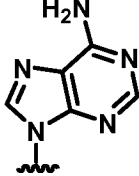
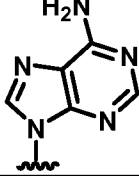
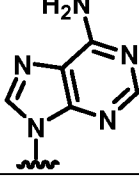
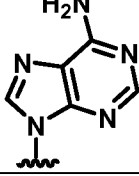
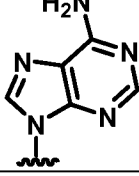
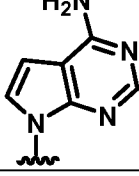
179	H	F	F	OH	Et	
180	H	F	F	F	Et	
181	H	H	H	OH	i-Bu	
182	H	H	H	F	i-Bu	
183	H	Me	Me	OH	i-Bu	
184	H	Me	Me	F	i-Bu	
185	H	F	F	OH	i-Bu	
186	H	F	F	F	i-Bu	
187	H	H	H	OH	i-Bu	

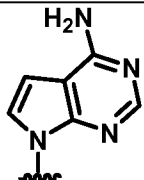
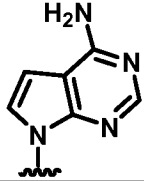
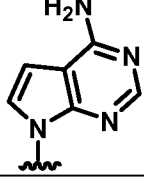
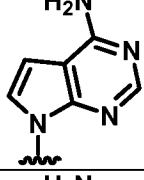
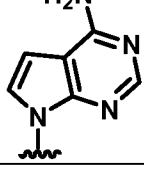
188	H	H	H	F	i-Bu	
189	H	Me	Me	OH	i-Bu	
190	H	Me	Me	F	i-Bu	
191	H	F	F	OH	i-Bu	
192	H	F	F	F	i-Bu	
193	H	H	H	OH	i-Bu	
194	H	H	H	F	i-Bu	
195	H	Me	Me	OH	i-Bu	
196	H	Me	Me	F	i-Bu	
197	H	F	F	OH	i-Bu	

198	H	F	F	F	i-Bu	
199	H	H	H	OH	i-Bu	
200	H	H	H	F	i-Bu	
201	H	Me	Me	OH	i-Bu	
202	H	Me	Me	F	i-Bu	
203	H	F	F	OH	i-Bu	
204	H	F	F	F	i-Bu	
205	H	H	H	OH	i-Bu	
206	H	H	H	F	i-Bu	
207	H	Me	Me	OH	i-Bu	

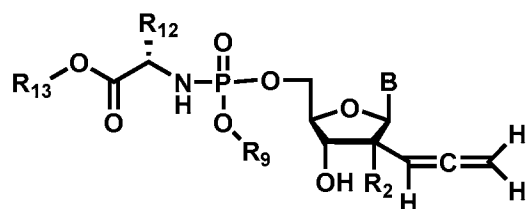
208	H	Me	Me	F	i-Bu	
209	H	F	F	OH	i-Bu	
210	H	F	F	F	i-Bu	
211	H	H	H	OH	i-Bu	
212	H	H	H	F	i-Bu	
213	H	Me	Me	OH	i-Bu	
214	H	Me	Me	F	i-Bu	
215	H	F	F	OH	i-Bu	
216	H	F	F	F	i-Bu	

217	H	H	H	OH	i-Bu	
218	H	H	H	F	i-Bu	
219	H	Me	Me	OH	i-Bu	
220	H	Me	Me	F	i-Bu	
221	H	F	F	OH	i-Bu	
222	H	F	F	F	i-Bu	
223	H	H	H	OH	i-Bu	
224	H	H	H	F	i-Bu	
225	H	Me	Me	OH	i-Bu	

226	H	Me	Me	F	i-Bu	
227	H	F	F	OH	i-Bu	
228	H	F	F	F	i-Bu	
229	H	H	H	OH	i-Bu	
230	H	H	H	F	i-Bu	
231	H	Me	Me	OH	i-Bu	
232	H	Me	Me	F	i-Bu	
233	H	F	F	OH	i-Bu	
234	H	F	F	F	i-Bu	
235	H	H	H	OH	i-Bu	

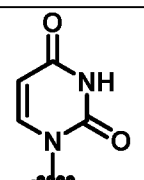
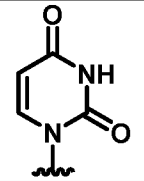
236	H	H	H	F	i-Bu	
237	H	Me	Me	OH	i-Bu	
238	H	Me	Me	F	i-Bu	
239	H	F	F	OH	i-Bu	
240	H	F	F	F	i-Bu	

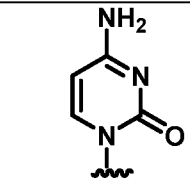
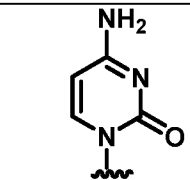
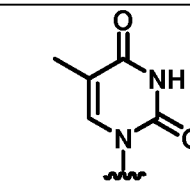
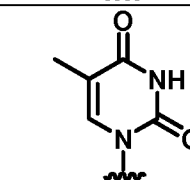
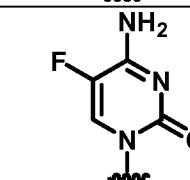
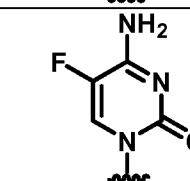
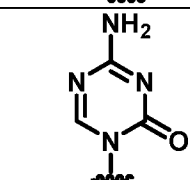
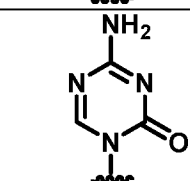
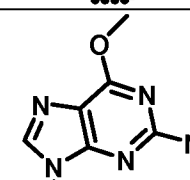
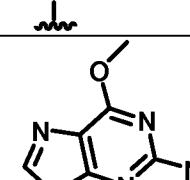
Compounds in Table 3 were illustrated according to Formula (V-1) wherein R_2 , R_9 , R_{12} , R_{13} , and B are delineated for each example in Table 3

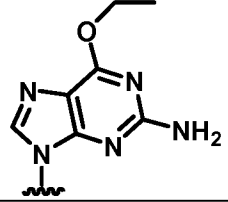
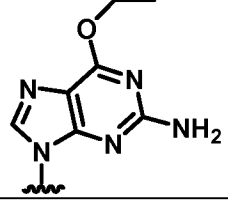
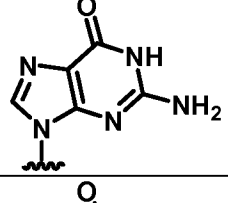
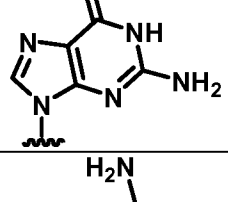
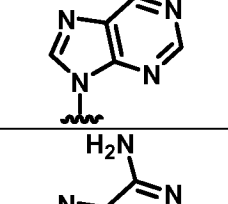
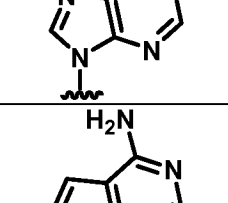
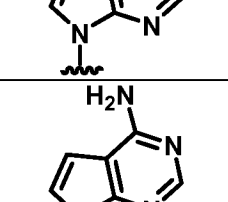
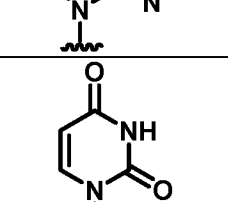
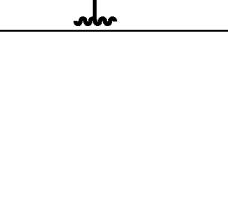


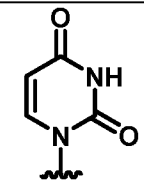
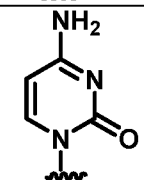
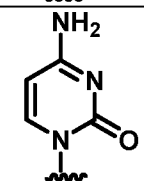
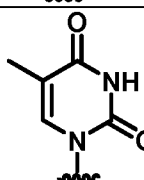
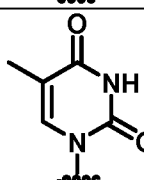
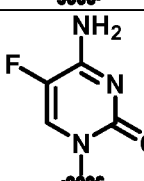
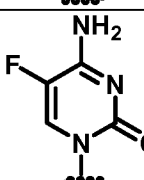
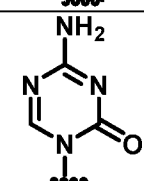
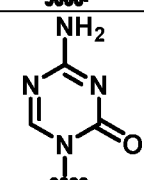
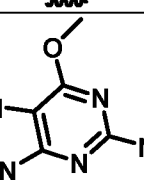
(V-1)

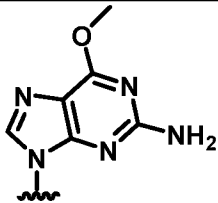
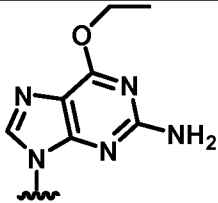
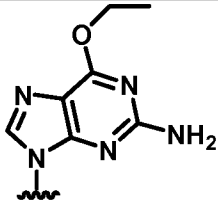
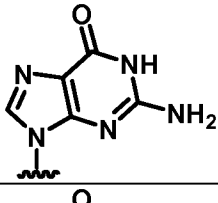
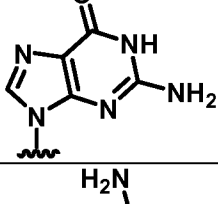
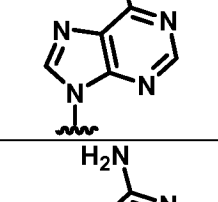
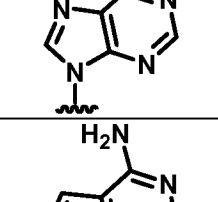
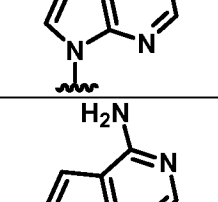
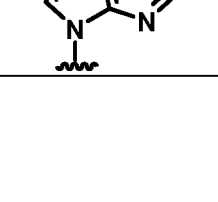
5

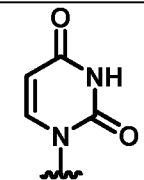
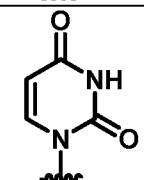
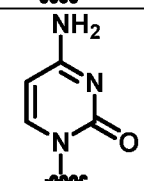
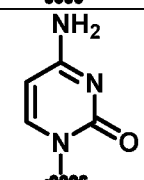
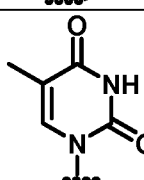
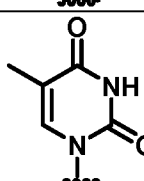
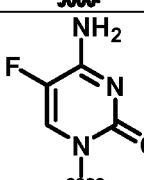
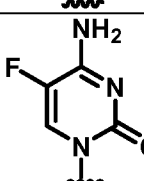
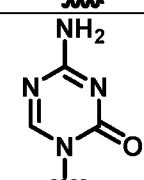
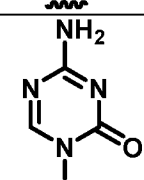
Example#	R_2	R_9	R_{12}	R_{13}	B
241	OH	Ph	Me	Me	
242	F	Ph	Me	Me	

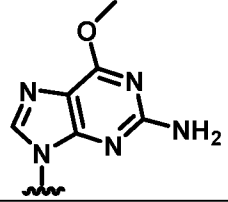
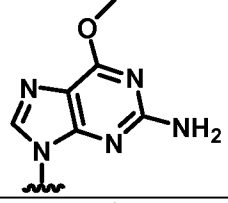
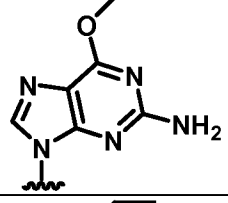
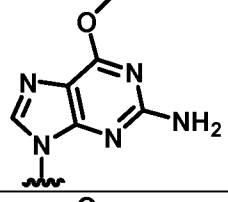
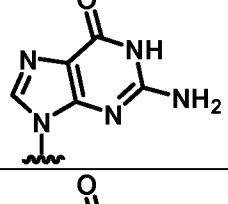
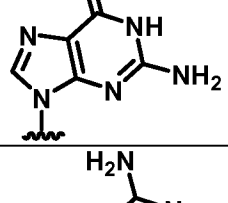
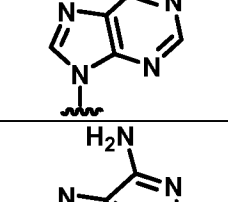
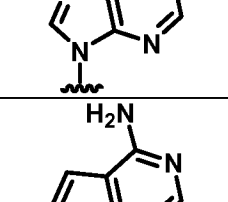
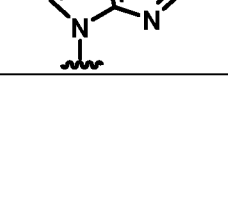
243	OH	Ph	Me	Me	
244	F	Ph	Me	Me	
245	OH	Ph	Me	Me	
246	F	Ph	Me	Me	
247	OH	Ph	Me	Me	
248	F	Ph	Me	Me	
249	OH	Ph	Me	Me	
250	F	Ph	Me	Me	
251	OH	Ph	Me	Me	
252	F	Ph	Me	Me	

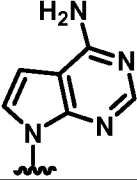
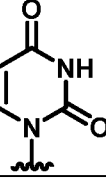
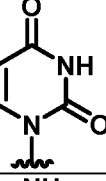
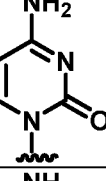
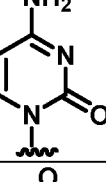
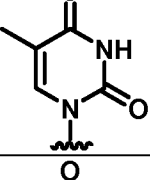
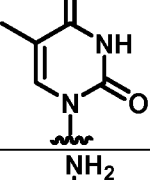
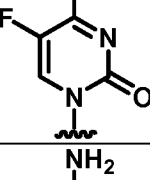
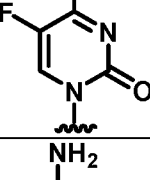
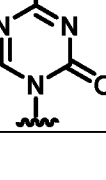
253	OH	Ph	Me	Me	
254	F	Ph	Me	Me	
255	OH	Ph	Me	Me	
256	F	Ph	Me	Me	
257	OH	Ph	Me	Me	
258	F	Ph	Me	Me	
259	OH	Ph	Me	Me	
260	F	Ph	Me	Me	
261	OH	1-Naphthyl	Me	Me	

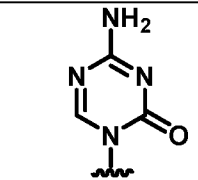
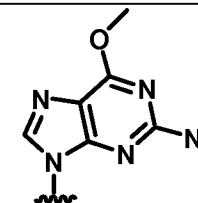
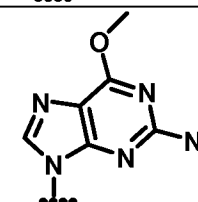
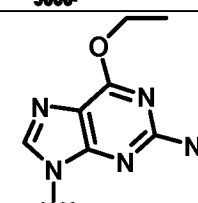
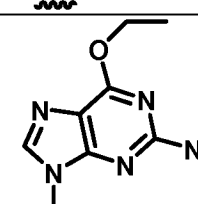
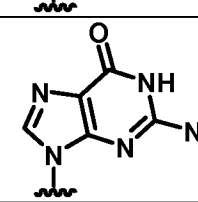
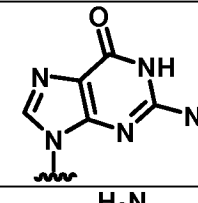
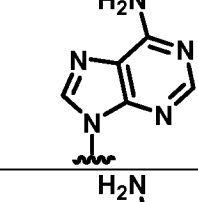
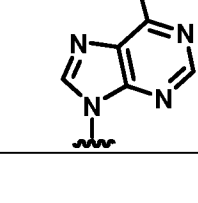
262	F	1-Naphthyl	Me	Me	
263	OH	1-Naphthyl	Me	Me	
264	F	1-Naphthyl	Me	Me	
265	OH	1-Naphthyl	Me	Me	
266	F	1-Naphthyl	Me	Me	
267	OH	1-Naphthyl	Me	Me	
268	F	1-Naphthyl	Me	Me	
269	OH	1-Naphthyl	Me	Me	
270	F	1-Naphthyl	Me	Me	
271	OH	1-Naphthyl	Me	Me	

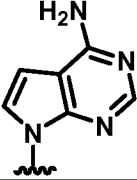
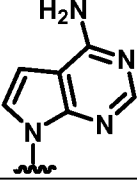
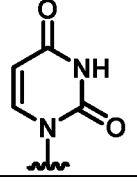
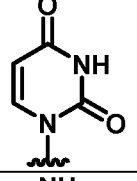
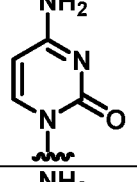
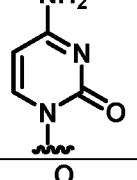
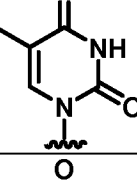
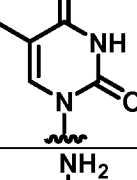
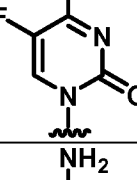
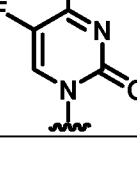
272	F	1-Naphthyl	Me	Me	
273	OH	1-Naphthyl	Me	Me	
274	F	1-Naphthyl	Me	Me	
275	OH	1-Naphthyl	Me	Me	
276	F	1-Naphthyl	Me	Me	
277	OH	1-Naphthyl	Me	Me	
278	F	1-Naphthyl	Me	Me	
279	OH	1-Naphthyl	Me	Me	
280	F	1-Naphthyl	Me	Me	

