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(54) Title: UNUSUAL NUCLEOSIDE LIBRARIES, COMPOUNDS, AND PREFERRED USES AS ANTIVIRAL AND ANTI-CANCER AGENTS

(57) Abstract: Nucleoside analog libraries are prepared in a combinatorial library approach. Particularly preferred compounds and libraries include nucleoside analogs in which the heterocyclic base is coupled to the sugar via a non-carbon atom, nucleoside analogs with a tricyclic heterocyclic base that includes benzimidazole, and nucleoside analogs in which a C2'-substituent is covalently bound to the sugar via a carbon atom. Contemplated nucleosides may be useful in treatment of various conditions, and particularly viral infections and neoplastic diseases.



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UNUSUAL NUCLEOSIDE LIBRARIES, COMPOUNDS AND PREFERRED USES AS ANTIVIRAL AND ANTICANCER AGENTS

5 Priority

This application claims priority to US 60/342,407 filed December 17,2001.

Field of The Invention

The field of the invention is combinatorial nucleoside libraries and related compounds.

10 Background of The Invention

Nucleosides and related compounds interact with many biological targets, and some nucleoside analogues have been used as antimetabolites for treatment of cancers and viral infections. After entry into the cell, many nucleoside analogues can be phosphorylated to monophosphates by nucleoside kinases, and then further phosphorylated by nucleoside
15 monophosphate kinases and nucleoside diphosphate kinases to give nucleoside triphosphates. Once a nucleoside analogue is converted to its triphosphate inside the cell, it can be incorporated into DNA or RNA. Incorporation of certain unnatural nucleoside analogues into nucleic acid replicates or transcripts can interrupt gene expression by early chain termination, or by interfering with function of the modified nucleic acids. In addition, certain nucleoside analogue
20 triphosphates are very potent, competitive inhibitors of DNA or RNA polymerases, which can significantly reduce the rate at which the natural nucleoside can be incorporated. Many anti-HIV nucleoside analogues fall into this category, including 3'-C-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, and 2',3'-dideoxythymidine.

Various nucleoside analogues can also act in other ways, for example, causing apoptosis
25 of cancer cells and/or modulating immune systems. In addition to nucleoside antimetabolites, a number of nucleoside analogues that show very potent anticancer and antiviral activities act through still other mechanisms. Some well-known nucleoside anticancer drugs are thymidylate synthase inhibitors such as 5-fluorouridine, and adenosine deaminase inhibitors such as 2-chloroadenosine. A well-studied anticancer compound, neplanocin A, is an inhibitor of S-adenosylhomocysteine hydrolase, which shows potent anticancer and antiviral activities.
30

Many of these nucleoside analogues that can inhibit tumor growth or viral infections are also toxic to normal mammalian cells, primarily because these nucleoside analogues lack

adequate selectivity between the normal cells and the virus-infected host cells or cancer cells. For this reason many otherwise promising nucleoside analogues fail to become therapeutics in the treatment of various diseases.

Selective inhibition of cancer cells or host cells infected by viruses has been an important subject for some time, and tremendous efforts have been made to search for more selective nucleoside analogues. In general, however, a large pool of nucleoside analogues is thought to be necessary in order to identify highly selective nucleoside analogues. Unfortunately, the classical method of synthesizing nucleosides and nucleotides having desired physiochemical properties, and then screening them individually, takes a significant amount of time to identify a lead molecule. Although thousands of nucleoside analogues were synthesized over the past decades, if both sugar and base modifications are considered, many additional analogues are still waiting to be synthesized.

During the last few years, combinatorial chemistry has been used to generate huge numbers of organic compounds, resulting in large compound libraries. If nucleosides could be made through a combinatorial chemistry approach, a large number of nucleoside analogues could be synthesized within months instead of decades, and large nucleoside libraries could be developed.

A combinatorial chemistry approach to nucleosides may also encourage a focus beyond previously addressed biological targets. For example, in the past nucleoside analogues were usually designed as potential inhibitors of DNA or RNA polymerases and several other enzymes and receptors, including inosine monophosphate dehydrogenase, protein kinases, and adenosine receptors. If a vast number of diversified nucleoside analogues could be created, their use may be far beyond these previously recognized biological targets, which would open a new era for the use of nucleoside analogues as human therapeutics.

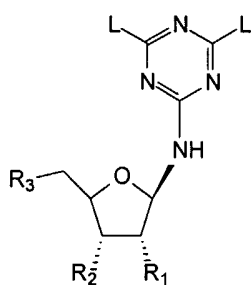
The generation of combinatorial libraries of chemical compounds by employing solid phase synthesis is well known in the art. For example, Geysen, et al. (*Proc. Natl. Acac. Sci. USA*, 3998 (1984)) describes the construction of a multi-amino acid peptide library; Houghton, et al. (*Nature*, 354, 84 (1991)) describes the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery; and Lam, et al. (*Nature*, 354, 82 (1991)) describes a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin.

Although a combinatorial chemistry approach has proven to work well with many types of compounds, there are certain hurdles to the generation of nucleoside libraries. Among numerous other difficulties, most nucleoside analogues contain a sugar moiety and a nucleoside base, which are linked together through a glycosidic bond. The formation of the glycosidic bond can be achieved through a few types of condensation reactions. However, most of the reactions do not give a very good yield of desired products, which may not be suitable to generations of nucleoside libraries. Moreover, the glycosidic bonds in many nucleosides are labile to acidic condition, and many useful reactions in combinatorial chemistry approaches cannot be used in the generation of nucleoside analogue libraries. As a result, many researchers focused their attention to areas in pharmaceutical chemistry that appear to present easier access to potential therapeutic molecules, and there seems to be a lack of methods for generating libraries of nucleosides and nucleotides using solid phase synthesis. Therefore, there is still a need to provide methods for generation of nucleoside and nucleotide libraries.

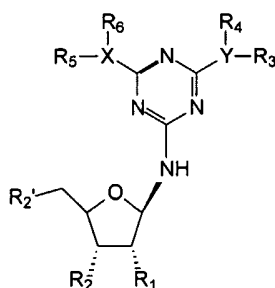
Summary of the Invention

The present invention is directed to nucleoside analog libraries and compounds represented in and derived from these libraries. In one aspect of the inventive subject matter, contemplated nucleoside libraries and compounds include nucleosides in which the heterocyclic base is coupled to a sugar portion via an intermediary atom other than carbon, and in some cases such nucleosides may further comprise at least one electrophilic center and at least one leaving group. Contemplated sugars include ribofuranose, substituted ribofuranose, carbocyclic ring systems, and arabinose (all in D-configuration or L-configuration), while contemplated heterocyclic bases include five-membered rings, six-membered rings, and fused aromatic systems that comprise nitrogen, sulfur, oxygen, or phosphorus.

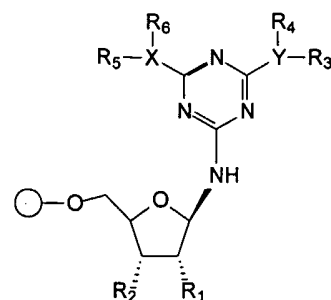
Therefore, contemplated compounds and libraries will have a structure according to Formulae 1, 2, 2A-2I, and 3, wherein the substituents are as described in the respective portions of the detailed description below (Library compounds will have H, OH, a phosphate, or other functional group instead of the solid phase).



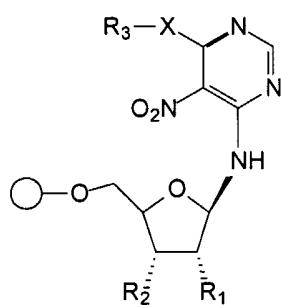
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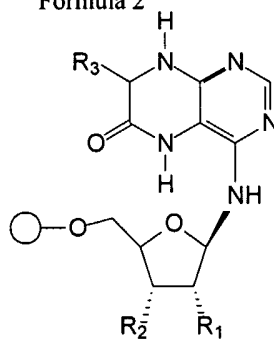
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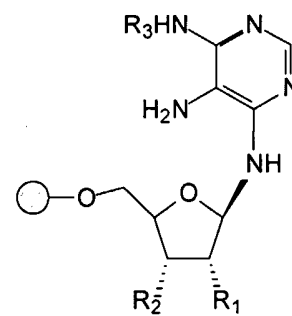
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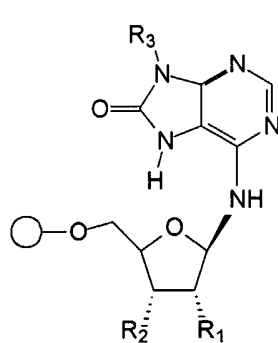
Formula 2A



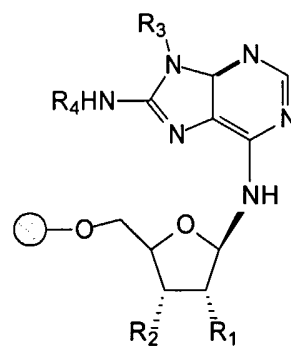
Formula 2C



Formula 2E

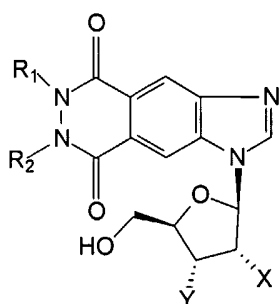


Formula 2G

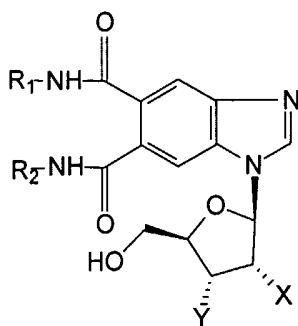


Formula 2I

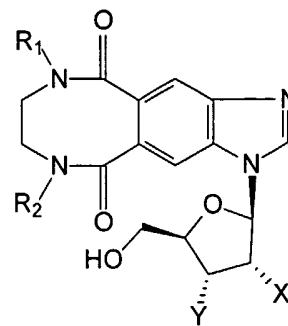
In another aspect of the inventive subject matter, contemplated libraries and compounds include nucleosides in which the heterocyclic base comprises a tricyclic heterocyclic base that includes a benzimidazole portion. Particularly contemplated sugars include ribofuranose, substituted ribofuranose, carbocyclic ring systems, and arabinose (in D-configuration or L-configuration), and especially contemplated compounds and libraries will have a structure according to Formulae 4B-H, Formulae 5A-B, Formulae 6A-F wherein the substituents are as described in the respective portions of the detailed description below (Libraries will include a solid phase, typically coupled to the C5'-atom).