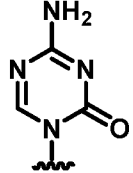
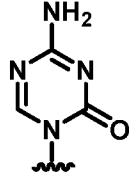
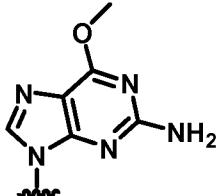
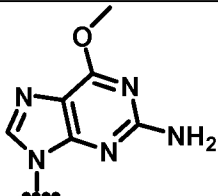
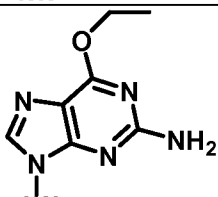
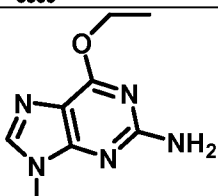
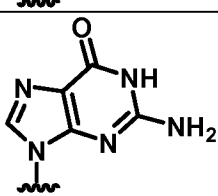
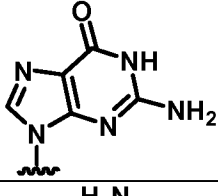
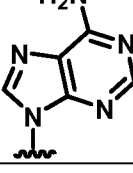
281	OH	Ph	H	Me	
282	F	Ph	H	Me	
283	OH	Ph	H	Me	
284	F	Ph	H	Me	
285	OH	Ph	H	Me	
286	F	Ph	H	Me	
287	OH	Ph	H	Me	
288	F	Ph	H	Me	
289	OH	Ph	H	Me	
290	F	Ph	H	Me	

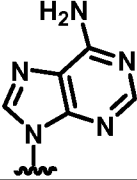
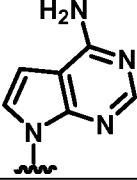
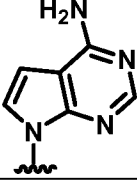
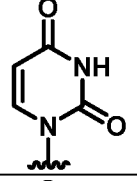
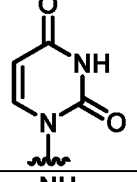
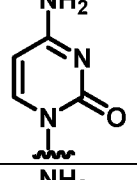
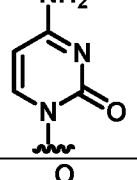
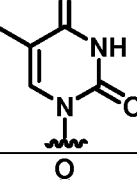
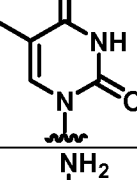
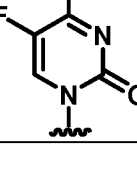
291	OH	Ph	H	Me	
292	F	Ph	H	Me	
293	OH	Ph	H	Me	
294	F	Ph	H	Me	
295	OH	Ph	H	Me	
296	F	Ph	H	Me	
297	OH	Ph	H	Me	
298	F	Ph	H	Me	
299	OH	Ph	H	Me	

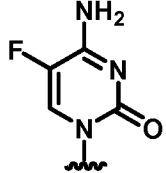
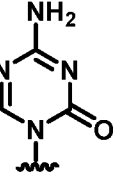
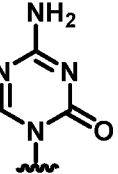
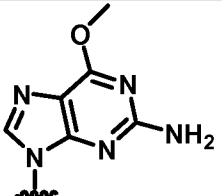
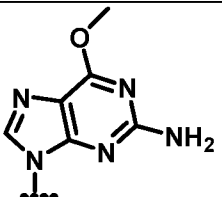
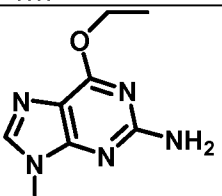
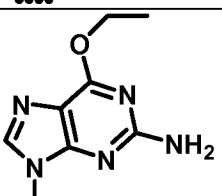
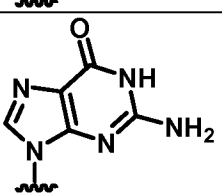
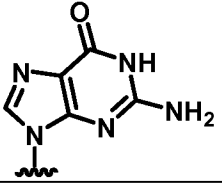
300	F	Ph	H	Me	
301	OH	1-Naphthyl	H	Me	
302	F	1-Naphthyl	H	Me	
303	OH	1-Naphthyl	H	Me	
304	F	1-Naphthyl	H	Me	
305	OH	1-Naphthyl	H	Me	
306	F	1-Naphthyl	H	Me	
307	OH	1-Naphthyl	H	Me	
308	F	1-Naphthyl	H	Me	
309	OH	1-Naphthyl	H	Me	

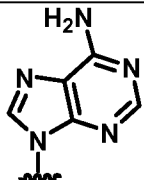
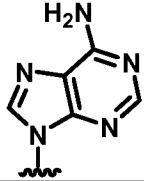
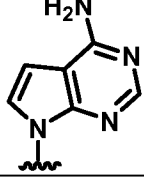
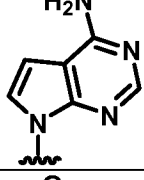
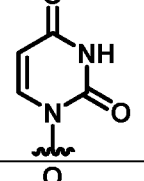
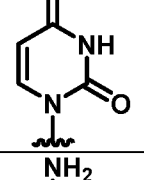
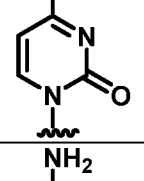
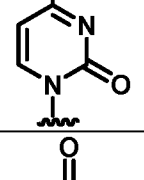
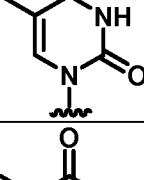
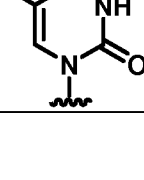
310	F	1-Naphthyl	H	Me	
311	OH	1-Naphthyl	H	Me	
312	F	1-Naphthyl	H	Me	
313	OH	1-Naphthyl	H	Me	
314	F	1-Naphthyl	H	Me	
315	OH	1-Naphthyl	H	Me	
316	F	1-Naphthyl	H	Me	
317	OH	1-Naphthyl	H	Me	
318	F	1-Naphthyl	H	Me	

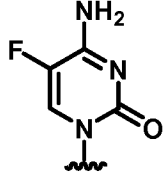
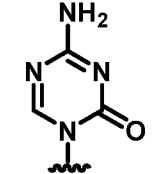
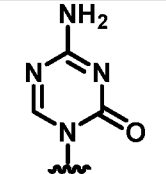
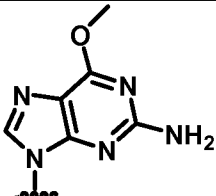
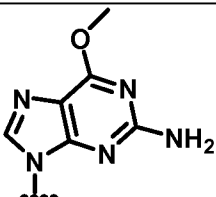
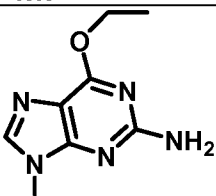
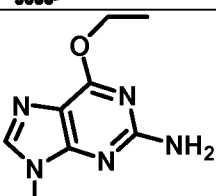
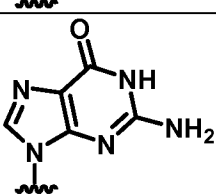
319	OH	1-Naphthyl	H	Me	
320	F	1-Naphthyl	H	Me	
321	OH	Ph	Me	n-Pentyl	
322	F	Ph	Me	n-Pentyl	
323	OH	Ph	Me	n-Pentyl	
324	F	Ph	Me	n-Pentyl	
325	OH	Ph	Me	n-Pentyl	
326	F	Ph	Me	n-Pentyl	
327	OH	Ph	Me	n-Pentyl	
328	F	Ph	Me	n-Pentyl	

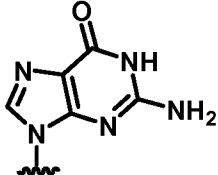
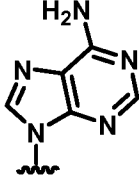
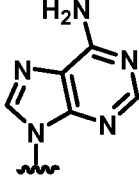
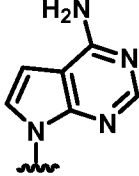
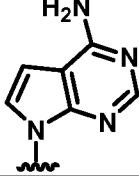
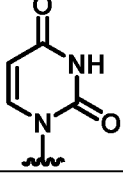
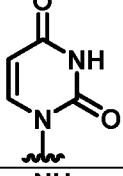
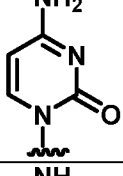
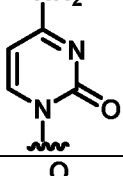
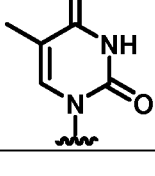
329	OH	Ph	Me	n-Pentyl	
330	F	Ph	Me	n-Pentyl	
331	OH	Ph	Me	n-Pentyl	
332	F	Ph	Me	n-Pentyl	
333	OH	Ph	Me	n-Pentyl	
334	F	Ph	Me	n-Pentyl	
335	OH	Ph	Me	n-Pentyl	
336	F	Ph	Me	n-Pentyl	
337	OH	Ph	Me	n-Pentyl	

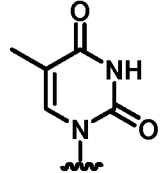
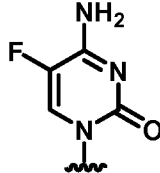
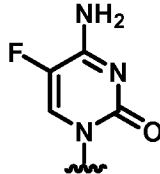
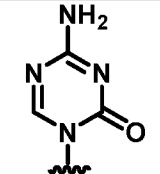
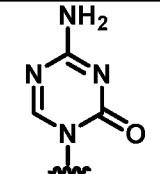
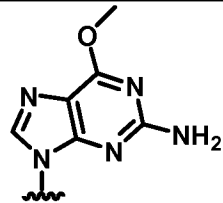
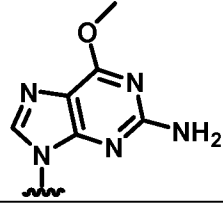
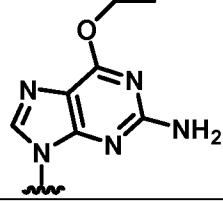
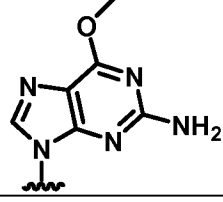
338	F	Ph	Me	n-Pentyl	
339	OH	Ph	Me	n-Pentyl	
340	F	Ph	Me	n-Pentyl	
341	OH	1-Naphthyl	Me	n-Pentyl	
342	F	1-Naphthyl	Me	n-Pentyl	
343	OH	1-Naphthyl	Me	n-Pentyl	
344	F	1-Naphthyl	Me	n-Pentyl	
345	OH	1-Naphthyl	Me	n-Pentyl	
346	F	1-Naphthyl	Me	n-Pentyl	
347	OH	1-Naphthyl	Me	n-Pentyl	

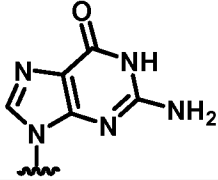
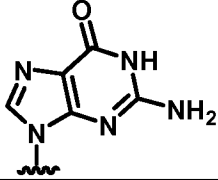
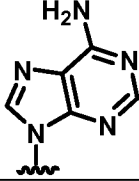
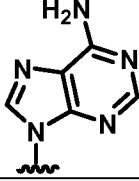
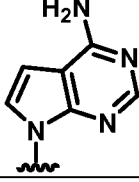
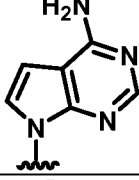
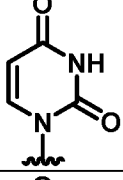
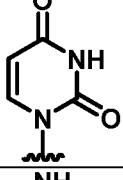
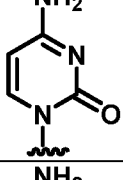
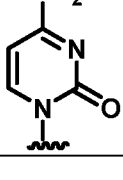
348	F	1-Naphthyl	Me	n-Pentyl	
349	OH	1-Naphthyl	Me	n-Pentyl	
350	F	1-Naphthyl	Me	n-Pentyl	
351	OH	1-Naphthyl	Me	n-Pentyl	
352	F	1-Naphthyl	Me	n-Pentyl	
353	OH	1-Naphthyl	Me	n-Pentyl	
354	F	1-Naphthyl	Me	n-Pentyl	
355	OH	1-Naphthyl	Me	n-Pentyl	
356	F	1-Naphthyl	Me	n-Pentyl	

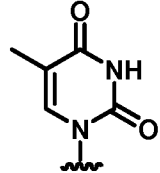
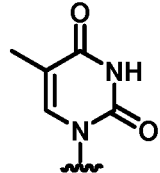
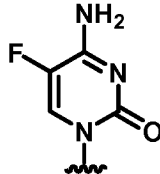
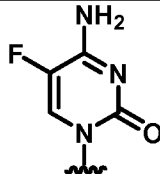
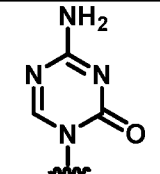
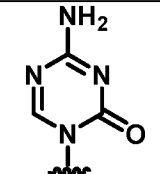
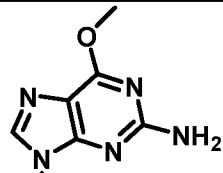
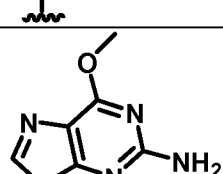
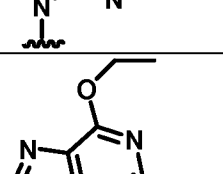
357	OH	1-Naphthyl	Me	n-Pentyl	
358	F	1-Naphthyl	Me	n-Pentyl	
359	OH	1-Naphthyl	Me	n-Pentyl	
360	F	1-Naphthyl	Me	n-Pentyl	
361	OH	Ph	H	n-Pentyl	
362	F	Ph	H	n-Pentyl	
363	OH	Ph	H	n-Pentyl	
364	F	Ph	H	n-Pentyl	
365	OH	Ph	H	n-Pentyl	
366	F	Ph	H	n-Pentyl	

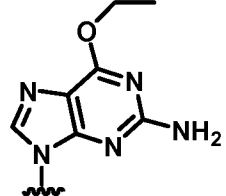
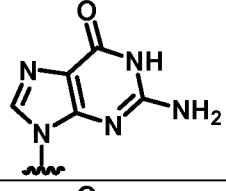
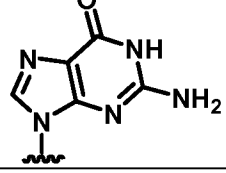
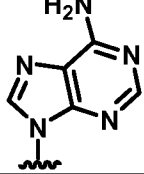
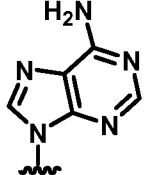
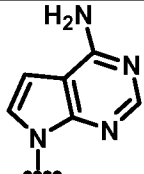
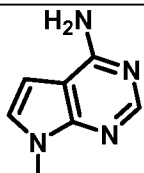
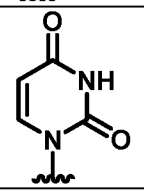
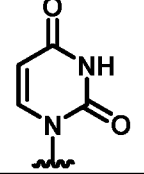
367	OH	Ph	H	n-Pentyl	
368	F	Ph	H	n-Pentyl	
369	OH	Ph	H	n-Pentyl	
370	F	Ph	H	n-Pentyl	
371	OH	Ph	H	n-Pentyl	
372	F	Ph	H	n-Pentyl	
373	OH	Ph	H	n-Pentyl	
374	F	Ph	H	n-Pentyl	
375	OH	Ph	H	n-Pentyl	

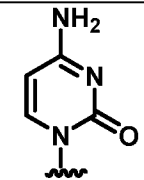
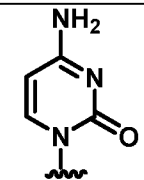
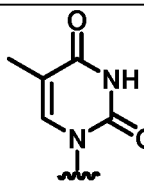
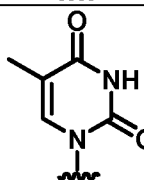
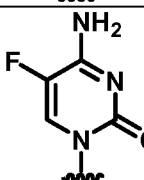
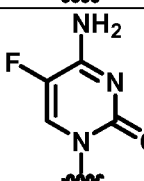
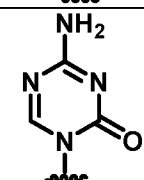
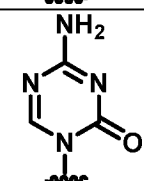
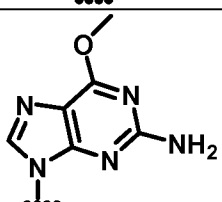
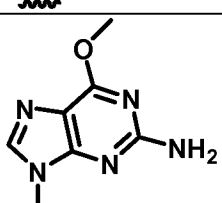
376	F	Ph	H	n-Pentyl	
377	OH	Ph	H	n-Pentyl	
378	F	Ph	H	n-Pentyl	
379	OH	Ph	H	n-Pentyl	
380	F	Ph	H	n-Pentyl	
381	OH	1-Naphthyl	H	n-Pentyl	
382	F	1-Naphthyl	H	n-Pentyl	
383	OH	1-Naphthyl	H	n-Pentyl	
384	F	1-Naphthyl	H	n-Pentyl	
385	OH	1-Naphthyl	H	n-Pentyl	