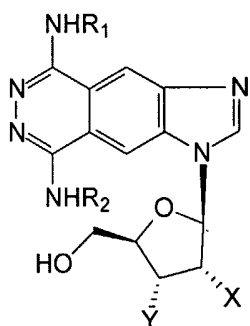
Formula 4B



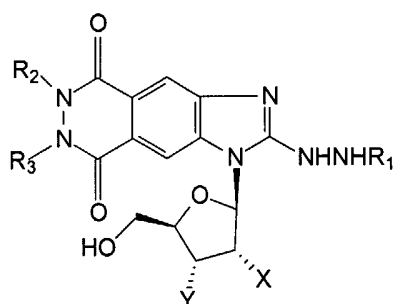
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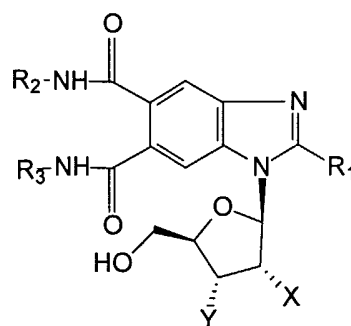
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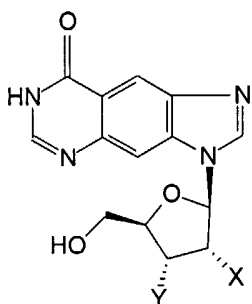
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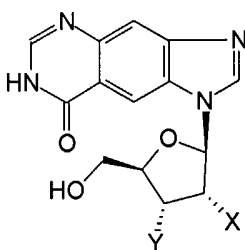
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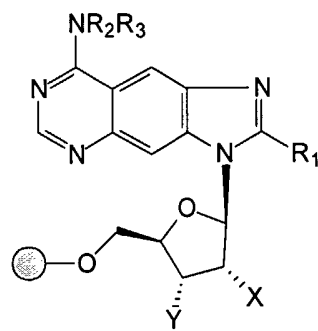
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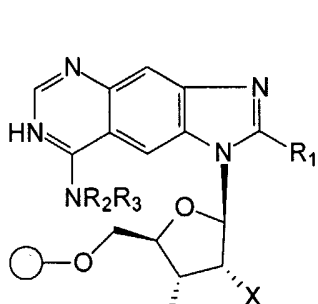
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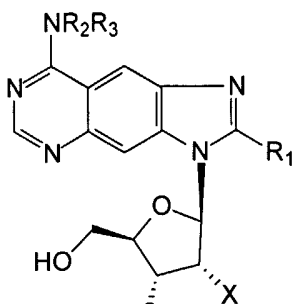
Formula 6B



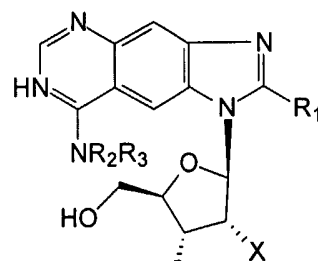
Formula 6C



Formula 6D



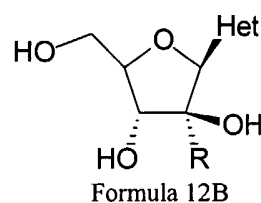
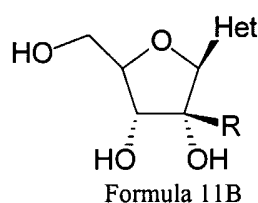
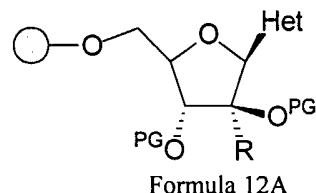
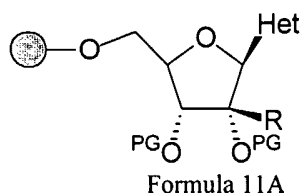
Formula 6E



Formula 6F

In a still further aspect of the inventive subject matter, contemplated libraries and compounds include nucleosides in which a C₂'-substituent is covalently bound to the sugar via a

carbon atom, and contemplated libraries and compounds will have a structure according to Formulae 11A-11B and 12A-12B, wherein the substituents are as described in the respective portions of the detailed description below.



Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

Detailed Description

The term "nucleoside library" as used herein refers to a plurality of chemically distinct nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs wherein at least some of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs include, or have been synthesized from a common precursor.

For example, a plurality of nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs that were prepared using 1'-azido or 1'-amino ribofuranose as a building block/precursor is considered a nucleoside library under the scope of this definition. Therefore, the term "common precursor" may encompass a starting material in a first step in a synthesis as well as a synthesis intermediate (*i.e.*, a compound derived from a starting material). In another example, at least one step in the synthesis of one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs is concurrent with at least one step in the synthesis of another one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and synthesis is preferably at least partially automated. In contrast, a collection of individually synthesized nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and especially a collection of compounds not obtained from a nucleoside library, is not considered a nucleoside library because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs will

not have a common precursor, and because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs are not concurrently produced.

It is further generally contemplated that the complexity of contemplated libraries is at least 20 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, more typically at least 100 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, and most typically at least 1000 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs. Consequently, a typical format of a nucleoside library will include multi-well plates, or a plurality of small volume (*i.e.*, less than 1ml) vessels coupled to each other. The term "library compound" as used herein refers to a nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog within a nucleoside library.

As also used herein, the terms "heterocycle" and "heterocyclic base" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, wherein the ring includes at least one atom other than a carbon atom. Particularly contemplated heterocyclic bases include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocycles may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" or "fused heterocyclic base" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine), and a 6-membered ring fused to another 6-membered or higher ring (*e.g.*, pyrido[4,5-d]pyrimidine, benzodiazepine). Examples of these and further preferred heterocyclic bases are given below. Still further contemplated heterocyclic bases may be aromatic, or may include one or more double or triple bonds. Moreover, contemplated heterocyclic bases and fused heterocycles may further be substituted in one or more positions (see below).

As further used herein, the term "sugar" refers to all carbohydrates and derivatives thereof, wherein particularly contemplated derivatives include deletion, substitution or addition of a chemical group or atom in the sugar. For example, especially contemplated deletions include 2'-deoxy and/or 3'-deoxy sugars. Especially contemplated substitutions include replacement of the ring-oxygen with sulfur or methylene, or replacement of a hydroxyl group with a halogen, an amino-, sulfhydryl-, or methyl group, and especially contemplated additions include methylene phosphonate groups. Further contemplated sugars also include sugar analogs

(*i.e.*, not naturally occurring sugars), and particularly carbocyclic ring systems. The term "carbocyclic ring system" as used herein refers to any molecule in which a plurality of carbon atoms form a ring, and in especially contemplated carbocyclic ring systems the ring is formed from 3, 4, 5, or 6 carbon atoms. Examples of these and further preferred sugars are given below.

5 The term "nucleoside" refers to all compounds in which a heterocyclic base is covalently coupled to a sugar, and an especially preferred coupling of the nucleoside to the sugar includes a C1'-(glycosidic) bond of a carbon atom in a sugar to a carbon- or heteroatom (typically nitrogen) in the heterocyclic base. The term "nucleoside analog" as used herein refers to all nucleosides in which the sugar is not a ribofuranose and/or in which the heterocyclic base is not a naturally
10 occurring base (*e.g.*, A, G, C, T, I, etc.). Similarly, the term "nucleotide" refers to a nucleoside to which a phosphate group is coupled to the sugar. Likewise, the term "nucleotide analog" refers to a nucleoside analog to which a phosphate group is coupled to the sugar.

 It should further be particularly appreciated that the terms nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog also includes all prodrug forms of a nucleoside,
15 nucleotide, nucleoside analog, and/or nucleotide analog, wherein the prodrug form may be activated/converted to the active drug/nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog in one or more than one step, and wherein the activation/conversion of the prodrug into the active drug/nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog may occur intracellularly or extracellularly (in a single step or multiple steps). Especially
20 contemplated prodrug forms include those that confer a particular specificity towards a diseased or infected cell or organ, and exemplary contemplated prodrug forms are described in "Prodrugs" by Kenneth B. Sloan (Marcel Dekker; ISBN: 0824786297), "Design of Prodrugs" by Hans Bundgaard (ASIN: 044480675X), or in copending US application number 09/594410, filed 06/16/2000, all of which are incorporated by reference herein. Particularly suitable prodrug
25 forms of the above compounds may include a moiety that is covalently coupled to at least one of the C2'-OH, C3'-OH, and C5'-OH, wherein the moiety is preferentially cleaved from the compound in a target cell (*e.g.*, Hepatocyte) or a target organ (*e.g.*, liver). While not limiting to the inventive subject matter it is preferred that cleavage of the prodrug into the active form of the drug is mediated (at least in part) by a cellular enzyme, particularly receptor, transporter and
30 cytochrome-associated enzyme systems (*e.g.*, CYP-system).