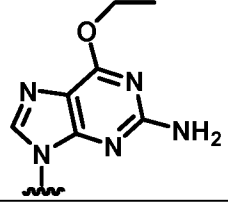
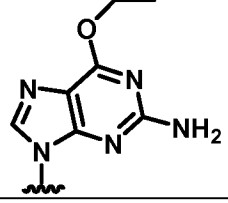
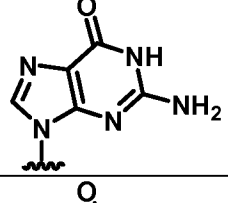
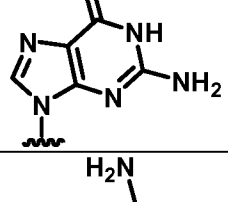
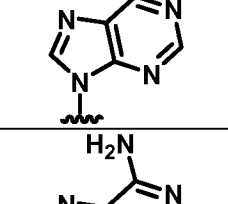
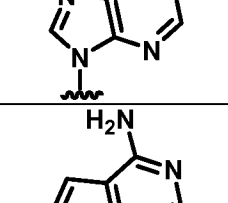
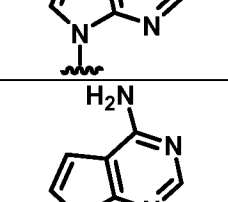
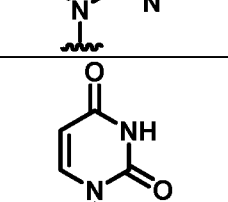
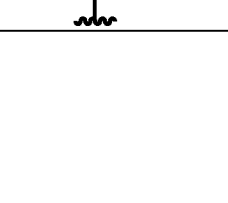
386	F	1-Naphthyl	H	n-Pentyl	
387	OH	1-Naphthyl	H	n-Pentyl	
388	F	1-Naphthyl	H	n-Pentyl	
389	OH	1-Naphthyl	H	n-Pentyl	
390	F	1-Naphthyl	H	n-Pentyl	
391	OH	1-Naphthyl	H	n-Pentyl	
392	F	1-Naphthyl	H	n-Pentyl	
393	OH	1-Naphthyl	H	n-Pentyl	
394	F	1-Naphthyl	H	n-Pentyl	

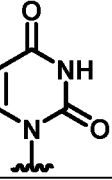
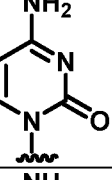
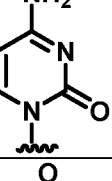
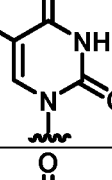
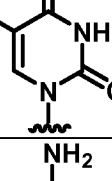
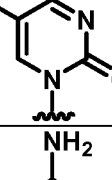
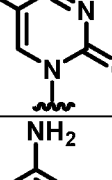
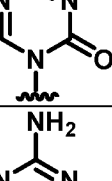
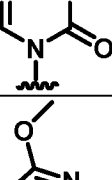
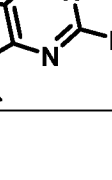
395	OH	1-Naphthyl	H	n-Pentyl	
396	F	1-Naphthyl	H	n-Pentyl	
397	OH	1-Naphthyl	H	n-Pentyl	
398	F	1-Naphthyl	H	n-Pentyl	
399	OH	1-Naphthyl	H	n-Pentyl	
400	F	1-Naphthyl	H	n-Pentyl	
401	OH	Ph	Me	i-Pr	
402	F	Ph	Me	i-Pr	
403	OH	Ph	Me	i-Pr	
404	F	Ph	Me	i-Pr	

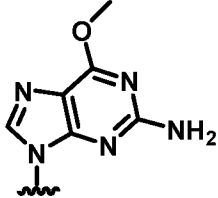
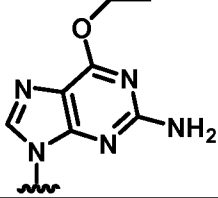
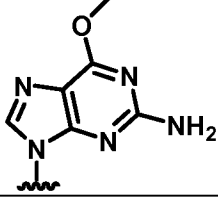
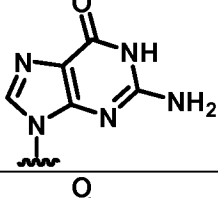
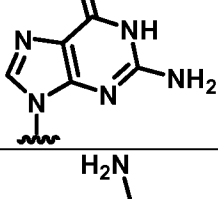
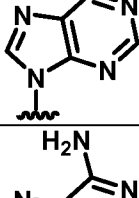
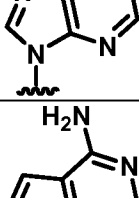
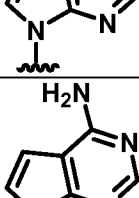
405	OH	Ph	Me	i-Pr	
406	F	Ph	Me	i-Pr	
407	OH	Ph	Me	i-Pr	
408	F	Ph	Me	i-Pr	
409	OH	Ph	Me	i-Pr	
410	F	Ph	Me	i-Pr	
411	OH	Ph	Me	i-Pr	
412	F	Ph	Me	i-Pr	
413	OH	Ph	Me	i-Pr	

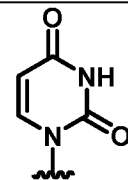
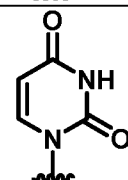
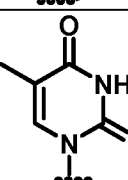
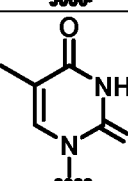
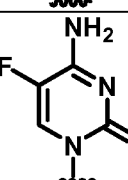
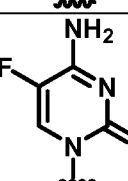
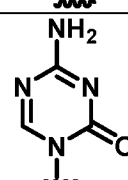
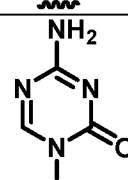
414	F	Ph	Me	i-Pr	
415	OH	Ph	Me	i-Pr	
416	F	Ph	Me	i-Pr	
417	OH	Ph	Me	i-Pr	
418	F	Ph	Me	i-Pr	
419	OH	Ph	Me	i-Pr	
420	F	Ph	Me	i-Pr	
421	OH	1-Naphthyl	Me	i-Pr	
422	F	1-Naphthyl	Me	i-Pr	

423	OH	1-Naphthyl	Me	i-Pr	
424	F	1-Naphthyl	Me	i-Pr	
425	OH	1-Naphthyl	Me	i-Pr	
426	F	1-Naphthyl	Me	i-Pr	
427	OH	1-Naphthyl	Me	i-Pr	
428	F	1-Naphthyl	Me	i-Pr	
429	OH	1-Naphthyl	Me	i-Pr	
430	F	1-Naphthyl	Me	i-Pr	
431	OH	1-Naphthyl	Me	i-Pr	
432	F	1-Naphthyl	Me	i-Pr	

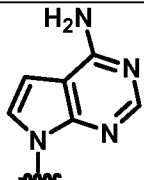
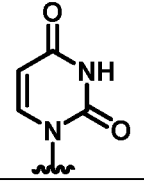
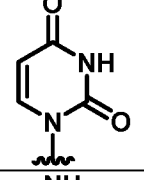
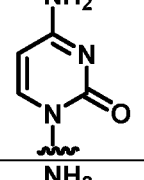
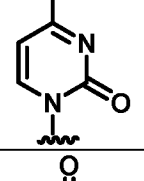
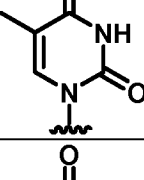
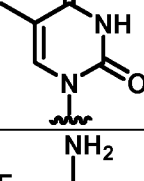
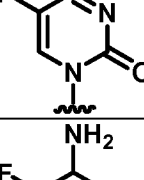
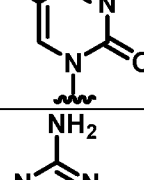
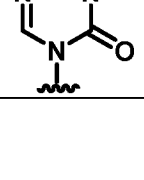
433	OH	1-Naphthyl	Me	i-Pr	
434	F	1-Naphthyl	Me	i-Pr	
435	OH	1-Naphthyl	Me	i-Pr	
436	F	1-Naphthyl	Me	i-Pr	
437	OH	1-Naphthyl	Me	i-Pr	
438	F	1-Naphthyl	Me	i-Pr	
439	OH	1-Naphthyl	Me	i-Pr	
440	F	1-Naphthyl	Me	i-Pr	
441	OH	Ph	H	i-Pr	

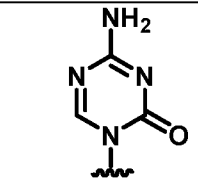
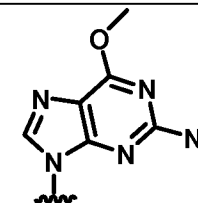
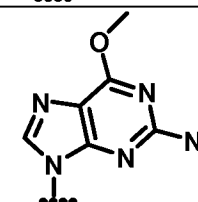
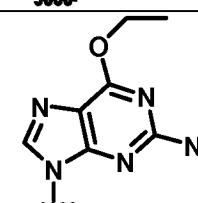
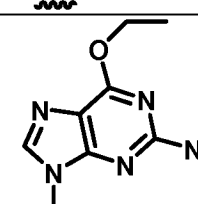
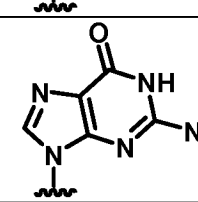
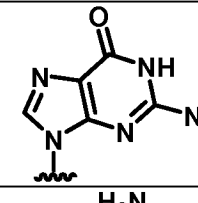
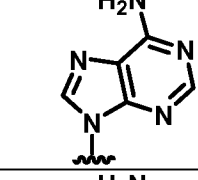
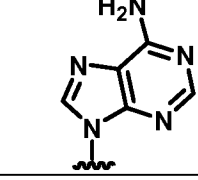
442	F	Ph	H	i-Pr	
443	OH	Ph	H	i-Pr	
444	F	Ph	H	i-Pr	
445	OH	Ph	H	i-Pr	
446	F	Ph	H	i-Pr	
447	OH	Ph	H	i-Pr	
448	F	Ph	H	i-Pr	
449	OH	Ph	H	i-Pr	
450	F	Ph	H	i-Pr	
451	OH	Ph	H	i-Pr	

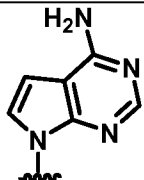
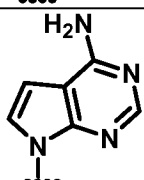
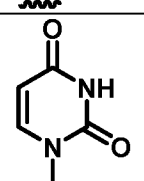
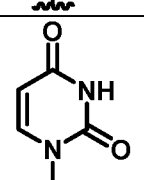
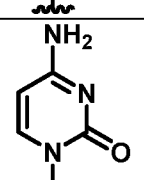
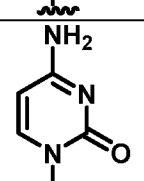
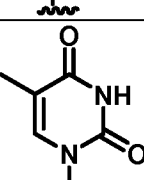
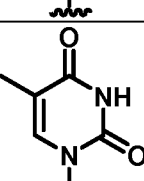
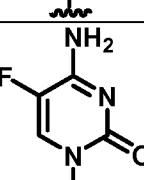
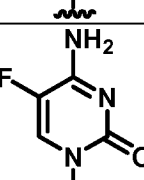
452	F	Ph	H	i-Pr	
453	OH	Ph	H	i-Pr	
454	F	Ph	H	i-Pr	
455	OH	Ph	H	i-Pr	
456	F	Ph	H	i-Pr	
457	OH	Ph	H	i-Pr	
458	F	Ph	H	i-Pr	
459	OH	Ph	H	i-Pr	
460	F	Ph	H	i-Pr	

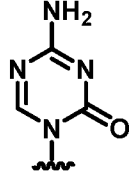
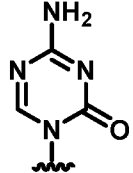
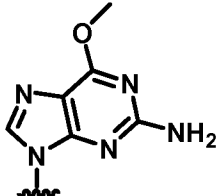
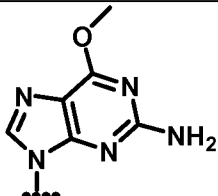
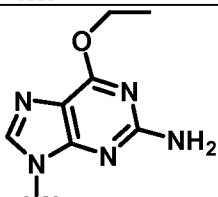
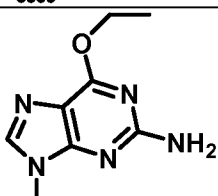
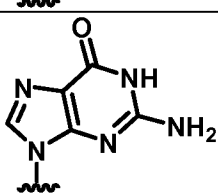
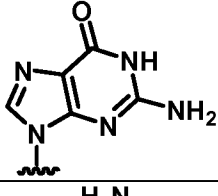
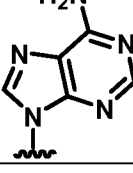
461	OH	1-Naphthyl	H	i-Pr	
462	F	1-Naphthyl	H	i-Pr	
463	OH	1-Naphthyl	H	i-Pr	
464	F	1-Naphthyl	H	i-Pr	
465	OH	1-Naphthyl	H	i-Pr	
466	F	1-Naphthyl	H	i-Pr	
467	OH	1-Naphthyl	H	i-Pr	
468	F	1-Naphthyl	H	i-Pr	
469	OH	1-Naphthyl	H	i-Pr	
470	F	1-Naphthyl	H	i-Pr	

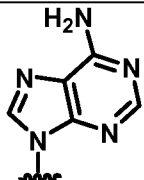
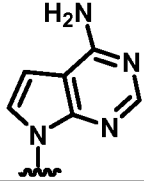
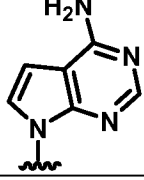
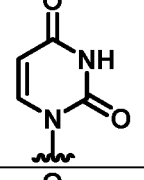
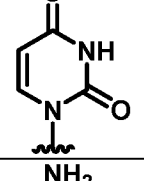
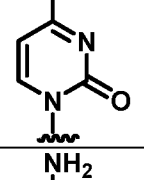
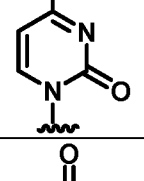
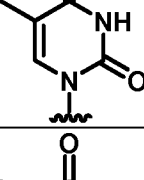
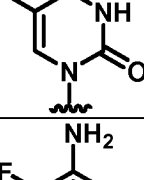
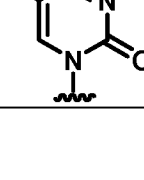
471	OH	1-Naphthyl	H	i-Pr	
472	F	1-Naphthyl	H	i-Pr	
473	OH	1-Naphthyl	H	i-Pr	
474	F	1-Naphthyl	H	i-Pr	
475	OH	1-Naphthyl	H	i-Pr	
476	F	1-Naphthyl	H	i-Pr	
477	OH	1-Naphthyl	H	i-Pr	
478	F	1-Naphthyl	H	i-Pr	
479	OH	1-Naphthyl	H	i-Pr	

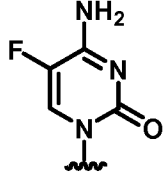
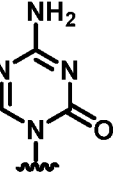
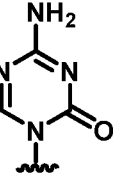
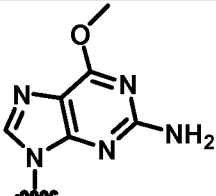
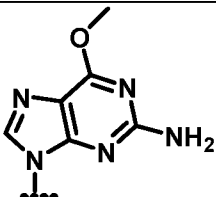
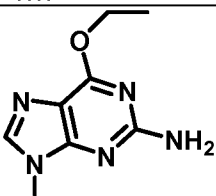
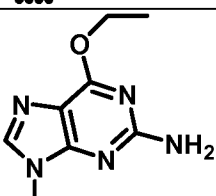
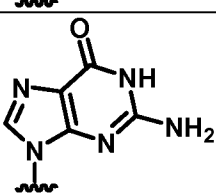
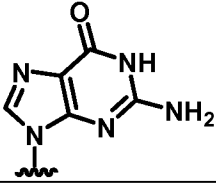
480	F	1-Naphthyl	H	i-Pr	
481	OH	Ph	Me	Benzyl	
482	F	Ph	Me	Benzyl	
483	OH	Ph	Me	Benzyl	
484	F	Ph	Me	Benzyl	
485	OH	Ph	Me	Benzyl	
486	F	Ph	Me	Benzyl	
487	OH	Ph	Me	Benzyl	
488	F	Ph	Me	Benzyl	
489	OH	Ph	Me	Benzyl	