Especially contemplated prodrugs comprise a cyclic phosphate, cyclic phosphonate and/or a cyclic phosphoamides, which are preferentially cleaved in a hepatocyte to produce the compound according to Formula 1 or 2. There are numerous such prodrugs known in the art, and all of those are considered suitable for use herein. However, especially contemplated prodrug forms are disclosed in WO 01/47935 (Novel Bisamidate Phosphonate Prodrugs), WO 01/18013 (Prodrugs For Liver Specific Drug Delivery), WO 00/52015 (Novel Phosphorus-Containing Prodrugs), and WO 99/45016 (Novel Prodrugs For Phosphorus-Containing Compounds), all of which are incorporated by reference herein. Consequently, especially suitable prodrug forms include those targeting a hepatocyte or the liver.

Still further particularly preferred prodrugs include those described by Renze et al. in Nucleosides Nucleotides Nucleic Acids 2001 Apr-Jul;20(4-7):931-4, by Balzarini et al. in Mol Pharmacol 2000 Nov;58(5):928-35, or in U.S. Pat. No. 6,312,662 to Erion et al., U.S. Pat. No. 6,271,212 to Chu et al., U.S. Pat. No. 6,207,648 to Chen et al., U.S. Pat. No. 6,166,089 and U.S. Pat. No. 6,077,837 to Kozak, U.S. Pat. No. 5,728,684 to Chen, and published U.S. Application with the number 20020052345 to Erion, all of which are incorporated by reference herein. Alternative contemplated prodrugs include those comprising a phosphate and/or phosphonate non-cyclic ester, and an exemplary collection of suitable prodrugs is described in U.S. Pat. No. 6,339,154 to Shepard et al., U.S. Pat. No. 6,352,991 to Zemlicka et al., and U.S. Pat. No. 6,348,587 to Schinazi et al. Still further particularly contemplated prodrug forms are described in FASEB J. 2000 Sep;14(12):1784-92, Pharm. Res. 1999, Aug 16:8 1179-1185, and Antimicrob. Agents Chemother 2000, Mar 44:3 477-483, all of which are incorporated by reference herein.

The terms "alkyl" and "unsubstituted alkyl" are used interchangeably herein and refer to any linear, branched, or cyclic hydrocarbon in which all carbon-carbon bonds are single bonds. The terms "alkenyl" and "unsubstituted alkenyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl with at least one carbon-carbon double bond. Furthermore, the terms "alkynyl" and "unsubstituted alkynyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl or alkenyl with at least one carbon-carbon triple bond. The terms "aryl" and "unsubstituted aryl" are used interchangeably herein and refer to any aromatic cyclic alkenyl or alkynyl. The term "alkaryl" is employed where an aryl is covalently bound to an alkyl, alkenyl, or alkynyl.

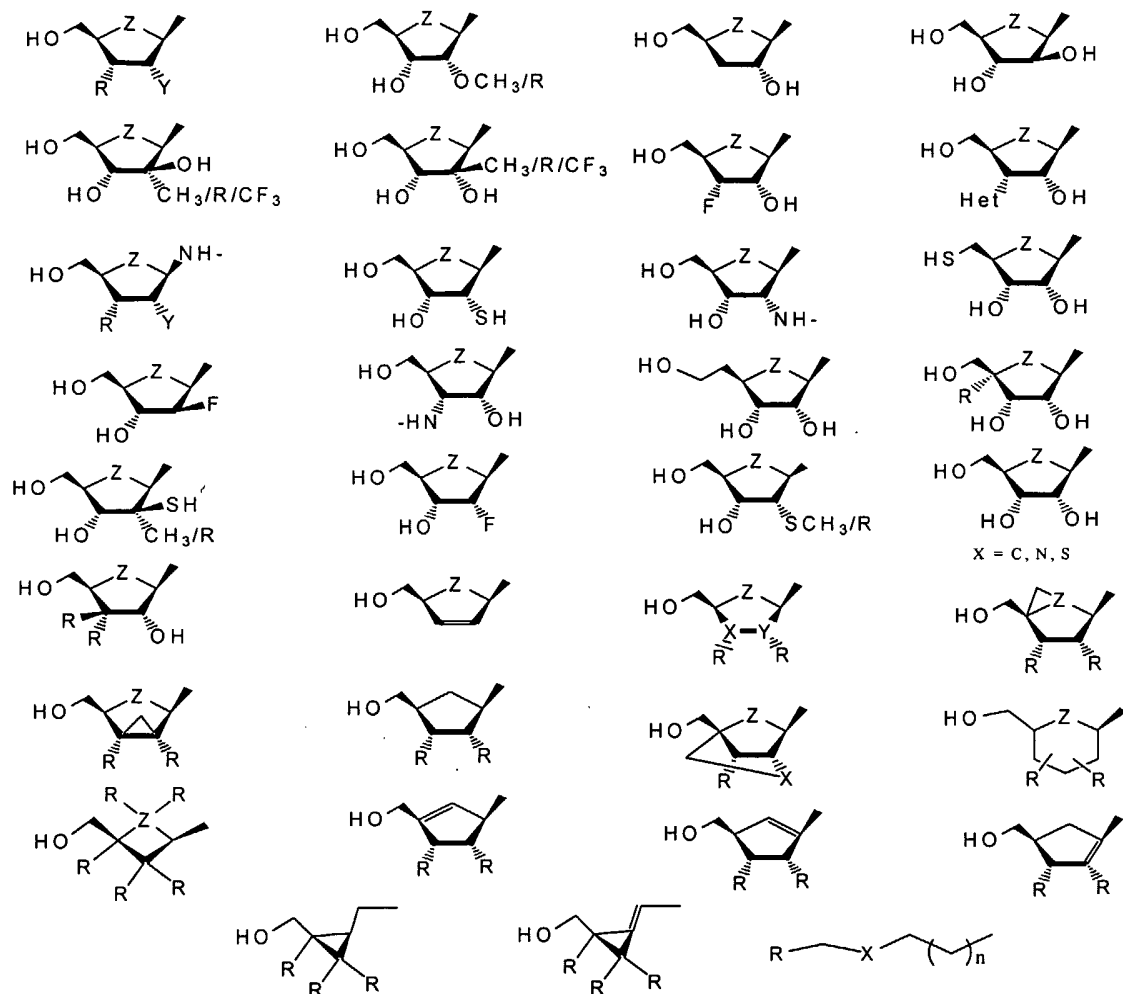
The term "substituted" as used herein refers to a replacement of an atom or chemical group (*e.g.*, H, NH₂, or OH) with a functional group, and particularly contemplated functional groups include nucleophilic groups (*e.g.*, -NH₂, -OH, -SH, -NC, etc.), electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, -NH₃⁺), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof. Thus, the term "functional group" and the term "substituent" are used interchangeably herein and refer to nucleophilic groups (*e.g.*, -NH₂, -OH, -SH, -NC, -CN etc.), electrophilic groups (*e.g.*, C(O)OR, C(X)OH, C(Halogen)OR, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, -NH₃⁺), and halogens.

Contemplated Sugars

It is contemplated that suitable sugars will have a general formula of C_nH_{2n}O_n, wherein n is between 2 and 8, and wherein (where applicable) the sugar is in the D- or L-configuration. Moreover, it should be appreciated that there are numerous equivalent modifications of such sugars known in the art (sugar analogs), and all of such modifications are specifically included herein. For example, some contemplated alternative sugars will include sugars in which the heteroatom in the cyclic portion of the sugar is an atom other than oxygen (*e.g.*, sulfur, carbon, or nitrogen) analogs, while other alternative sugars may not be cyclic but in a linear (open-chain) form. Suitable sugars may also include one or more double bonds. Still further specifically contemplated alternative sugars include those with one or more non-hydroxyl substituents, and particularly contemplated substituents include mono-, di-, and triphosphates (preferably as C5' esters), alkyl groups, alkoxygroups, halogens, amino groups and amines, sulfur-containing substituents, etc. It is still further contemplated that all contemplated substituents (hydroxyl substituents and non-hydroxyl substituents) may be directed in the alpha or beta position.

Numerous of the contemplated sugars and sugar analogs are commercially available. However, where contemplated sugars are not commercially available, it should be recognized that there are various methods known in the art to synthesize such sugars. For example, suitable protocols can be found in "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan (Gordon & Breach Science Pub; ISBN: 3718659212), in U.S. Pat Nos. 4,880,782 and 3,817,982, in WO88/00050, or in EP199,451. An exemplary collection of further contemplated sugars and sugar analogs is depicted below, wherein all of the exemplary sugars may be in D- or L-

configuration, and wherein at least one of the substituents may further be in either alpha or beta orientation.

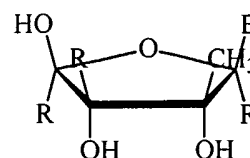
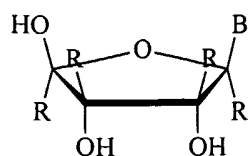


X, Y, Z = O, S, Se, NH, NR, CH₂, CHR, P(O), P(O)OR

R = H, OH, NHR, halo, CH₂OH, COOH, N₃, alkyl, aryl, alkynyl, heterocycles, OR, SR, P(O)(OR)₂

OCOR, NHCOR, NHSO₂R, NH₂NH₂, amidine, substituted amidine, guanidine, substituted guanidine

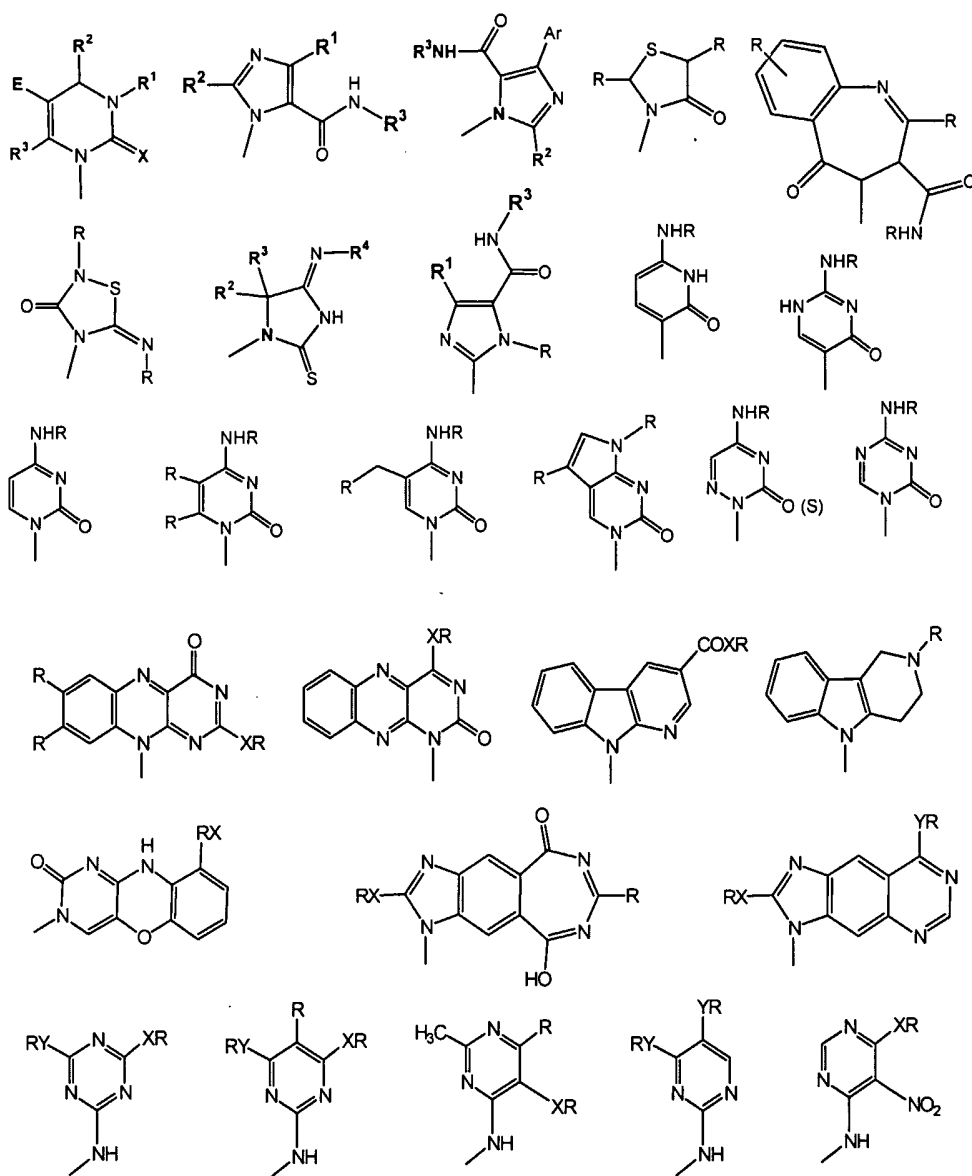
An especially contemplated class of sugars comprises alkylated sugars, wherein one or
 5 more alkyl groups (or other functional groups, including alkenyl, alkynyl, aryl, halogen, CF₃,
 CHF₂, CCl₃, CHCl₂, N₃, NH₂, etc.) are covalently bound to sugar at the C'₁, C'₂, C'₃, C'₄, or C'₅
 atom. In such alkylated sugars, it is especially preferred that the sugar portion comprises a
 furanose (most preferably a D- or L-ribofuranose), and that at least one of the alkyl groups is a
 methyl group. Of course, it should be recognized that the alkyl group may or may not be
 10 substituted with one or more functional groups. One exemplary class of preferred sugars is
 depicted below:

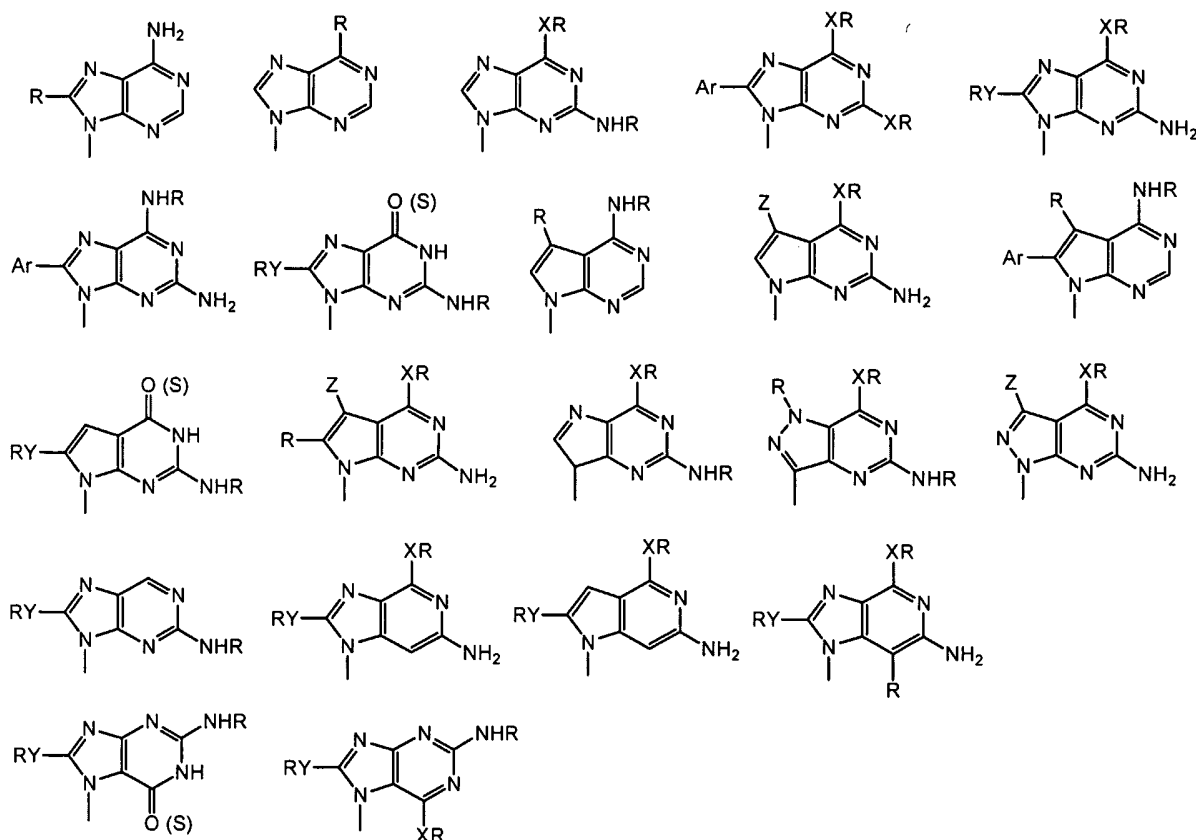


in which B is hydrogen, hydroxyl, or a heterocyclic base, R is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl (branched, linear, or cyclic), with R including between one and twenty carbon atoms.

5 Contemplated Heterocyclic Bases

It is generally contemplated that all compounds in which a plurality of atoms (wherein at least one atom is an atom other than a carbon atom) form a ring via a plurality of covalent bonds are considered a suitable heterocyclic base. However, particularly contemplated heterocyclic bases have between one and three rings, wherein especially preferred rings include 5- and 6-
 10 membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocycles may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-
 15 membered ring (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine), and a 6-membered ring fused to another 6-membered or higher ring (*e.g.*, pyrido[4,5-d]pyrimidine, benzodiazepine). An exemplary collection of appropriate heterocyclic bases is depicted below, wherein all of the depicted heterocyclic bases may further include one or more functional groups, double and triple bonds, and any chemically reasonable combination thereof. It should further be appreciated that all of the contemplated heterocyclic bases may be coupled to contemplated sugars via a carbon atom or
 20 a non-carbon atom in the heterocyclic base.





Contemplated Solid Phases

It is generally contemplated that all known types of solid phases are suitable for use herein, so long as contemplated nucleosides (or sugar, or heterocyclic base) can be coupled to such solid phases, and so long as the coupled nucleoside (or sugar, or heterocyclic base) will remain coupled to the solid phase during at least one chemical reaction on the nucleoside (or sugar, or heterocyclic base). Especially contemplated solid phases (*i.e.*, solid supports) include Merrifield resins, ArgoGel (available from Argonaut, San Francisco, CA), Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), TentaGel S AC, TentaGel PHB, or TentaGel S NH₂ resin (polystyrene-polyethylene glycol copolymer resins available from Rappe Polymere, Tübingen, Germany). Alternatively, contemplated solid supports may also include glass, as described in U. S. Pat. No. 5,143,854. Another preferred solid support comprises a "soluble" polymer support, which may be fabricated by copolymerization of polyethylene glycol, polyvinylalcohol, or polyvinylalcohol with polyvinyl pyrrolidone or derivatives thereof (*e.g.*, see Janda and Hyunsoo (1996) *Methods Enzymol.* 267:234-247; Gravert and Janda (1997) *Chemical Reviews* 97:489-509; and Janda and Hyunsoo, PCT publication No. WO 96/03418).