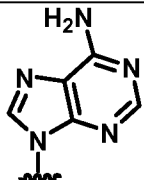
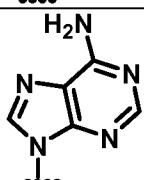
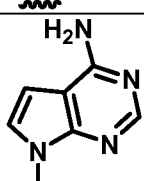
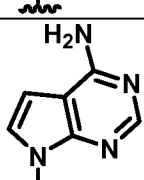
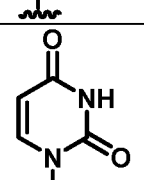
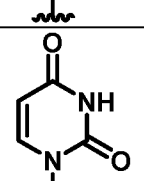
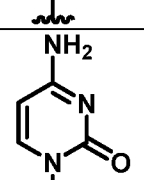
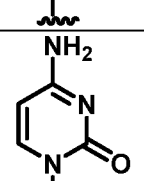
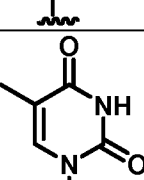
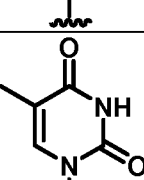
490	F	Ph	Me	Benzyl	
491	OH	Ph	Me	Benzyl	
492	F	Ph	Me	Benzyl	
493	OH	Ph	Me	Benzyl	
494	F	Ph	Me	Benzyl	
495	OH	Ph	Me	Benzyl	
496	F	Ph	Me	Benzyl	
497	OH	Ph	Me	Benzyl	
498	F	Ph	Me	Benzyl	

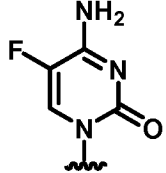
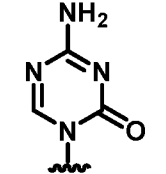
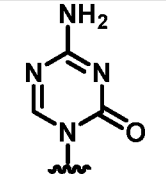
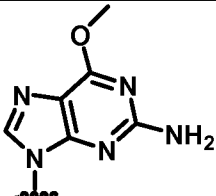
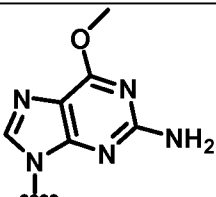
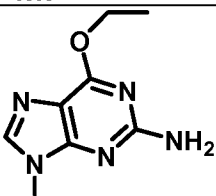
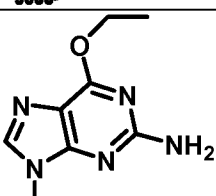
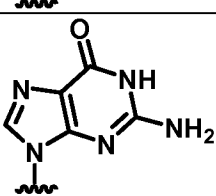
499	OH	Ph	Me	Benzyl	
500	F	Ph	Me	Benzyl	
501	OH	1-Naphthyl	Me	Benzyl	
502	F	1-Naphthyl	Me	Benzyl	
503	OH	1-Naphthyl	Me	Benzyl	
504	F	1-Naphthyl	Me	Benzyl	
505	OH	1-Naphthyl	Me	Benzyl	
506	F	1-Naphthyl	Me	Benzyl	
507	OH	1-Naphthyl	Me	Benzyl	
508	F	1-Naphthyl	Me	Benzyl	

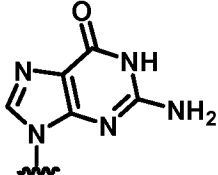
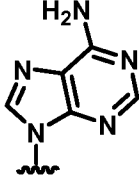
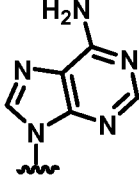
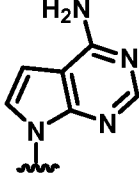
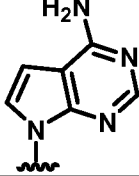
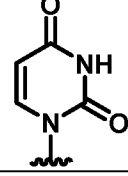
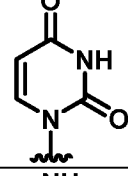
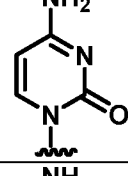
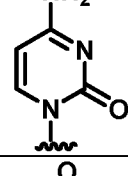
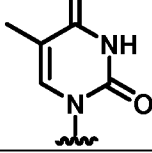
509	OH	1-Naphthyl	Me	Benzyl	
510	F	1-Naphthyl	Me	Benzyl	
511	OH	1-Naphthyl	Me	Benzyl	
512	F	1-Naphthyl	Me	Benzyl	
513	OH	1-Naphthyl	Me	Benzyl	
514	F	1-Naphthyl	Me	Benzyl	
515	OH	1-Naphthyl	Me	Benzyl	
516	F	1-Naphthyl	Me	Benzyl	
517	OH	1-Naphthyl	Me	Benzyl	

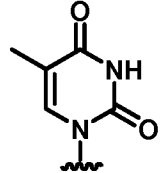
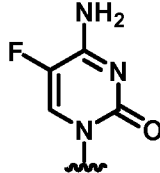
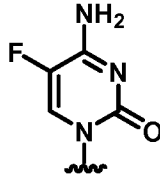
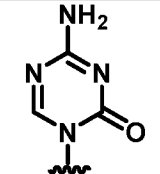
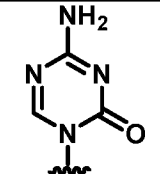
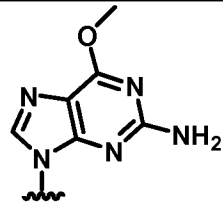
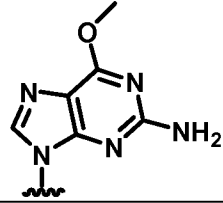
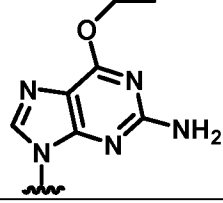
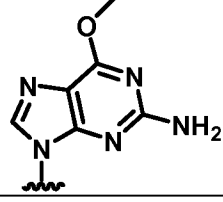
518	F	1-Naphthyl	Me	Benzyl	
519	OH	1-Naphthyl	Me	Benzyl	
520	F	1-Naphthyl	Me	Benzyl	
521	OH	Ph	H	Benzyl	
522	F	Ph	H	Benzyl	
523	OH	Ph	H	Benzyl	
524	F	Ph	H	Benzyl	
525	OH	Ph	H	Benzyl	
526	F	Ph	H	Benzyl	
527	OH	Ph	H	Benzyl	

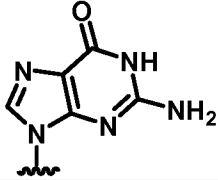
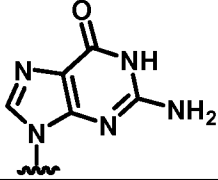
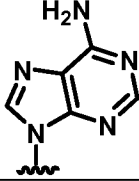
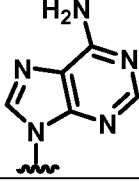
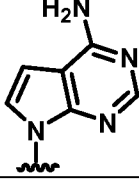
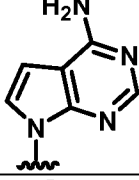
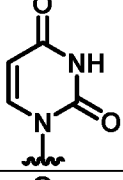
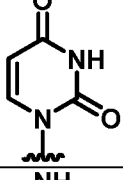
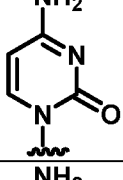
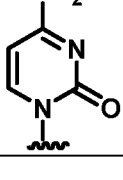
528	F	Ph	H	Benzyl	
529	OH	Ph	H	Benzyl	
530	F	Ph	H	Benzyl	
531	OH	Ph	H	Benzyl	
532	F	Ph	H	Benzyl	
533	OH	Ph	H	Benzyl	
534	F	Ph	H	Benzyl	
535	OH	Ph	H	Benzyl	
536	F	Ph	H	Benzyl	

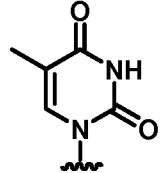
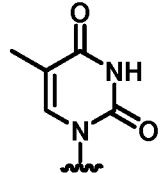
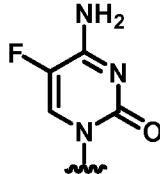
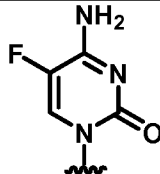
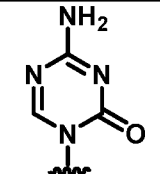
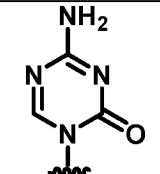
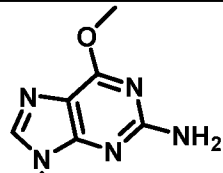
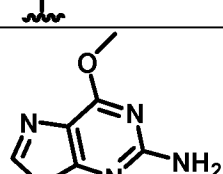
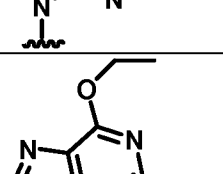
537	OH	Ph	H	Benzyl	
538	F	Ph	H	Benzyl	
539	OH	Ph	H	Benzyl	
540	F	Ph	H	Benzyl	
541	OH	1-Naphthyl	H	Benzyl	
542	F	1-Naphthyl	H	Benzyl	
543	OH	1-Naphthyl	H	Benzyl	
544	F	1-Naphthyl	H	Benzyl	
545	OH	1-Naphthyl	H	Benzyl	
546	F	1-Naphthyl	H	Benzyl	

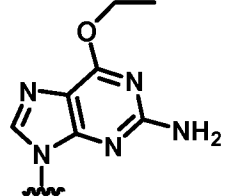
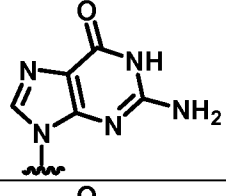
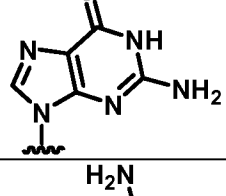
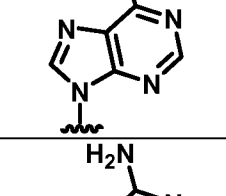
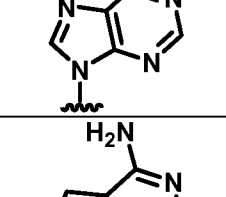
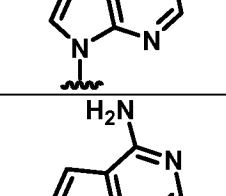
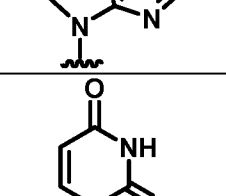
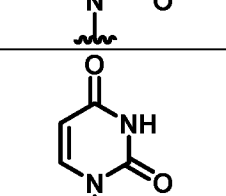
547	OH	1-Naphthyl	H	Benzyl	
548	F	1-Naphthyl	H	Benzyl	
549	OH	1-Naphthyl	H	Benzyl	
550	F	1-Naphthyl	H	Benzyl	
551	OH	1-Naphthyl	H	Benzyl	
552	F	1-Naphthyl	H	Benzyl	
553	OH	1-Naphthyl	H	Benzyl	
554	F	1-Naphthyl	H	Benzyl	
555	OH	1-Naphthyl	H	Benzyl	

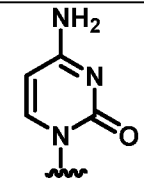
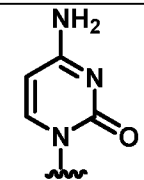
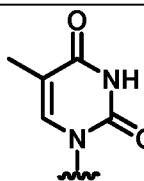
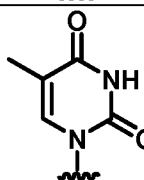
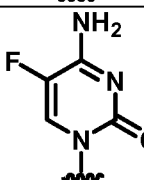
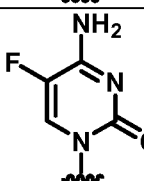
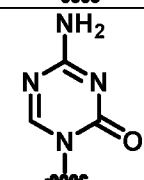
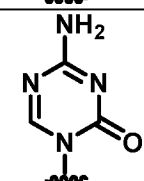
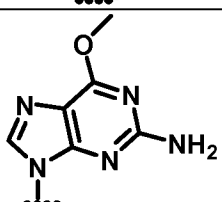
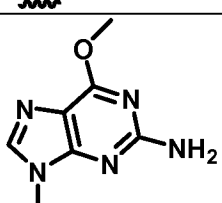
556	F	1-Naphthyl	H	Benzyl	
557	OH	1-Naphthyl	H	Benzyl	
558	F	1-Naphthyl	H	Benzyl	
559	OH	1-Naphthyl	H	Benzyl	
560	F	1-Naphthyl	H	Benzyl	
561	OH	Ph	Me	t-BuCH ₂ -	
562	F	Ph	Me	t-BuCH ₂ -	
563	OH	Ph	Me	t-BuCH ₂ -	
564	F	Ph	Me	t-BuCH ₂ -	
565	OH	Ph	Me	t-BuCH ₂ -	

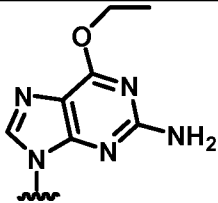
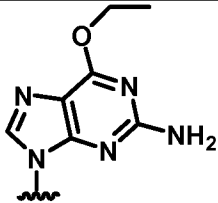
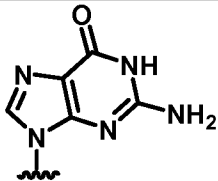
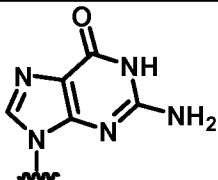
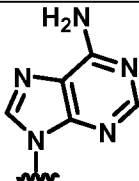
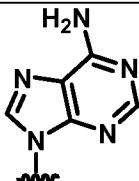
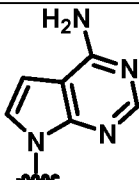
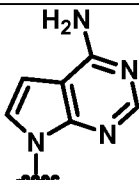
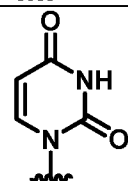
566	F	Ph	Me	t-BuCH ₂ -	
567	OH	Ph	Me	t-BuCH ₂ -	
568	F	Ph	Me	t-BuCH ₂ -	
569	OH	Ph	Me	t-BuCH ₂ -	
570	F	Ph	Me	t-BuCH ₂ -	
571	OH	Ph	Me	t-BuCH ₂ -	
572	F	Ph	Me	t-BuCH ₂ -	
573	OH	Ph	Me	t-BuCH ₂ -	
574	F	Ph	Me	t-BuCH ₂ -	

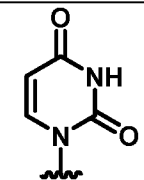
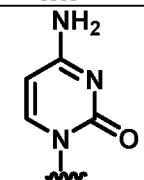
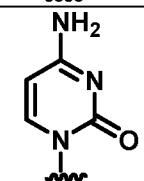
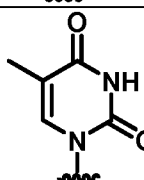
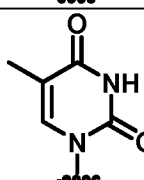
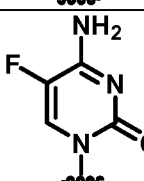
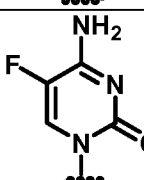
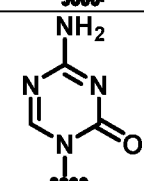
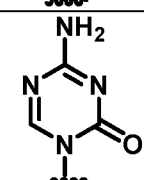
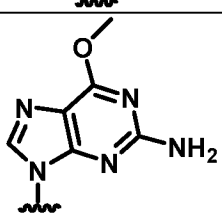
575	OH	Ph	Me	t-BuCH ₂ -	
576	F	Ph	Me	t-BuCH ₂ -	
577	OH	Ph	Me	t-BuCH ₂ -	
578	F	Ph	Me	t-BuCH ₂ -	
579	OH	Ph	Me	t-BuCH ₂ -	
580	F	Ph	Me	t-BuCH ₂ -	
581	OH	1-Naphthyl	Me	t-BuCH ₂ -	
582	F	1-Naphthyl	Me	t-BuCH ₂ -	
583	OH	1-Naphthyl	Me	t-BuCH ₂ -	
584	F	1-Naphthyl	Me	t-BuCH ₂ -	

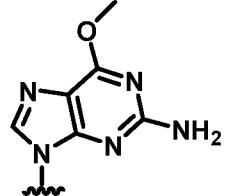
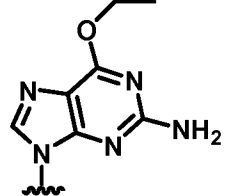
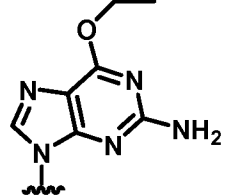
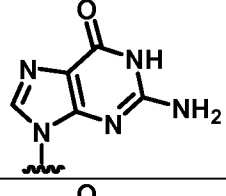
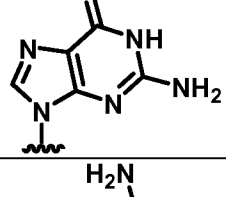
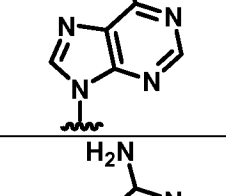
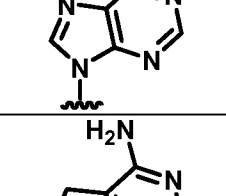
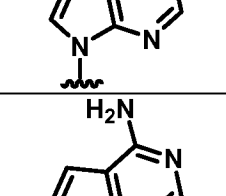
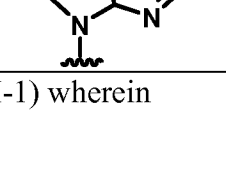
585	OH	1-Naphthyl	Me	t-BuCH ₂ -	
586	F	1-Naphthyl	Me	t-BuCH ₂ -	
587	OH	1-Naphthyl	Me	t-BuCH ₂ -	
588	F	1-Naphthyl	Me	t-BuCH ₂ -	
589	OH	1-Naphthyl	Me	t-BuCH ₂ -	
590	F	1-Naphthyl	Me	t-BuCH ₂ -	
591	OH	1-Naphthyl	Me	t-BuCH ₂ -	
592	F	1-Naphthyl	Me	t-BuCH ₂ -	
593	OH	1-Naphthyl	Me	t-BuCH ₂ -	