Consequently, it should be recognized that there are numerous methods of coupling nucleosides, sugars, or heterocyclic bases to solid phases that may be appropriate, and a particular method will generally depend on the particular type of solid phase and/or type of sugar. Thus, all of such known methods are contemplated suitable for use herein, and exemplary
5 suitable solid phase coupling reactions are described, for example, in "Organic Synthesis on Solid Phase – Supports, Linkers, Reactions" by Florencio Zaragoza Dorwald et al. John Wiley & Sons; ISBN: 3527299505, or in "Solid-Phase Synthesis and Combinatorial Technologies" by Pierfausto Seneci, John Wiley & Sons; ISBN: 0471331953.

Contemplated Combinatorial Reactions

10 It is generally contemplated that all known types of combinatorial reactions and/or reaction sequences may be used in conjunction with the teaching presented herein so long as such combinatorial reactions between a substrate and at least two distinct reagents will result in at least two distinct products.

Contemplated combinatorial reactions and/or reaction sequences may therefore be
15 performed sequentially, in parallel, or in any chemically reasonable combination thereof. It is still further contemplated that suitable combinatorial reactions and/or reaction sequences may be performed in a single compartment or multiple compartments. Preferred combinatorial reactions and/or reaction sequences include at least one step in which a substrate or reaction intermediate is coupled to a solid phase (with may include the wall of the reaction compartment or a solid or
20 soluble polymers), and that the solid phase is physically separated from another substrate on another solid phase. While not limiting to the inventive subject matter, it is generally preferred that contemplated solid phase synthesis is at least partially automated. There are numerous methods and protocols for combinatorial chemistry known in the art, and exemplary suitable protocols and methods are described in "Solid-Phase Synthesis and Combinatorial
25 Technologies" by Pierfausto Seneci (John Wiley & Sons; ISBN: 0471331953) or in "Combinatorial Chemistry and Molecular Diversity in Drug Discovery" by Eric M. Gordon and James F. Kerwin (Wiley-Liss; ISBN: 0471155187).

Contemplated Libraries and Nucleosides

The inventors discovered that nucleoside analog libraries can be prepared in various
30 combinatorial library approaches, including libraries in which diverse heterocyclic bases and/or diverse nucleoside analogs are prepared from precursor nucleosides (or modified sugars) that are

derivatized in subsequent/parallel modification reactions, and libraries in which a modified heterocyclic base is coupled to a sugar portion.

C₁'-non-carbon-bridged Nucleoside Libraries

In one particularly contemplated aspect of the inventive subject matter, the inventors have discovered that nucleosides with the general structure A-M-B can be synthesized, in which A comprises a sugar, M comprises an intermediary atom other than carbon (*e.g.*, nitrogen, oxygen, or sulfur, which may be introduced via an amino group, a hydroxyl group, or a thiol group on the sugar), and B comprises a heterocyclic base, wherein M is covalently bound to a carbon atom of the sugar and further covalently bound to the heterocyclic base. Especially contemplated heterocyclic bases include natural (*e.g.*, A, G, C, T, U, I, etc.) and non-natural heterocyclic bases (*e.g.*, substituted or unsubstituted triazine, purine, or pyrimidine, etc.). Further contemplated heterocyclic bases include those contemplated above.

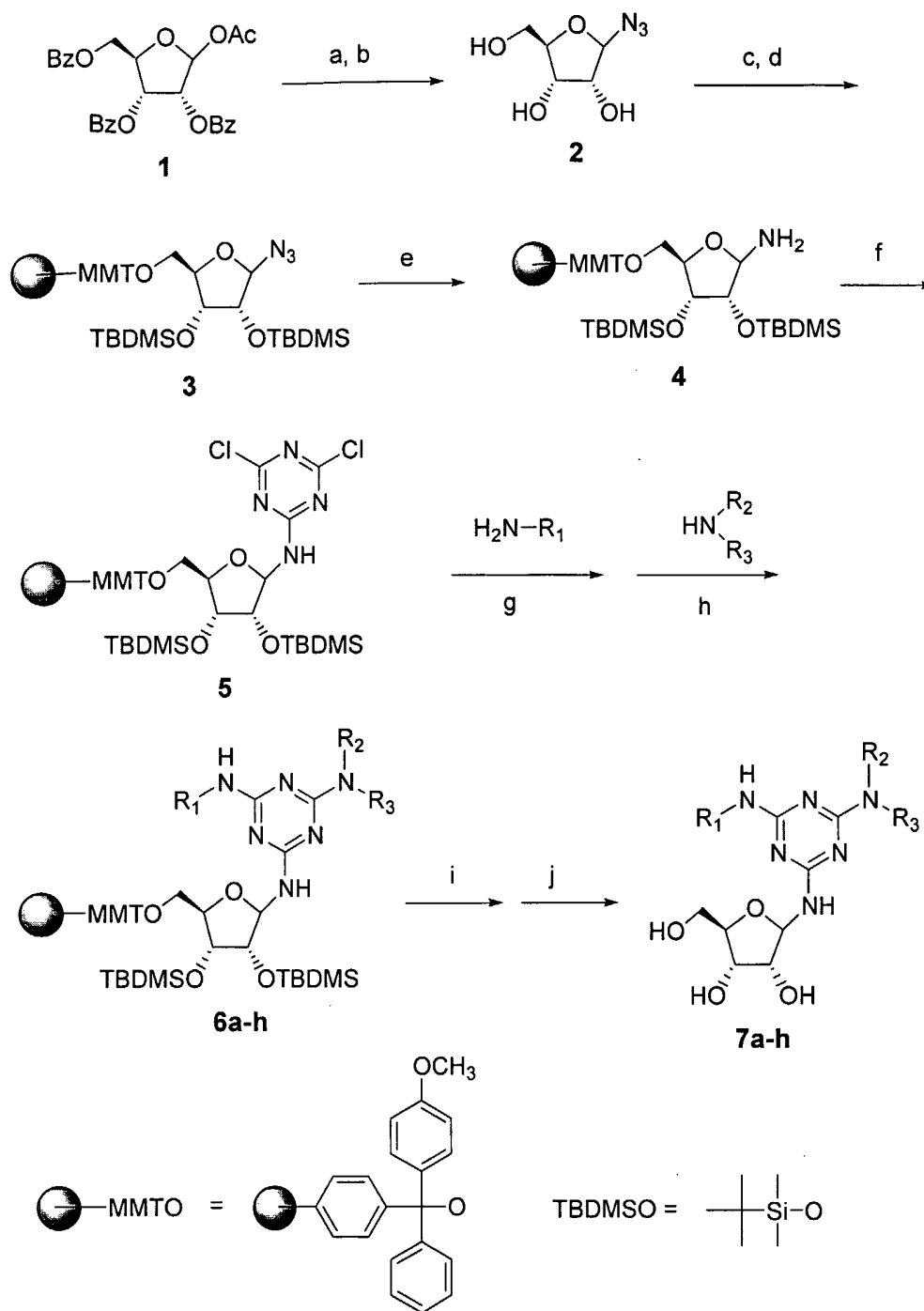
Such nucleosides may further include an electrophilic center and a leaving group in the heterocyclic base, and in a particularly preferred aspect, the heterocyclic base comprises a five-membered ring, a six-membered ring, or a fused aromatic system with a heteroatom (*e.g.*, N, S, O, or P). It is further generally contemplated that all known sugars may be employed in such contemplated nucleosides. However, in some preferred compounds, the sugar comprises a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, or an arabinose (wherein the sugar may be in D-configuration or L-configuration). Exemplary libraries, compounds, and their synthesis are given below.

Triazole Libraries and Compounds

Contemplated triazole libraries compounds may be synthesized by various synthetic routes, and an exemplary route for synthesis of contemplated compound is depicted in Schemes 1 through 4. Here, as depicted in **Scheme 1**, a 1'-azidoribofuranose is formed from commercially available protected ribofuranose and coupled to a solid support (the remaining OH groups on the sugar are protected). Reduction of the azido group yields the corresponding 1'-amino group (in alpha or beta orientation), which is then reacted with 2,4,6-trichloro-1,3,5-triazine. The remaining Cl substituents on the heterocyclic base serve as leaving groups (which may be replaced by one or more alternative leaving groups) and are covalently bound to an electrophilic carbon atom in the triazine, respectively. These carbon atoms then serve as electrophilic centers for subsequent substitution reactions with various nucleophiles (*e.g.*, primary and/or secondary

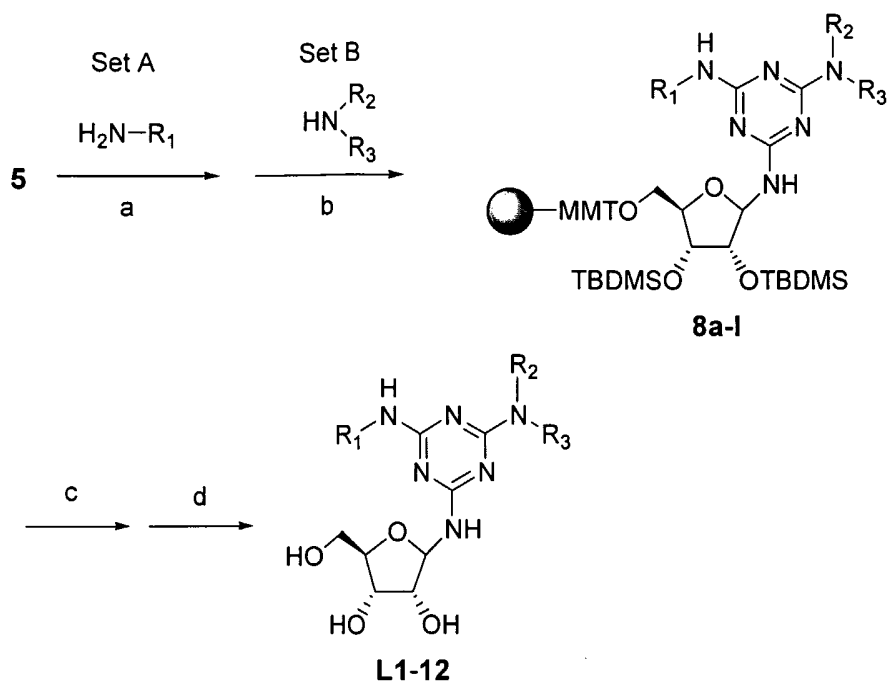
amines), to which various moieties may be coupled. At least one moiety may then further be chemically modified. After coupling of the substrates to the triazine heterocyclic base, the protecting groups are removed and the sugar is cleaved from the solid phase. An exemplary diversification reaction is shown in more detail in **Scheme 2** in which primary amines and

5 secondary amines are employed as nucleophiles.



Conditions: a, SnCl_4 , NaN_3 ; b, NaCN , MeOH ; c, polystyrene MMT-Cl resin, DMAP, pyridine; d, *t*-butyldimethylsilyl chloride, imidazole; e, PMe_3 ; f, 2,4,6-trichloro-1,3,5-triazine, diisopropylethylamine; g, amine, diisopropylethylamine, 0 °C to rt; h, amine, diisopropylethylamine, 75-80 °C; i, tetrabutylammonium fluoride; j, 2% trifluoroacetic acid in 1,2-dichloroethane.

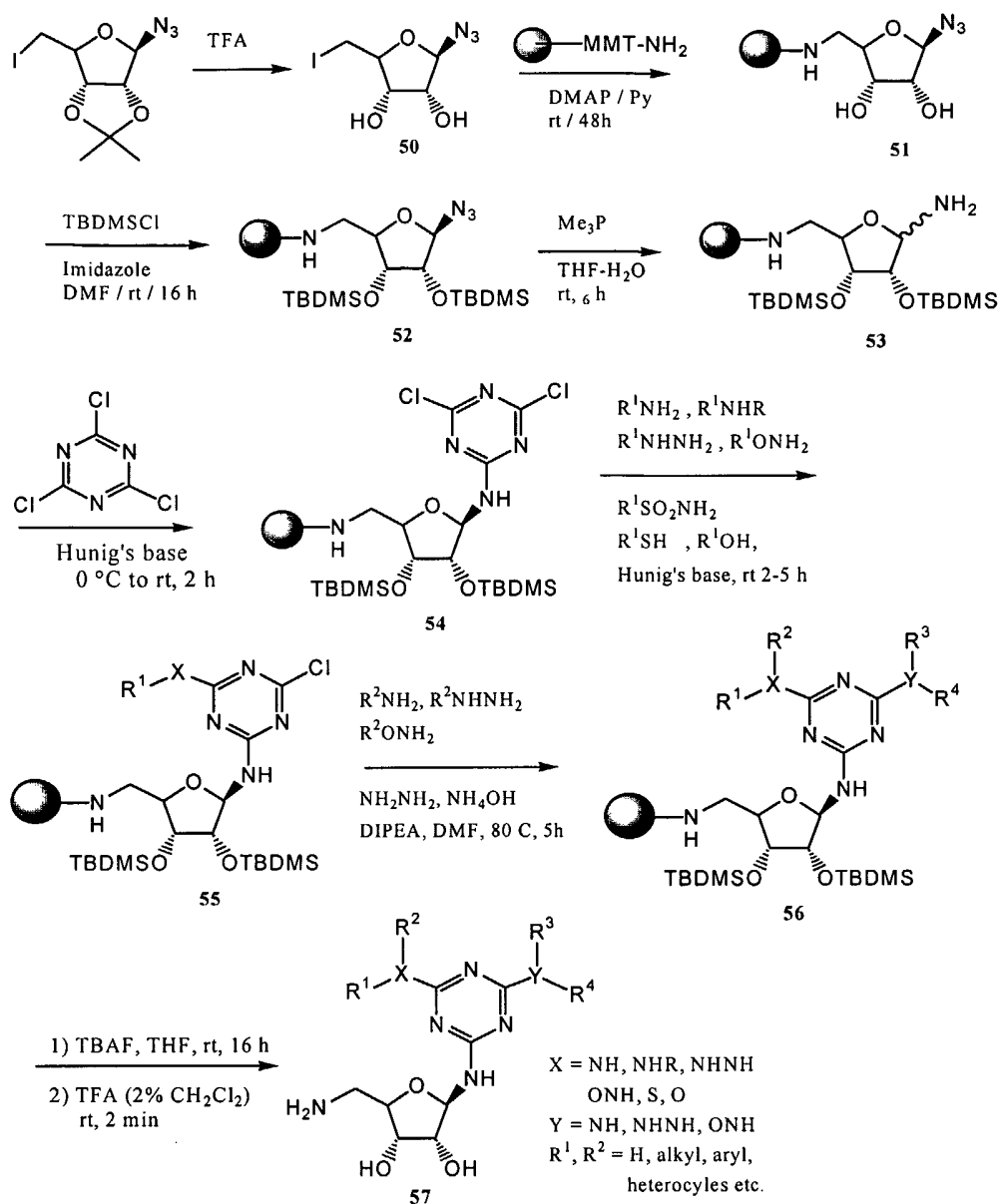
Scheme 1



Conditions: a, Set A amine building blocks, diisopropylethylamine, 0 °C to rt; b, Set B amine building blocks, diisopropylethylamine, 75-80 °C; c, 1M tetrabutylammonium fluoride in THF; d, 2% trifluoroacetic acid in dichloromethane, 1 min.

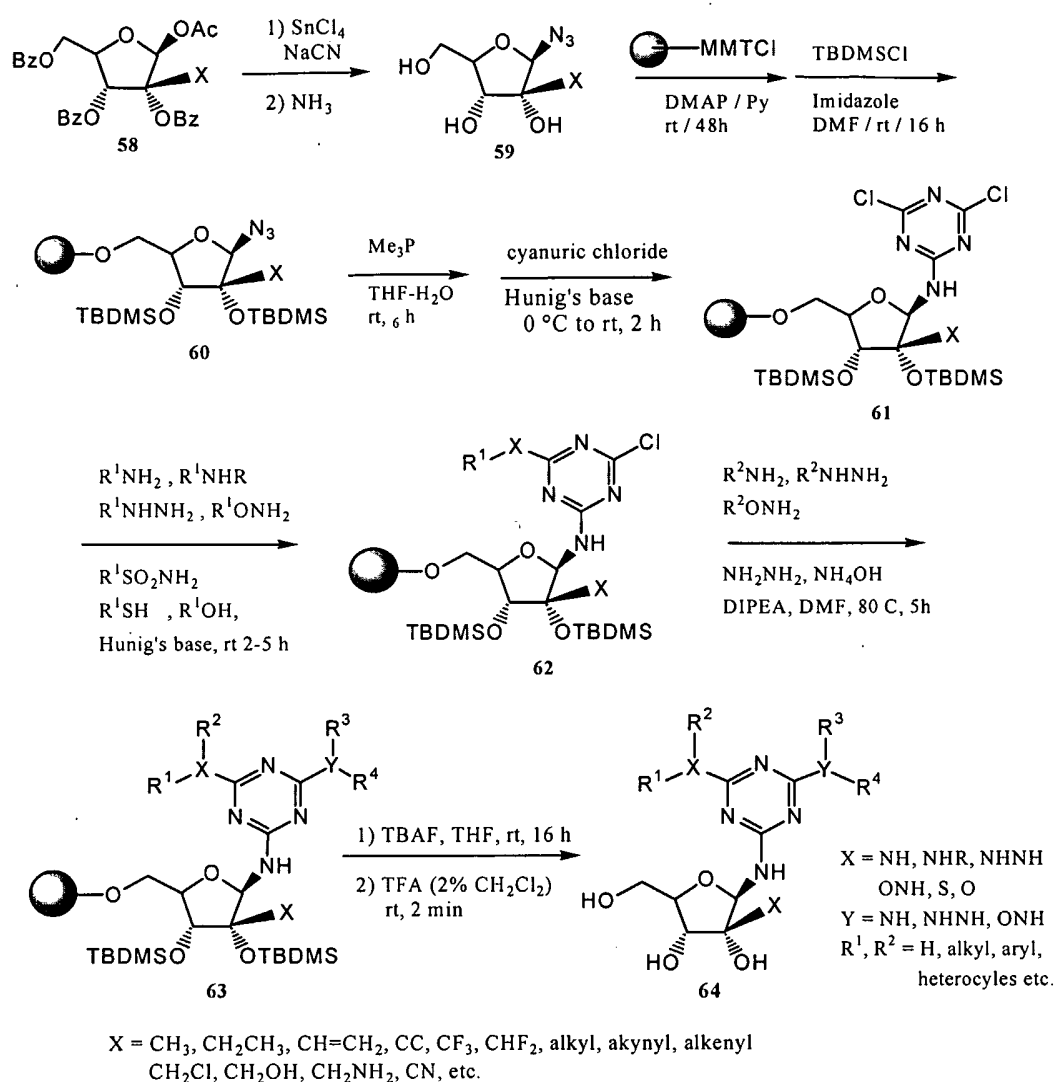
Scheme 2

Alternatively, and especially where it is desired that the C_{5'}-substituent is a group other than a hydroxyl group (*e.g.*, 5'-amino group), a synthetic strategy as depicted in **Scheme 3** may be employed.