594	F	1-Naphthyl	Me	t-BuCH ₂ -	
595	OH	1-Naphthyl	Me	t-BuCH ₂ -	
596	F	1-Naphthyl	Me	t-BuCH ₂ -	
597	OH	1-Naphthyl	Me	t-BuCH ₂ -	
598	F	1-Naphthyl	Me	t-BuCH ₂ -	
599	OH	1-Naphthyl	Me	t-BuCH ₂ -	
600	F	1-Naphthyl	Me	t-BuCH ₂ -	
601	OH	Ph	H	t-BuCH ₂ -	
602	F	Ph	H	t-BuCH ₂ -	

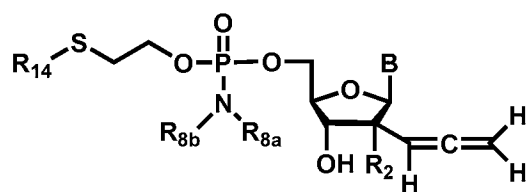
603	OH	Ph	H	t-BuCH ₂ -	
604	F	Ph	H	t-BuCH ₂ -	
605	OH	Ph	H	t-BuCH ₂ -	
606	F	Ph	H	t-BuCH ₂ -	
607	OH	Ph	H	t-BuCH ₂ -	
608	F	Ph	H	t-BuCH ₂ -	
609	OH	Ph	H	t-BuCH ₂ -	
610	F	Ph	H	t-BuCH ₂ -	
611	OH	Ph	H	t-BuCH ₂ -	
612	F	Ph	H	t-BuCH ₂ -	

613	OH	Ph	H	t-BuCH ₂ -	
614	F	Ph	H	t-BuCH ₂ -	
615	OH	Ph	H	t-BuCH ₂ -	
616	F	Ph	H	t-BuCH ₂ -	
617	OH	Ph	H	t-BuCH ₂ -	
618	F	Ph	H	t-BuCH ₂ -	
619	OH	Ph	H	t-BuCH ₂ -	
620	F	Ph	H	t-BuCH ₂ -	
621	OH	1-Naphthyl	H	t-BuCH ₂ -	

622	F	1-Naphthyl	H	t-BuCH ₂ -	
623	OH	1-Naphthyl	H	t-BuCH ₂ -	
624	F	1-Naphthyl	H	t-BuCH ₂ -	
625	OH	1-Naphthyl	H	t-BuCH ₂ -	
626	F	1-Naphthyl	H	t-BuCH ₂ -	
627	OH	1-Naphthyl	H	t-BuCH ₂ -	
628	F	1-Naphthyl	H	t-BuCH ₂ -	
629	OH	1-Naphthyl	H	t-BuCH ₂ -	
630	F	1-Naphthyl	H	t-BuCH ₂ -	
631	OH	1-Naphthyl	H	t-BuCH ₂ -	

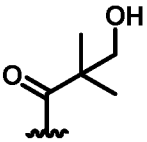
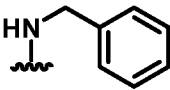
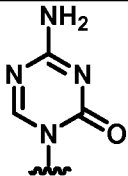
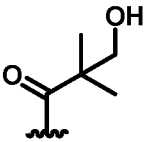
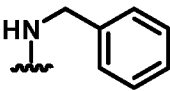
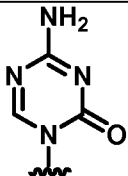
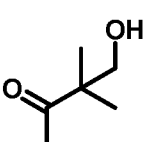
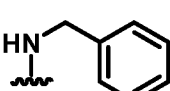
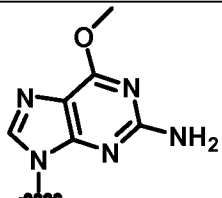
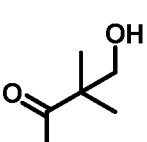
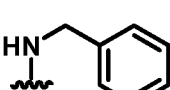
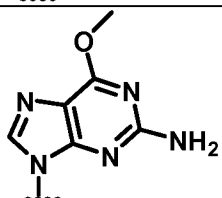
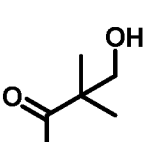
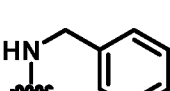
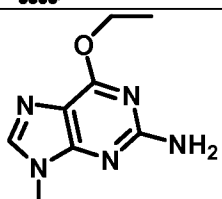
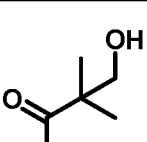
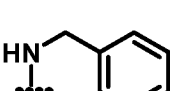
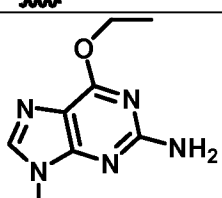
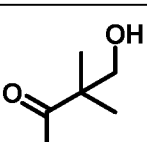
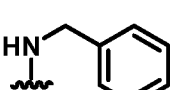
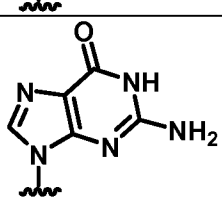
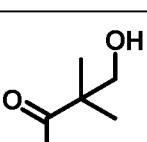
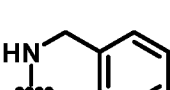
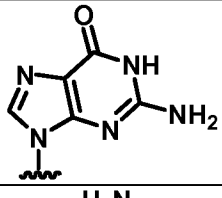
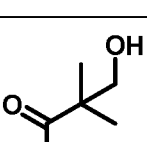
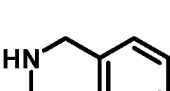
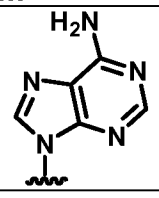
632	F	1-Naphthyl	H	t-BuCH ₂ -	
633	OH	1-Naphthyl	H	t-BuCH ₂ -	
634	F	1-Naphthyl	H	t-BuCH ₂ -	
635	OH	1-Naphthyl	H	t-BuCH ₂ -	
636	F	1-Naphthyl	H	t-BuCH ₂ -	
637	OH	1-Naphthyl	H	t-BuCH ₂ -	
638	F	1-Naphthyl	H	t-BuCH ₂ -	
639	OH	1-Naphthyl	H	t-BuCH ₂ -	
640	F	1-Naphthyl	H	t-BuCH ₂ -	

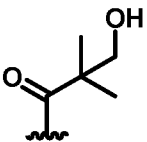
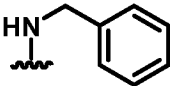
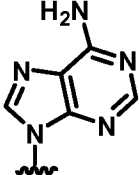
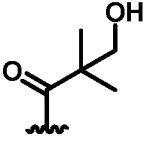
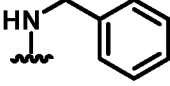
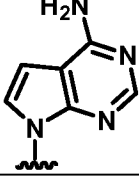
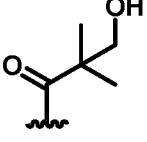
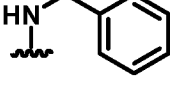
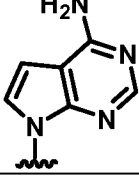
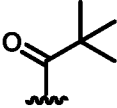
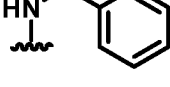
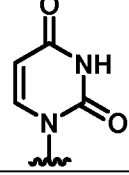
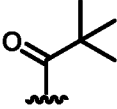
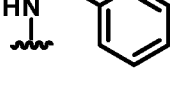
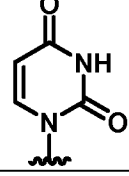
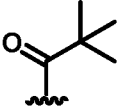
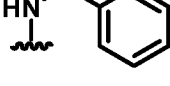
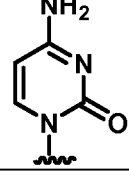
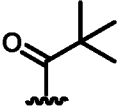
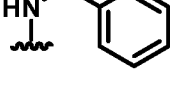
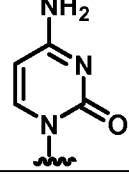
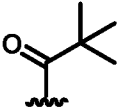
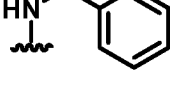
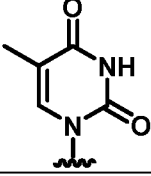
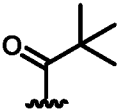
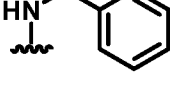
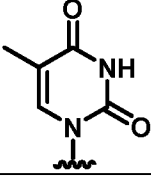
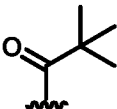
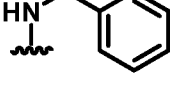
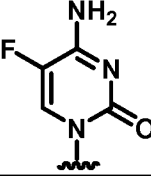
Compounds in Table 4 were illustrated according to Formula (VI-1) wherein R₂, R₉, R₁₂, R₁₃, and B are delineated for each example in Table 4

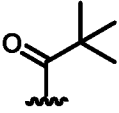
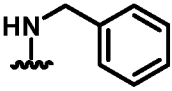
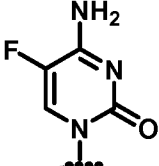
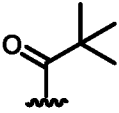
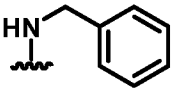
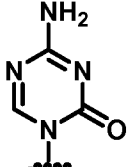
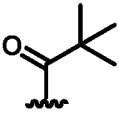
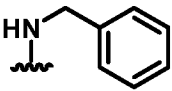
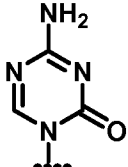
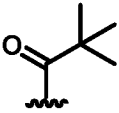
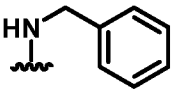
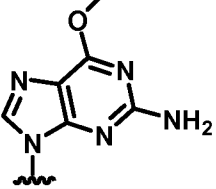
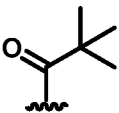
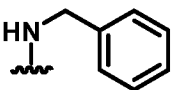
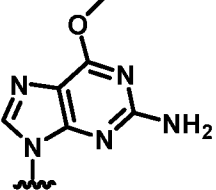
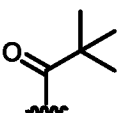
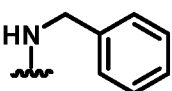
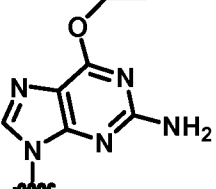
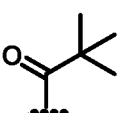
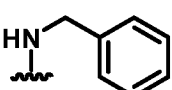
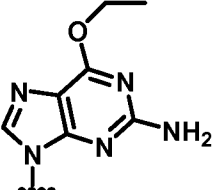
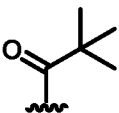
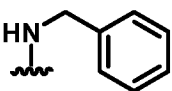
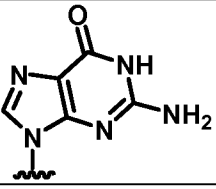
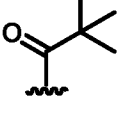
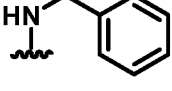
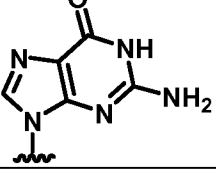


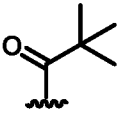
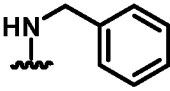
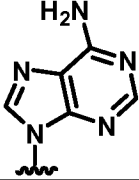
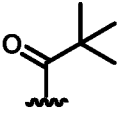
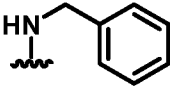
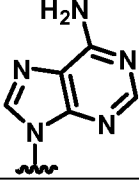
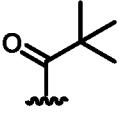
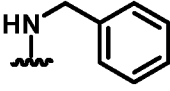
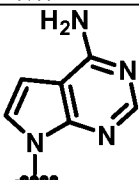
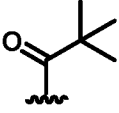
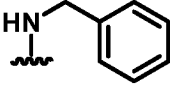
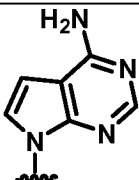
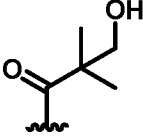
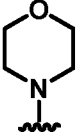
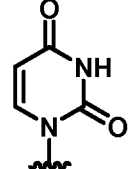
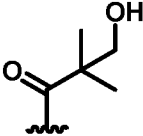
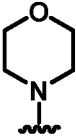
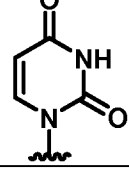
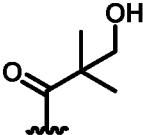
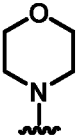
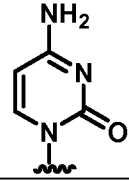
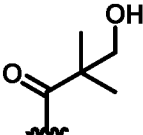
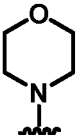
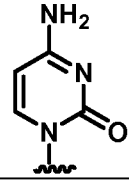
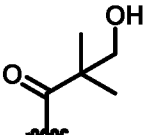
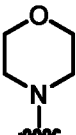
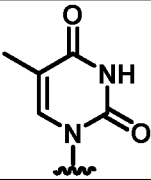
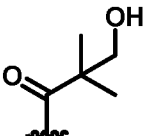
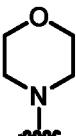
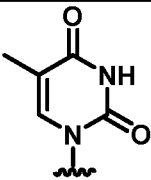
(VI-1)

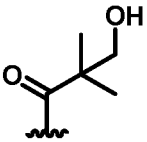
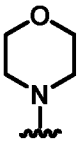
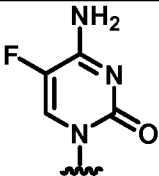
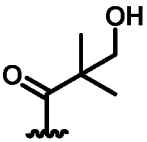
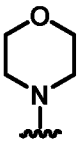
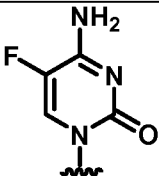
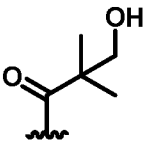
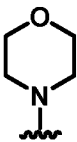
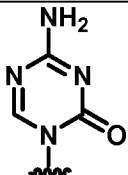
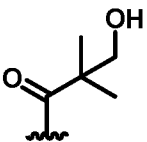
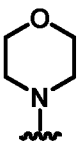
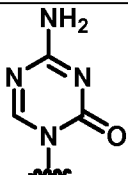
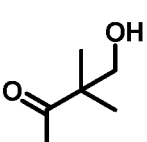
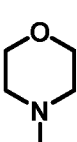
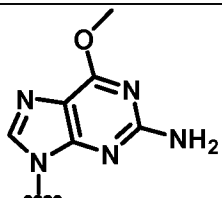
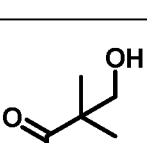
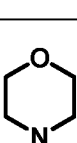
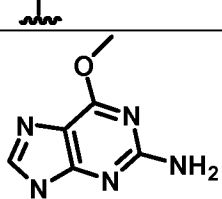
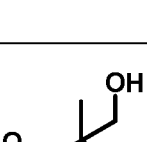
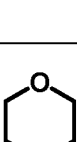
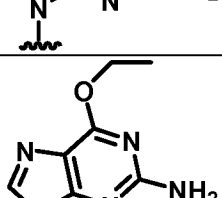
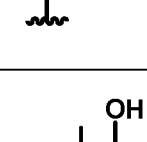
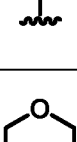
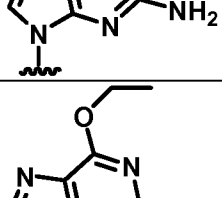
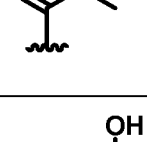
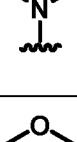
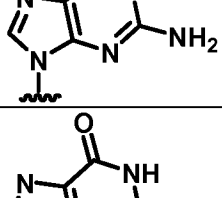
Example#	R ₂	R ₁₄	NR _{8a} R _{8b}	B
641	OH			
642	F			
643	OH			
644	F			
645	OH			
646	F			
647	OH			
648	F			

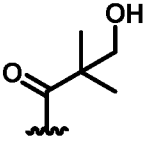
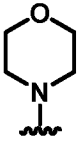
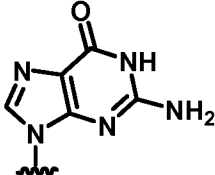
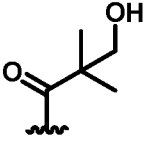
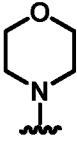
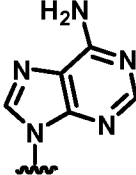
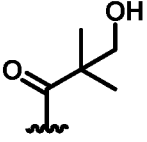
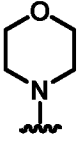
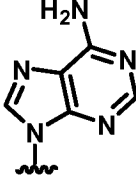
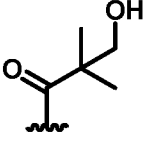
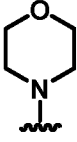
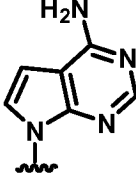
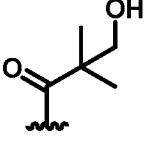
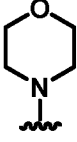
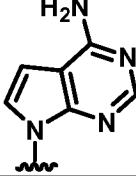
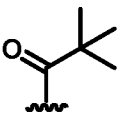
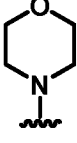
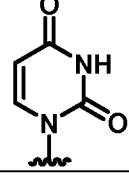
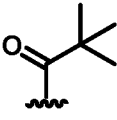
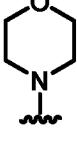
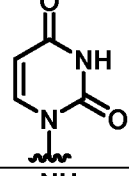
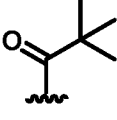
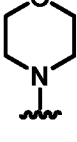
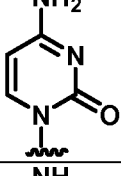
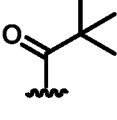
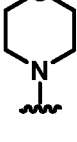
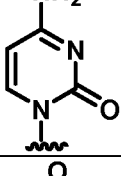
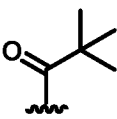
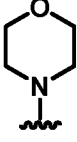
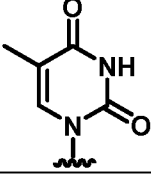
649	OH			
650	F			
651	OH			
652	F			
653	OH			
654	F			
655	OH			
656	F			
657	OH			

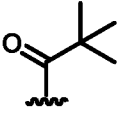
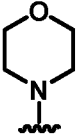
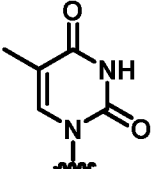
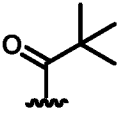
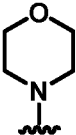
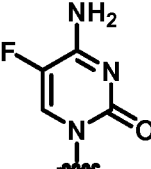
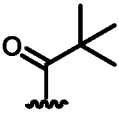
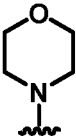
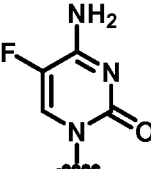
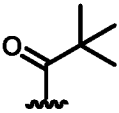
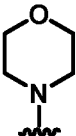
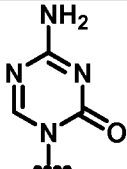
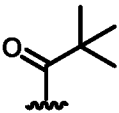
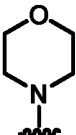
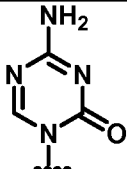
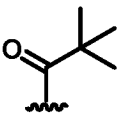
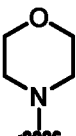
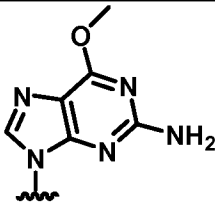
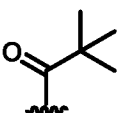
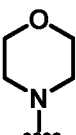
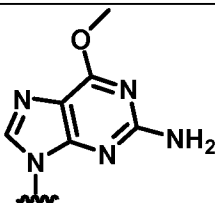
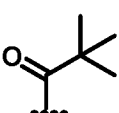
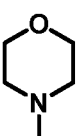
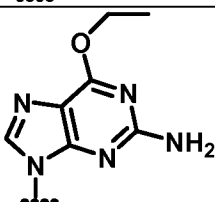
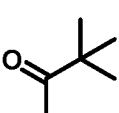
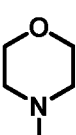
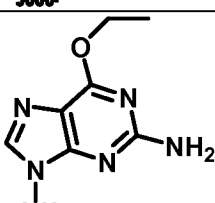
658	F			
659	OH			
660	F			
661	OH			
662	F			
663	OH			
664	F			
665	OH			
666	F			
667	OH			

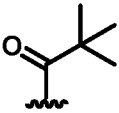
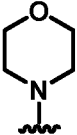
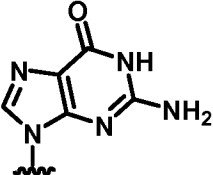
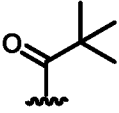
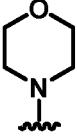
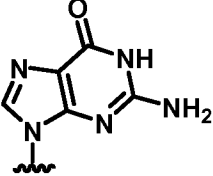
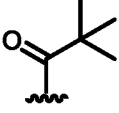
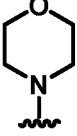
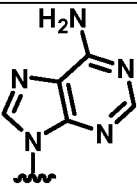
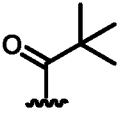
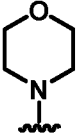
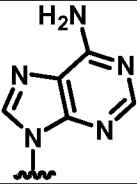
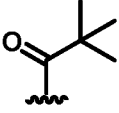
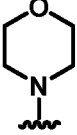
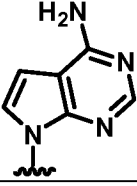
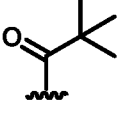
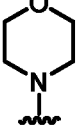
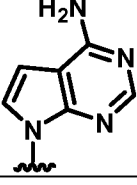
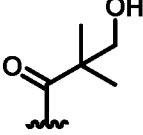
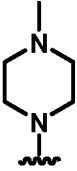
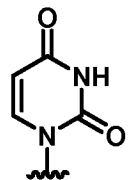
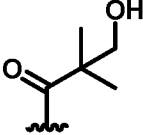
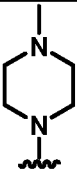
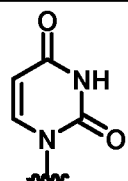
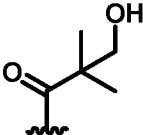
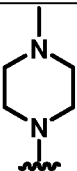
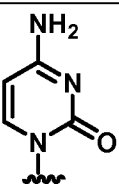
668	F			
669	OH			
670	F			
671	OH			
672	F			
673	OH			
674	F			
675	OH			
676	F			

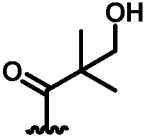
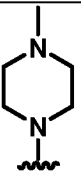
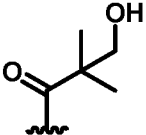
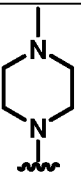
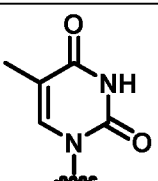
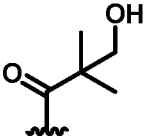
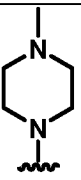
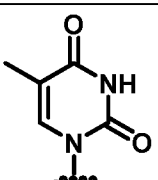
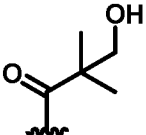
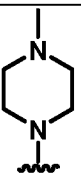
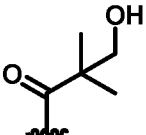
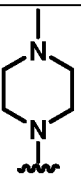
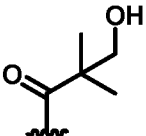
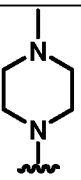
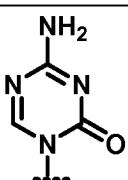
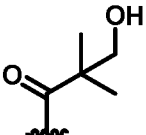
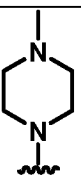
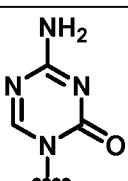
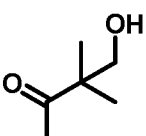
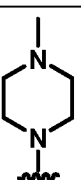
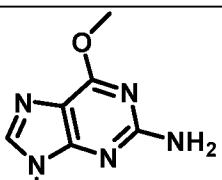
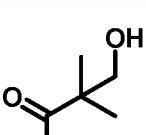
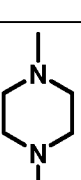
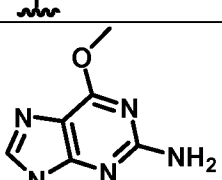
677	OH			
678	F			
679	OH			
680	F			
681	OH			
682	F			
683	OH			
684	F			
685	OH			
686	F			

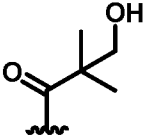
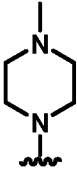
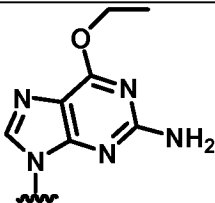
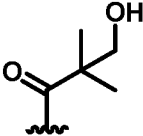
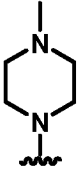
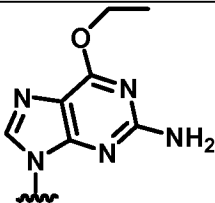
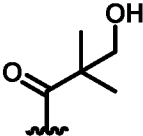
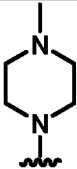
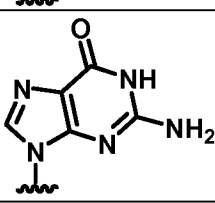
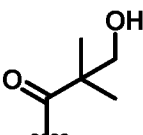
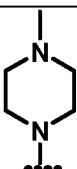
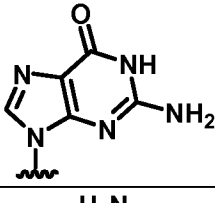
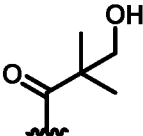
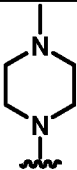
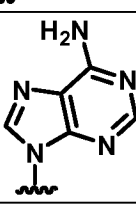
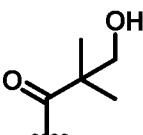
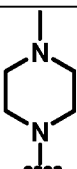
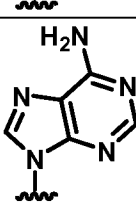
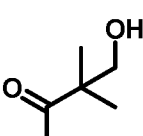
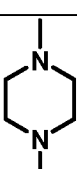
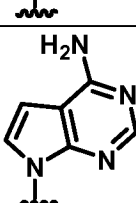
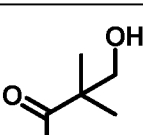
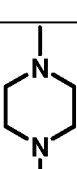
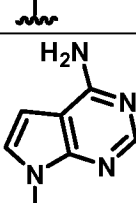
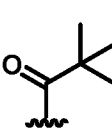
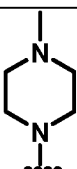
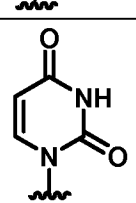
687	OH			
688	F			
689	OH			
690	F			
691	OH			
692	F			
693	OH			
694	F			
695	OH			

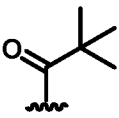
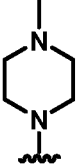
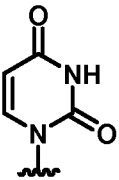
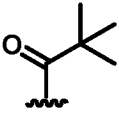
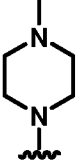
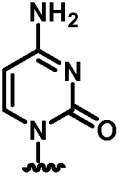
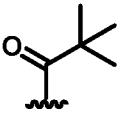
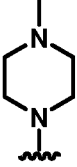
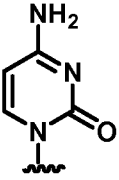
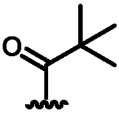
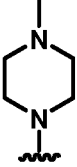
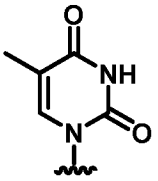
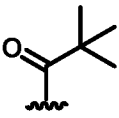
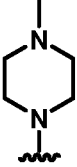
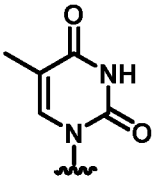
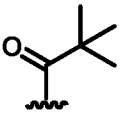
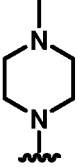
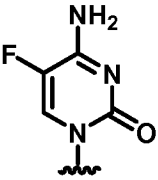
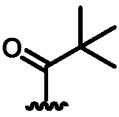
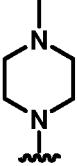
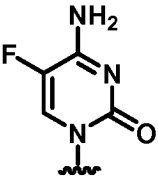
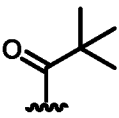
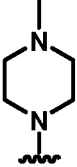
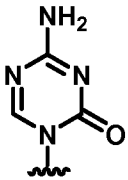
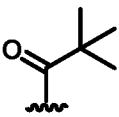
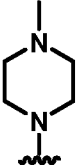
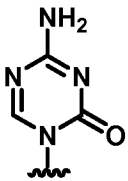
696	F			
697	OH			
698	F			
699	OH			
700	F			
701	OH			
702	F			
703	OH			
704	F			
705	OH			

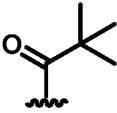
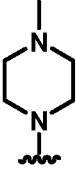
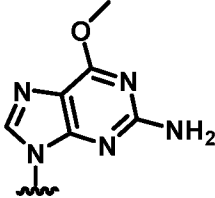
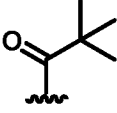
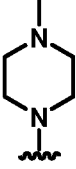
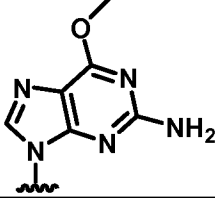
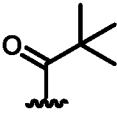
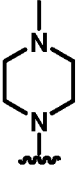
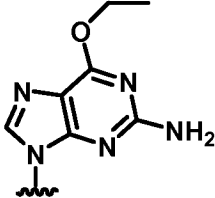
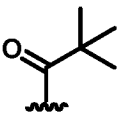
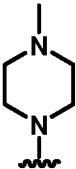
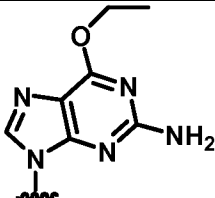
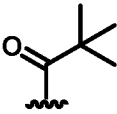
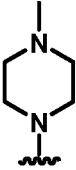
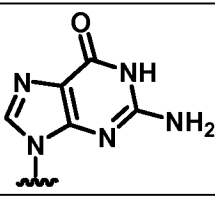
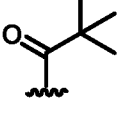
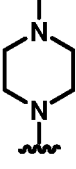
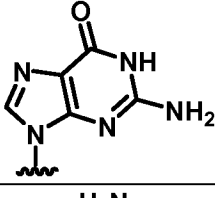
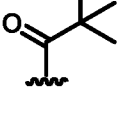
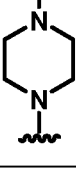
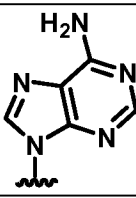
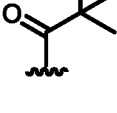
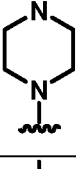
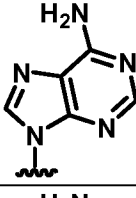
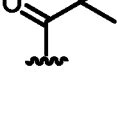
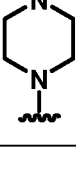
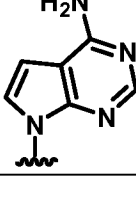
706	F			
707	OH			
708	F			
709	OH			
710	F			
711	OH			
712	F			
713	OH			
714	F			

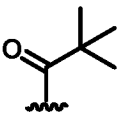
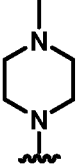
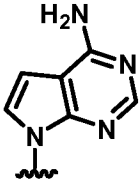
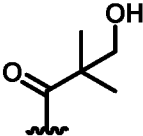
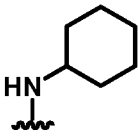
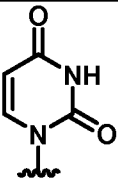
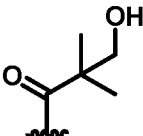
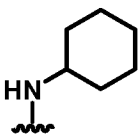
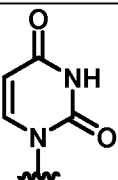
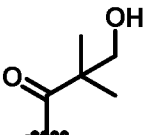
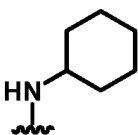
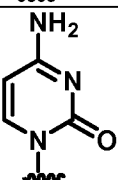
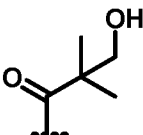
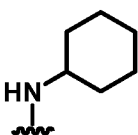
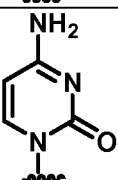
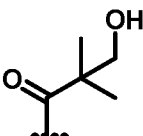
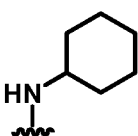
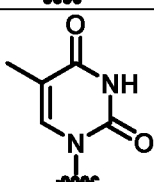
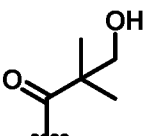
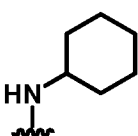
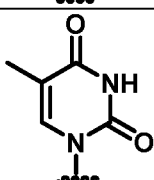
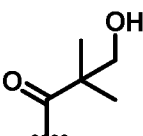
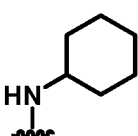
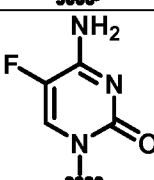
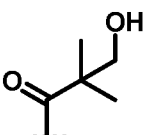
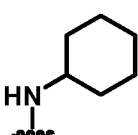
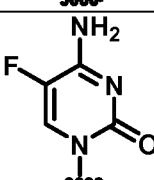
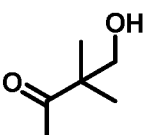
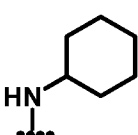
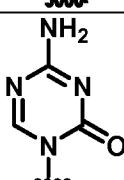
715	OH			
716	F			
717	OH			
718	F			
719	OH			
720	F			
721	OH			
722	F			
723	OH			