Scheme 3

In still further contemplated aspects, and particularly where a nucleoside library with a substituent on the C₂'- or C₃'-position on the sugar portion is desired, a suitably modified sugar may be employed as depicted in **Scheme 4**, wherein the C₂'-modified sugar is first converted into the corresponding azido sugar that is then coupled to the heterocyclic base.



Scheme 4

With respect to the heterocyclic base, it should be recognized that numerous heterocyclic bases other than a trichlorotriazine are also appropriate so long as such heterocyclic bases comprise at least one reactive group that can react with a reagent to derivatize/modify the heterocyclic base. However, it is generally preferred that alternative heterocyclic bases include at least one electrophilic center and at least one leaving group. For example, a particularly contemplated alternative heterocyclic base is dichlorodiazine or chlorotriazine.

Further contemplated heterocyclic bases include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine), fused heterocycles (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine, pyrido[4,5-d]pyrimidine, or benzodiazepine). Numerous of contemplated heterocyclic bases are commercially available, and all of these commercially available heterocyclic bases are contemplated suitable for use herein.

Moreover, where a particular heterocyclic base is not commercially available, it is contemplated that such heterocyclic bases can be prepared following standard procedures well known in the art (see *e.g.*, Advanced Organic Chemistry: Structure and Mechanisms (Part A) by Francis A. Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306462435; or Advanced Organic Chemistry :
5 Reactions and Synthesis (Part B) by Francis Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306434571, or Compendium of Organic Synthetic Methods, Volume 9, by Michael B. Smith, John Wiley & Sons; ISBN: 0471145793).

The term "electrophilic center" as used herein refers to all atoms in a molecule that may be subject to attack of a nucleophile, and especially contemplated reactions of such nucleophiles
10 include nucleophilic (aromatic) substitution reactions. The term "leaving group" as used herein refers to any group that has an appreciable electron-withdrawing ability, is a relatively weak base once it has left the molecule it was previously attached to, and is polarizable at least to some degree. There are numerous leaving groups known in the art, and all of them are considered suitable for use herein. However, especially preferred leaving groups include halogens, tosyl,
15 mesyl, and triflate groups. Still further, the terms "nucleophilic reagent" and "nucleophilic substrate" are used interchangeably herein. Similarly, the terms "electrophilic reagent" and "electrophilic substrate" are used interchangeably herein.

Likewise, it is contemplated that numerous sugars other than a ribofuranose are also suitable for use in conjunction with the teachings presented herein, and it is especially
20 contemplated that alternative sugars include ribofuranose, substituted ribofuranose, carbocyclic ring systems, and arabinose (in D-configuration or L-configuration). Moreover, it is contemplated that sugar derivatives of sugars with four, five, or six carbon atoms may be also employed, and especially contemplated derivatives include substituents other than OH groups (*e.g.*, N₃, halogen, OCH₃, etc.). Exemplary synthesis of nucleoside libraries and nucleosides with
25 C₂'- and C₅'-modifications are depicted in Schemes 3 and 4 above, wherein the modification of the sugar is introduced in one or more reactions prior to coupling the sugar to the heterocyclic base (or in which the modification is already present as shown in Scheme 4). Alternatively, however, it should also be recognized that the particular step in which the modification is introduced into the nucleoside (or sugar) is not limiting to the inventive subject matter.
30 Consequently, it is contemplated that the sugar modification may also be introduced during or after coupling of the sugar to the heterocyclic base.

Still further contemplated exemplary alternative sugars are depicted above in the section entitled "Contemplated Sugars". It should still further be appreciated that the azido group in the azido sugar, which is employed as starting material for coupling the heterocyclic base to the sugar may be in a position other than the C₁'-position, and especially preferred alternative positions include C₂'- and C₃'-position. Therefore, contemplated nucleosides will also include nucleosides in which the heterocyclic base is attached to a position other than the C₁'-atom. Moreover, while the compounds in the Schemes 1-4 above include C2' and C3' substituents in alpha orientation, one or more of the substituents may also be in beta orientation.

Consequently, the nature of protecting groups for the sugar will vary considerably, and while it is particularly contemplated that suitable protection groups include benzyl-, acetyl-, and TBDMS groups, numerous alternative protection groups are also considered suitable. Among other groups, a collection of appropriate alternative protection groups and their reactions is described in Protective Groups in Organic Synthesis by Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons; ISBN: 0471160199.

Furthermore, the solid phase and methods of coupling the solid phase to the nucleoside will at least in part depend on the particular sugar and position of coupling. Therefore, it is contemplated that all known solid phases are suitable for use in conjunction with the teachings presented herein, and exemplary suitable solid phases are described, for example, in Organic Synthesis on Solid Phase – Supports, Linkers, Reactions; by Florencio Zaragoza Dorwald et al. John Wiley & Sons; ISBN: 3527299505, or in Solid-Phase Synthesis and Combinatorial Technologies by Pierfausto Seneci, John Wiley & Sons; ISBN: 0471331953. Preferred solid phases, however, include Merrifield resins, ArgoGel (available from Argonaut, San Francisco, CA), Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), TentaGel S AC, TentaGel PHB, or TentaGel S NH₂ resin (polystyrene-polyethylene glycol copolymer resins available from Rappe Polymere, Tübingen, Germany).

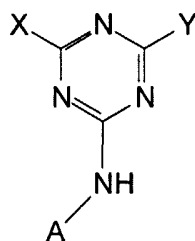
With respect to reagents that may react with one or more reactive groups in the heterocyclic base, it should be recognized that all reagents are suitable for use herein that have sufficient reactivity (with or without prior activation and/or catalyst) to be coupled to the reactive group in the heterocyclic base. For example, where the reactive group comprises an electrophilic center, suitable substrates will include various nucleophilic reagents (*e.g.*, primary and secondary substituted and unsubstituted amines, thiols, alcohols) and Grignard-type compounds (*e.g.*, alkyl-

MgBr). There are numerous nucleophilic reagents and Grignard-type compounds commercially available, and where such reagents are not commercially available, it is contemplated that they may be prepared from commercially available precursors using protocols well known in the art (*supra*). Particularly suitable nucleophilic substrates are listed in the experimental section below.

- 5 Moreover, it should be recognized that suitable reagents, once introduced in the heterocyclic base, may further be derivatized. For example, where a reagent has a nucleophilic group, such a group may be modified via a nucleophilic substitution reaction with an additional reagent (*e.g.*, electrophilic reagent).

Consequently, it should be recognized that a nucleoside library may include a first library
10 compound and a second library compound, wherein each of the first and second library compounds has a structure A-M-B, wherein A comprises a sugar, M comprises an intermediary atom other than carbon, and B comprises a heterocyclic base, wherein M is covalently bound to a carbon atom of the sugar and further covalently bound to the heterocyclic base, and wherein the first library compound and the second library compound are chemically distinct. The term
15 "chemically distinct" as used herein means not identical, wherein not identical includes non-identity in mass, elemental composition, and stereochemistry. For example, L-adenosine is considered not identical with D-adenosine, because the stereochemistry of the sugar portion in the nucleoside is distinct.

In a particularly preferred aspect of the inventive subject matter, a nucleoside library with
20 at least two library compounds is prepared in which one of the at least two library compounds has a structure according to Formula 1 with a first set of substituents A, X, and Y, and wherein another one of the at least two library compounds has a structure according to Formula 1 with a second set of substituents A, X, and Y:

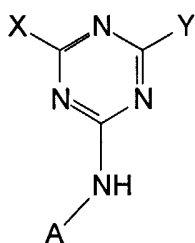


25 **Formula 1**

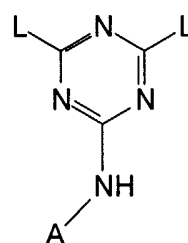
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected, X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR, and wherein R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A, X, and Y in the first set are the same as the substituents A, X, and Y in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Thus, contemplated compounds may have a structure according to Formulae 2 or 3