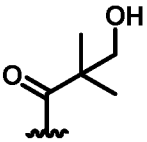
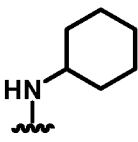
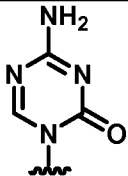
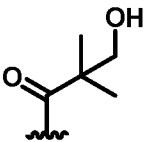
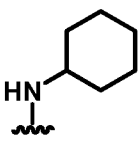
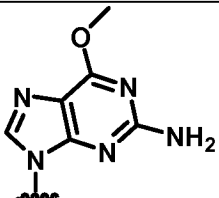
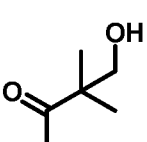
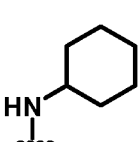
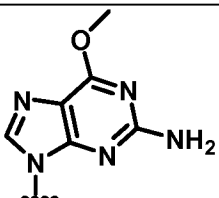
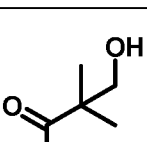
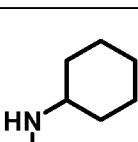
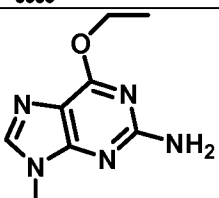
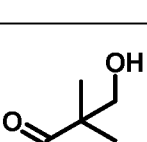
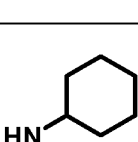
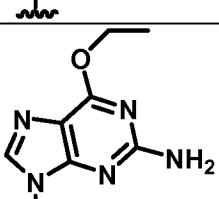
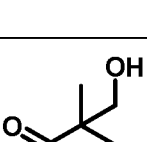
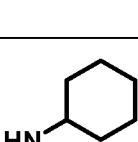
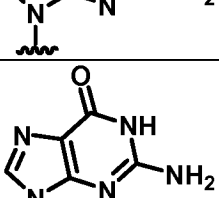
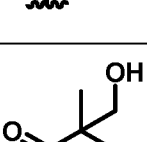
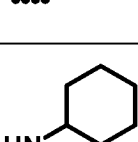
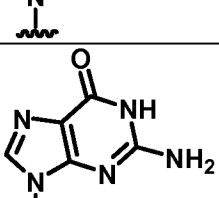
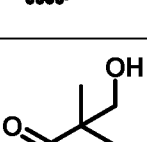
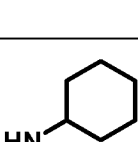
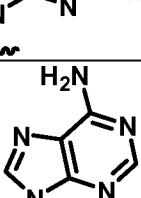
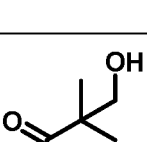
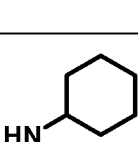
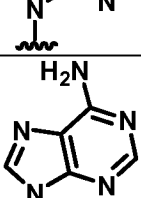
724	F			
725	OH			
726	F			
727	OH			
728	F			
729	OH			
730	F			
731	OH			
732	F			

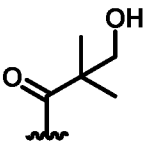
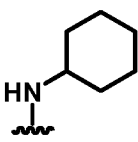
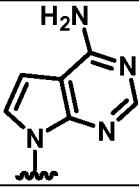
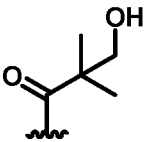
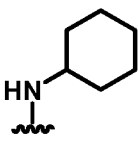
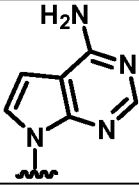
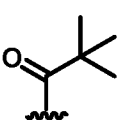
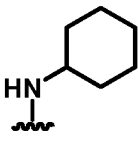
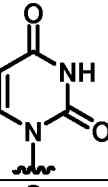
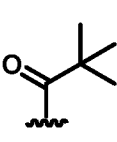
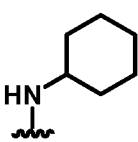
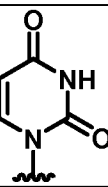
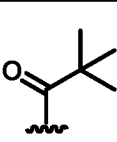
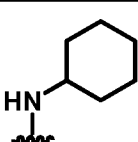
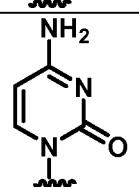
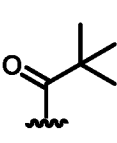
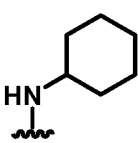
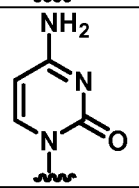
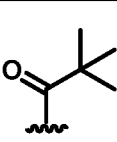
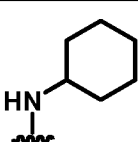
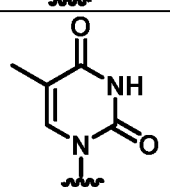
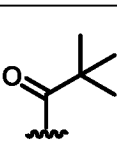
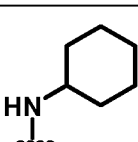
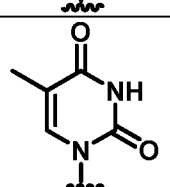
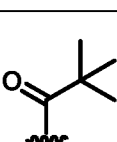
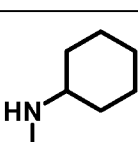
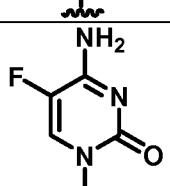
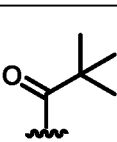
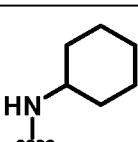
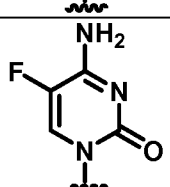
733	OH			
734	F			
735	OH			
736	F			
737	OH			
738	F			
739	OH			
740	F			
741	OH			

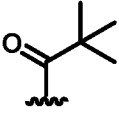
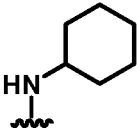
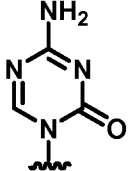
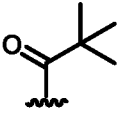
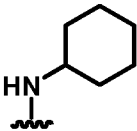
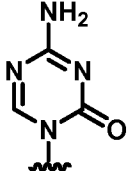
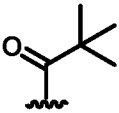
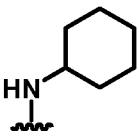
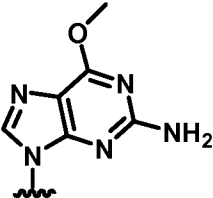
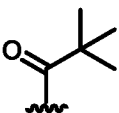
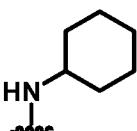
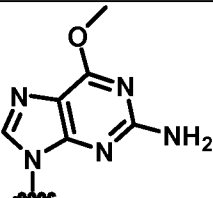
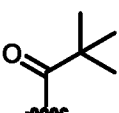
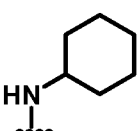
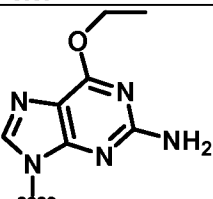
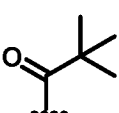
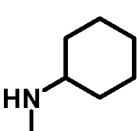
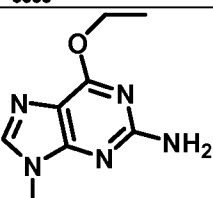
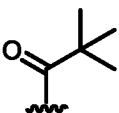
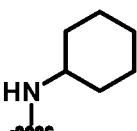
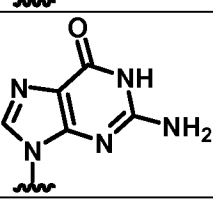
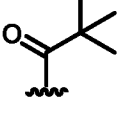
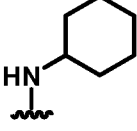
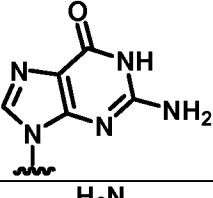
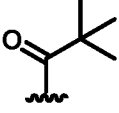
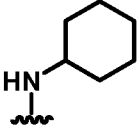
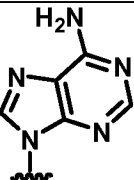
742	F			
743	OH			
744	F			
745	OH			
746	F			
747	OH			
748	F			
749	OH			
750	F			

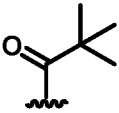
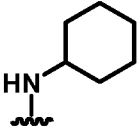
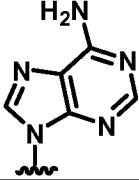
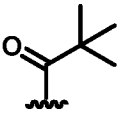
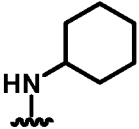
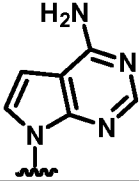
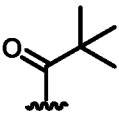
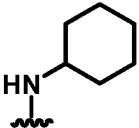
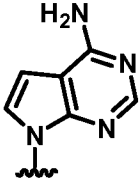
751	OH			
752	F			
753	OH			
754	F			
755	OH			
756	F			
757	OH			
758	F			
759	OH			

760	F			
761	OH			
762	F			
763	OH			
764	F			
765	OH			
766	F			
767	OH			
768	F			
769	OH			

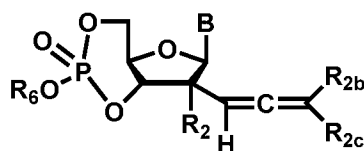
770	F			
771	OH			
772	F			
773	OH			
774	F			
775	OH			
776	F			
777	OH			
778	F			

779	OH			
780	F			
781	OH			
782	F			
783	OH			
784	F			
785	OH			
786	F			
787	OH			
788	F			

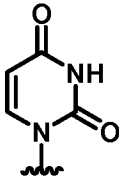
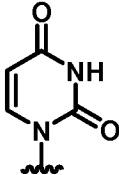
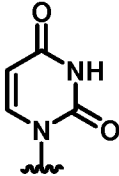
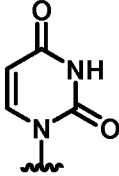
789	OH			
790	F			
791	OH			
792	F			
793	OH			
794	F			
795	OH			
796	F			
797	OH			

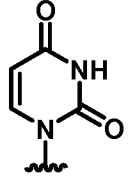
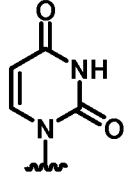
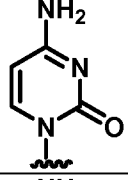
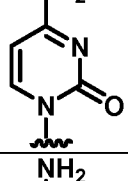
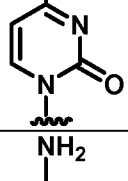
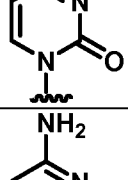
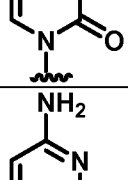
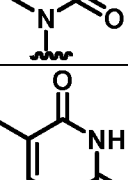
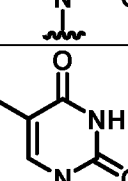
798	F			
799	OH			
800	F			

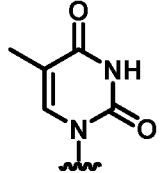
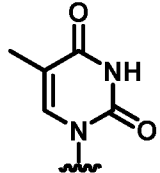
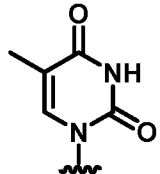
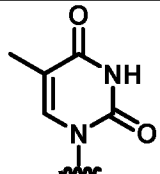
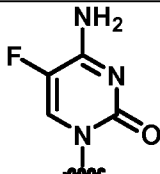
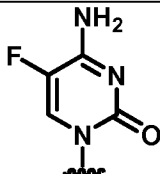
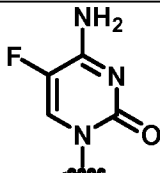
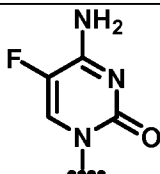
Compounds in Table 5 were illustrated according to Formula (VII-1) wherein R_2 , R_{2b} , R_{2c} , R_6 , and B are delineated for each example in Table 5

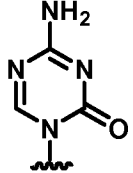
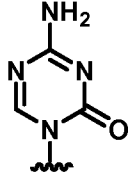
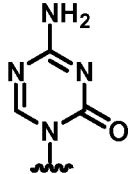
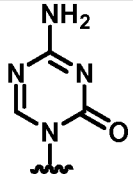
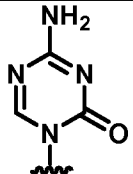
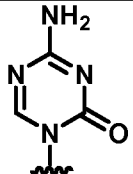
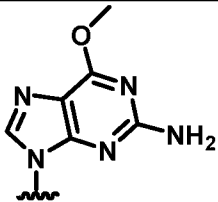
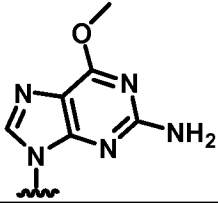
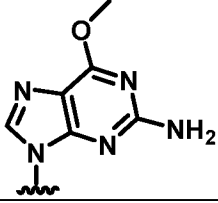


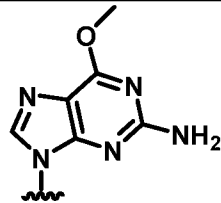
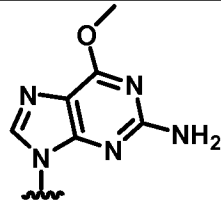
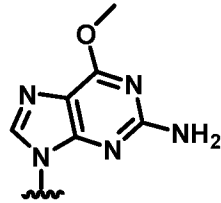
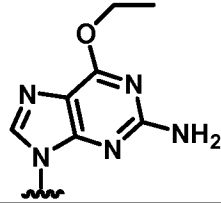
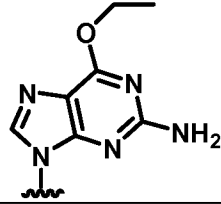
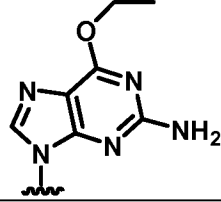
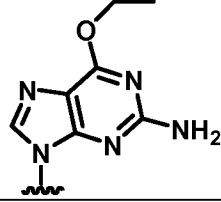
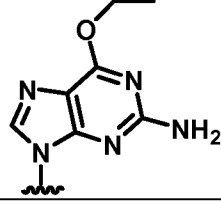
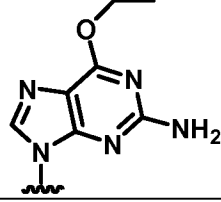
(VII-1)

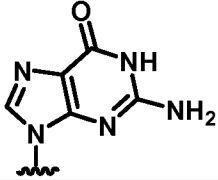
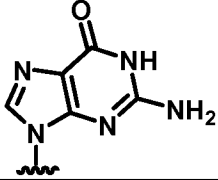
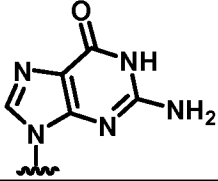
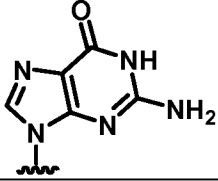
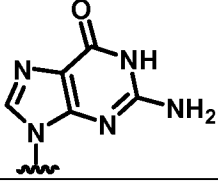
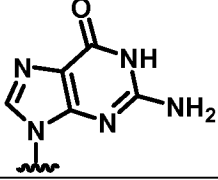
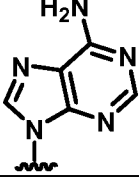
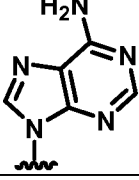
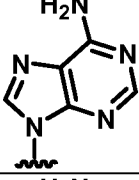
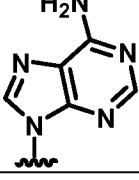
Example#	R_6	R_{2b}	R_{2c}	R_2	B
801	i-Pr	H	H	OH	
802	i-Pr	H	H	F	
803	i-Pr	Me	Me	OH	
804	i-Pr	Me	Me	F	

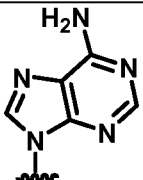
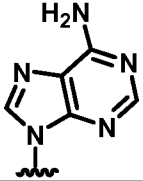
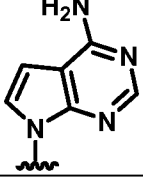
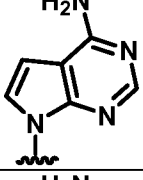
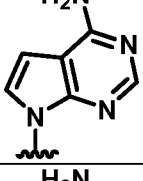
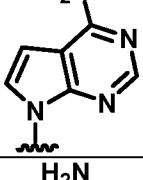
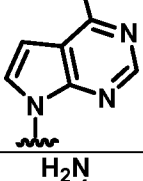
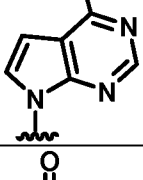
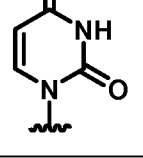
805	i-Pr	F	F	OH	
806	i-Pr	F	F	F	
807	i-Pr	H	H	OH	
808	i-Pr	H	H	F	
809	i-Pr	Me	Me	OH	
810	i-Pr	Me	Me	F	
811	i-Pr	F	F	OH	
812	i-Pr	F	F	F	
813	i-Pr	H	H	OH	
814	i-Pr	H	H	F	

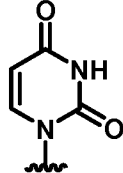
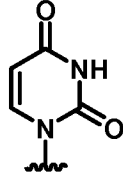
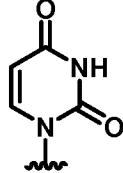
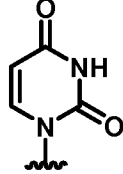
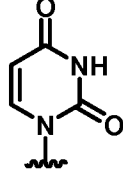
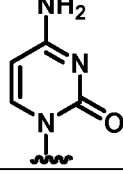
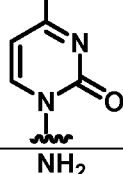
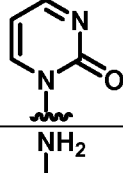
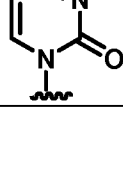
815	i-Pr	Me	Me	OH	
816	i-Pr	Me	Me	F	
817	i-Pr	F	F	OH	
818	i-Pr	F	F	F	
819	i-Pr	H	H	OH	
820	i-Pr	H	H	F	
821	i-Pr	Me	Me	OH	
822	i-Pr	Me	Me	F	
823	i-Pr	F	F	OH	
824	i-Pr	F	F	F	

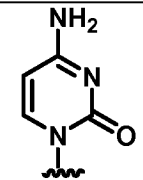
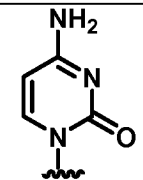
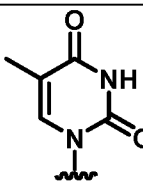
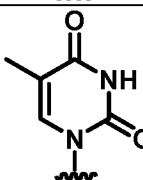
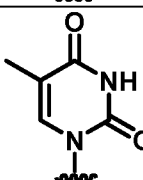
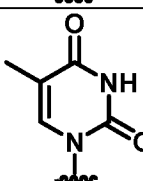
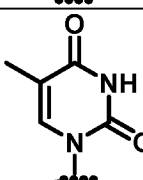
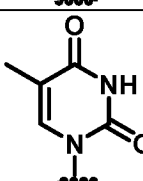
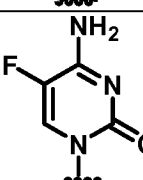
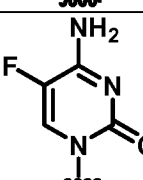
825	i-Pr	H	H	OH	
826	i-Pr	H	H	F	
827	i-Pr	Me	Me	OH	
828	i-Pr	Me	Me	F	
829	i-Pr	F	F	OH	
830	i-Pr	F	F	F	
831	i-Pr	H	H	OH	
832	i-Pr	H	H	F	
833	i-Pr	Me	Me	OH	

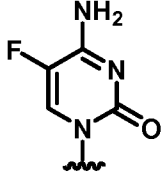
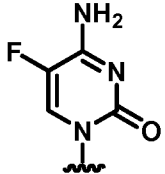
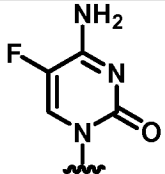
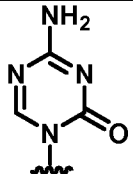
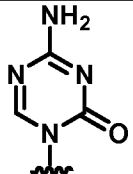
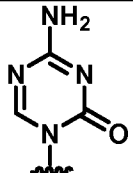
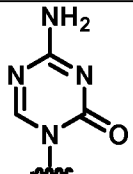
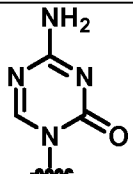
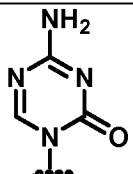
834	i-Pr	Me	Me	F	
835	i-Pr	F	F	OH	
836	i-Pr	F	F	F	
837	i-Pr	H	H	OH	
838	i-Pr	H	H	F	
839	i-Pr	Me	Me	OH	
840	i-Pr	Me	Me	F	
841	i-Pr	F	F	OH	
842	i-Pr	F	F	F	

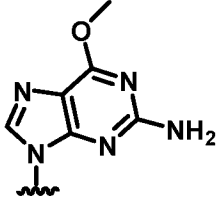
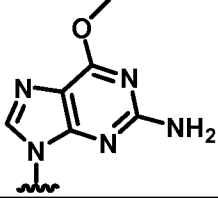
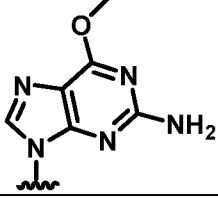
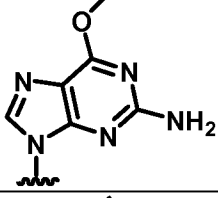
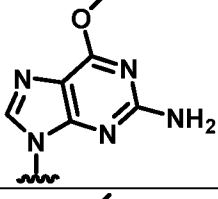
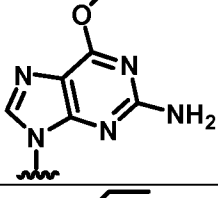
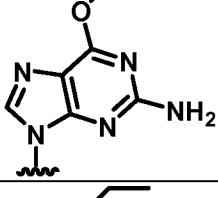
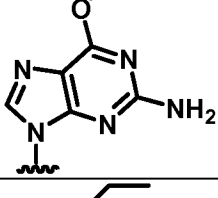
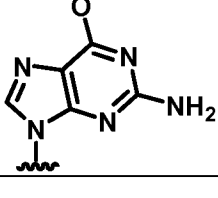
843	i-Pr	H	H	OH	
844	i-Pr	H	H	F	
845	i-Pr	Me	Me	OH	
846	i-Pr	Me	Me	F	
847	i-Pr	F	F	OH	
848	i-Pr	F	F	F	
849	i-Pr	H	H	OH	
850	i-Pr	H	H	F	
851	i-Pr	Me	Me	OH	
852	i-Pr	Me	Me	F	

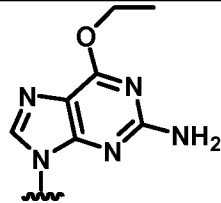
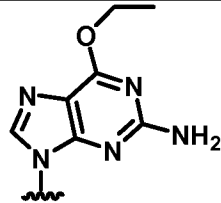
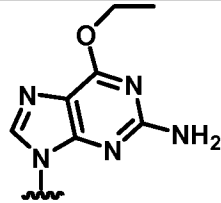
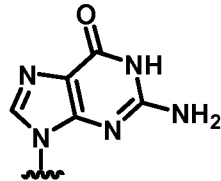
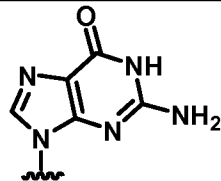
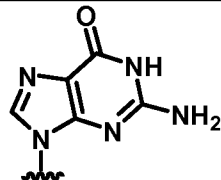
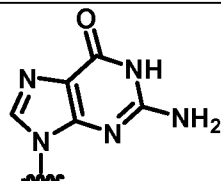
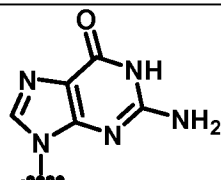
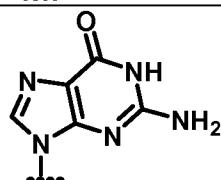
853	i-Pr	F	F	OH	
854	i-Pr	F	F	F	
855	i-Pr	H	H	OH	
856	i-Pr	H	H	F	
857	i-Pr	Me	Me	OH	
858	i-Pr	Me	Me	F	
859	i-Pr	F	F	OH	
860	i-Pr	F	F	F	
861	Et	H	H	OH	

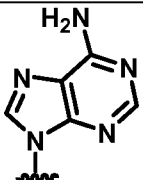
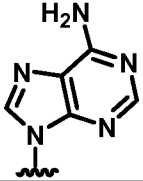
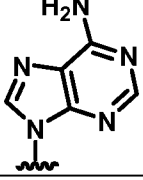
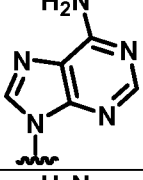
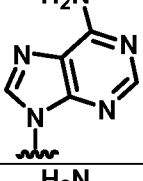
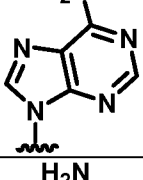
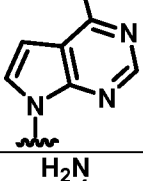
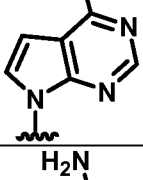
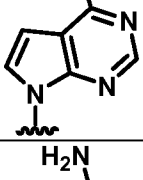
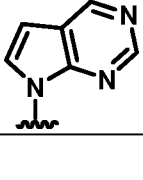
862	Et	H	H	F	
863	Et	Me	Me	OH	
864	Et	Me	Me	F	
865	Et	F	F	OH	
866	Et	F	F	F	
867	Et	H	H	OH	
868	Et	H	H	F	
869	Et	Me	Me	OH	
870	Et	Me	Me	F	

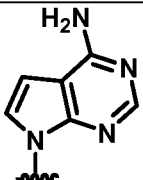
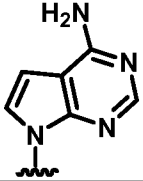
871	Et	F	F	OH	
872	Et	F	F	F	
873	Et	H	H	OH	
874	Et	H	H	F	
875	Et	Me	Me	OH	
876	Et	Me	Me	F	
877	Et	F	F	OH	
878	Et	F	F	F	
879	Et	H	H	OH	
880	Et	H	H	F	

881	Et	Me	Me	OH	
882	Et	Me	Me	F	
883	Et	F	F	OH	
884	Et	F	F	F	
885	Et	H	H	OH	
886	Et	H	H	F	
887	Et	Me	Me	OH	
888	Et	Me	Me	F	
889	Et	F	F	OH	
890	Et	F	F	F	

891	Et	H	H	OH	
892	Et	H	H	F	
893	Et	Me	Me	OH	
894	Et	Me	Me	F	
895	Et	F	F	OH	
896	Et	F	F	F	
897	Et	H	H	OH	
898	Et	H	H	F	
899	Et	Me	Me	OH	

900	Et	Me	Me	F	
901	Et	F	F	OH	
902	Et	F	F	F	
903	Et	H	H	OH	
904	Et	H	H	F	
905	Et	Me	Me	OH	
906	Et	Me	Me	F	
907	Et	F	F	OH	
908	Et	F	F	F	

909	Et	H	H	OH	
910	Et	H	H	F	
911	Et	Me	Me	OH	
912	Et	Me	Me	F	
913	Et	F	F	OH	
914	Et	F	F	F	
915	Et	H	H	OH	
916	Et	H	H	F	
917	Et	Me	Me	OH	
918	Et	Me	Me	F	

919	Et	F	F	OH	
920	Et	F	F	F	

9. A pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.
10. A method of treating a viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 9.
11. The method according to claim 10, wherein the viral infection is hepatitis C virus.
12. A method of inhibiting the replication of hepatitis C virus, the method comprising supplying a hepatitis C viral NS3 protease inhibitory amount of the pharmaceutical composition of claim 9.
13. The method of claim 10 further comprising administering concurrently an additional anti-hepatitis C virus agent.
14. The method of claim 11, wherein said additional anti-hepatitis C virus agent is selected from the group consisting of α -interferon, β -interferon, ribavarin, and adamantine.
15. The method of claim 12, wherein said additional anti-hepatitis C virus agent is an inhibitor of hepatitis C virus helicase, polymerase, metalloprotease, or IRES.

16. The pharmaceutical composition of claim 9, further comprising another anti-HCV agent.

17. The pharmaceutical composition of claim 9, further comprising an agent
5 selected from interferon, ribavirin, amantadine, another HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site inhibitor.

18. The pharmaceutical composition of claim 9, further comprising pegylated
10 interferon.

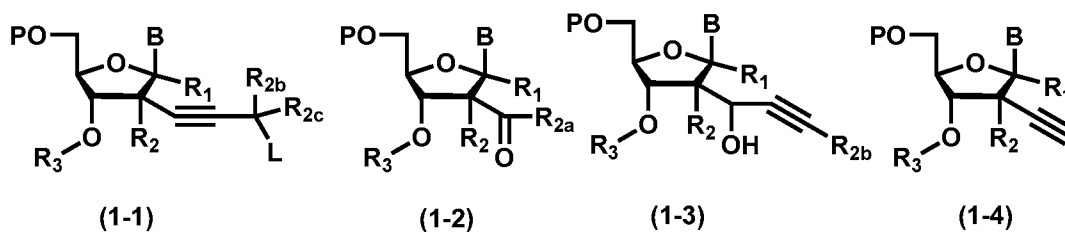
19. The pharmaceutical composition of claim 9, further comprising another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator.

20. The composition of claim 9, further comprising a cytochrome P450
15 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof.

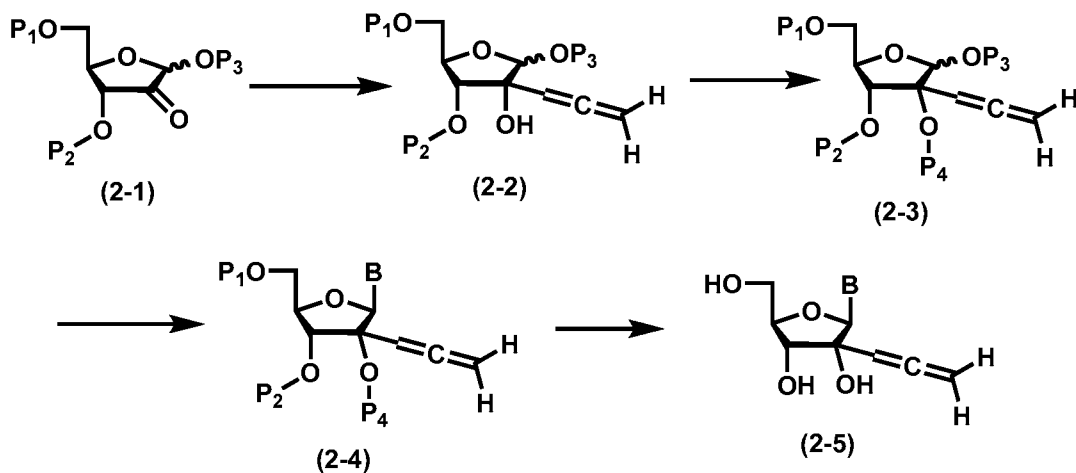
21. The composition of claim 20, wherein the cytochrome P450 monooxygenase
inhibitor is ritonavir.

22. A method of co-administering to a patient in need of anti-hepatitis C viral
20 treatment comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof and a compound as set forth in claim 1 or a pharmaceutically acceptable salt thereof.

23. A process to afford the 2'-allenic moiety comprising the steps of treating a
nucleoside derivative with a 2'-substituent containing an alkyne represented by
formulae (1-1), (1-3) and (1-4) or carbonyl moiety represented by formulae (1-2),
wherein, R₁, R₂, R_{2a}, R_{2b}, R_{2c}, R₃, and B are as previously defined; P is a hydroxy
25 protecting group; and L is a leaving group such as halide, OAc, OMe, OTMS, OTHP,
30 the like



24. A process to afford the 2'-allenic moiety comprising the steps of treating a ketone compound represented by formulae (2-1) with propargyl bromide in the presence of metal halide to introduce 2'-allenyl group, followed by protection, glycosylation of the appropriate nucleobase and global deprotection



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/29381

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/04; A61K 31/70 (2012.01)

USPC - : 514/25; 514/49-50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/25

IPC: A01N 43/04; A61K 31/70 (2012.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC:514/49-50 (See Search Words below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: PGPB, USPT, USOC, EPAB, JPAB

Google: Scholar/Patents: nucleoside hepatitis hiv hcv allene C=C pyrimidine 2'-allene alkene antiviral synthesis anti-hcv pegylated interferon ritonavir combination ns3 protease polymerase synthesis propargyl bromide glycosylation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 20100074889 A1 (QUI et al) 25 March 2010 (25.03.2010) para [0035]-[0051];[0063];[0071];[0076];[0079]-[0082];[0087];[0089];[0091];[0103];[0193];[0197];[0201];[0202]; [0208]; [0209];Scheme 1 and 2;pg 22, Table	1-24
Y	US 7,589,077 B2 (KUMAR et al) 15 September 2009 (15.09.2009) Col 9, In 1-41 ; Col 10, In 18-21	1-23
Y	LI et al. Synthesis of 2-C-Branched Nucleosides, Organic Preparations and Procedures International, 2010, 42:191-283. pg 216, Scheme 25; pg 213, Scheme 29	24

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 June 2012 (12.06.2012)

Date of mailing of the international search report

28 JUN 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774