Formula 2



Formula 3

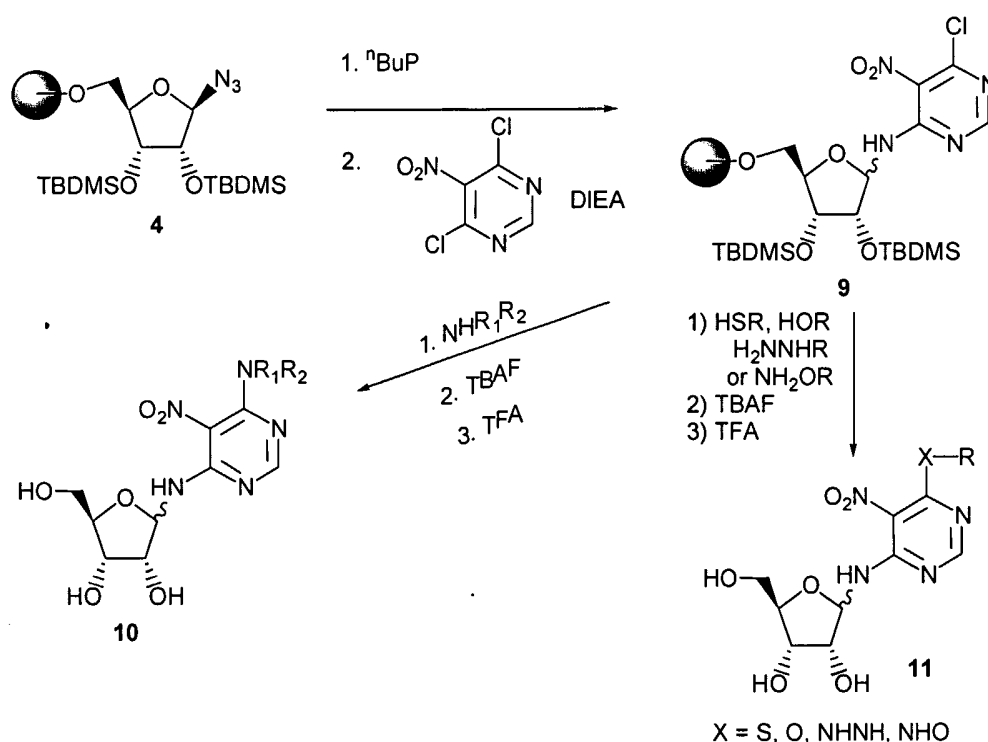
wherein A is a sugar, wherein the sugar is optionally protected and optionally coupled to a solid phase, X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR, and wherein R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein L is a leaving group, preferably independently selected from the group consisting of Cl, Br, Tosyl, and Mesyl.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of, or in

addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Nitropyrimidine Libraries and Compounds

5 In still further especially preferred aspects, the inventors discovered that a heterocyclic base may also be formed from a substituted nitropyrimidine, which is further modified to a substituted nitropyrimidine library (and library compounds) as shown in **Scheme 5** below.



Scheme 5

10 Here, a suitably protected 1'-azidosugar which may or may not be coupled to a solid phase is reacted with 5-nitro-4,6-dichloropyrimidine to generate the corresponding nucleoside in which the heterocyclic base is coupled to the sugar with a nitrogen atom. The nitro group in the heterocyclic base serves as an electron-withdrawing group, while the vicinal chlorine atom is employed as a leaving group that is replaced by a nucleophilic substrate to generate the

15 corresponding substituted C_1' -N-nucleoside or nucleoside library. Deprotection and cleavage of the nucleoside or nucleoside library will then yield the nitropyrimidine compound(s).

With respect to the azido sugar, it should be recognized that numerous sugars other than the depicted C_{1'}-ribofuranose are also appropriate, and it is contemplated that all known sugars are suitable, so long as such sugars include an azido group, or a group that can be converted to an azido group. Especially alternative sugars include those contemplated above in the section
5 entitled "Contemplated Sugars". Further particularly contemplated sugars include arabinose and xylose sugars, all of which may or may not be further substituted by one or more substituents. Still further, it should be recognized that the azido group may be positioned in a position other than the C_{1'}-position, and especially contemplated alternative positions include the C_{2'}, C_{3'}, and C_{5'}-position.

10 In further contemplated aspects of the inventive subject matter, it should be appreciated that the chemical nature of the solid phase may vary considerably, and it should be recognized that all known solid phases are considered suitable for use herein (see *e.g.*, section entitled "Contemplated Solid Phases", *supra*). Similarly, with respect to the protection group(s) it is contemplated that the same considerations as for suitable protecting groups in synthetic schemes
15 described above apply.

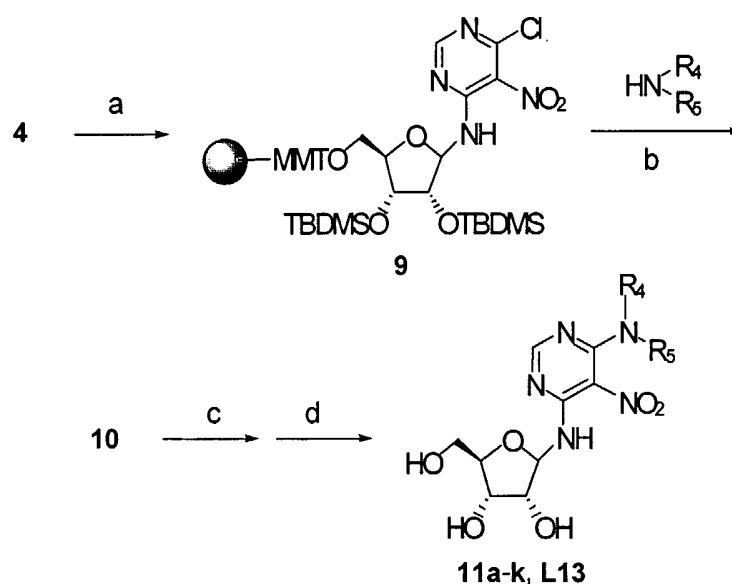
It is generally contemplated that suitable nucleosides may advantageously be produced from 5-nitro-4,6-dichloropyrimidine. However, in alternative aspects it is contemplated that all heterocyclic bases are suitable, so long as such heterocyclic bases include a ring atom as electrophilic center that forms a covalent bond with the nitrogen of the C_{1'}-azido sugar.

20 Consequently, alternative heterocyclic bases will include 5-membered rings, 6-membered rings, and fused ring systems of 5-membered rings and 6-membered rings, wherein all of the contemplated heterocyclic bases may include one or more heteroatoms (particularly contemplated heteroatoms include nitrogen, sulfur, and oxygen).

Furthermore, suitable heterocyclic bases need not be limited to nitro group containing
25 heterocyclic bases, and it is generally contemplated that all groups with an electron-withdrawing effect are appropriate. Thus, alternative groups include carboxylic acid groups, -CF₃, etc. Similarly, it is contemplated that the leaving group need not be restricted to a chlorine atom. There are numerous known leaving groups known in the art, and all of the known leaving groups are considered suitable for use herein. For example, alternative leaving groups include halogens
30 (*e.g.*, Br), nitrophenyl, tosylate or mesylate groups.

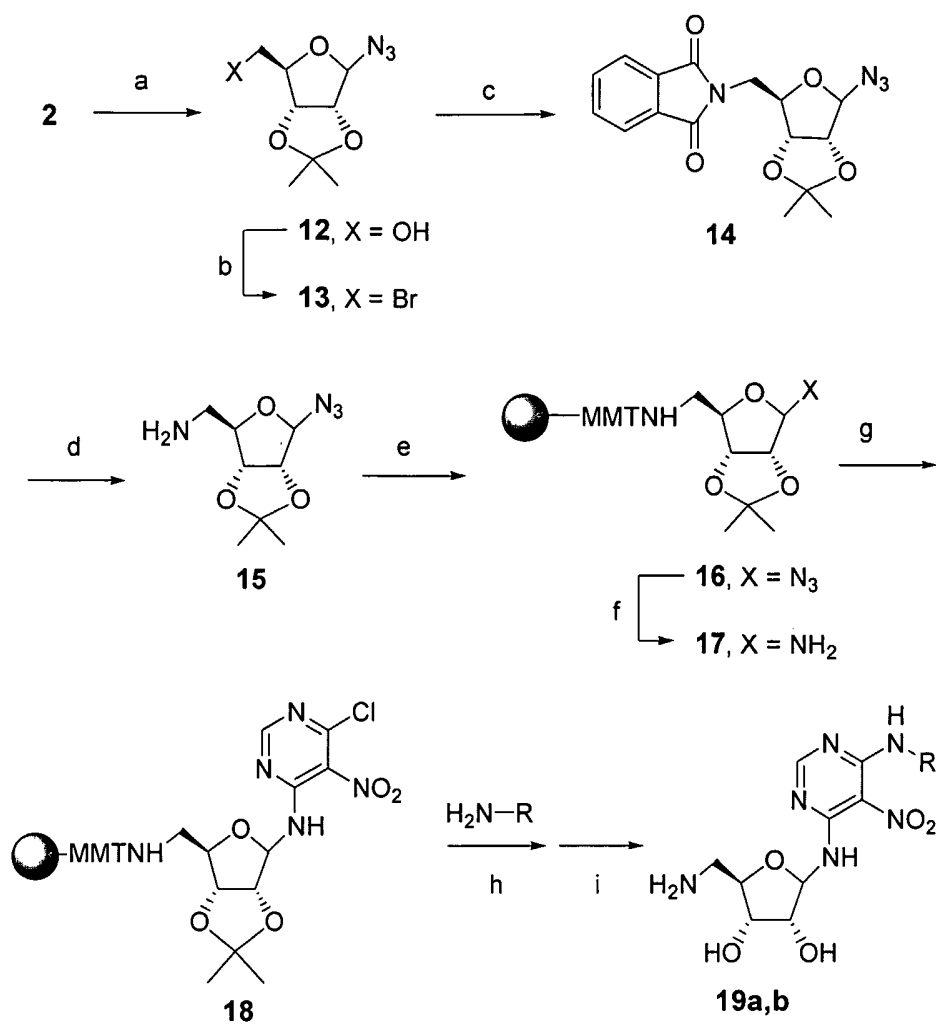
With respect to suitable nucleophilic substrates it should be recognized that numerous reagents and compounds are suitable, and especially contemplated nucleophilic substrates include those having a nitrogen atom, and especially primary and/or secondary amines, and those having an oxygen or sulfur atom (*e.g.*, various alcohols and/or thiols). Moreover, suitable nucleophilic substrates also include reagents that form a C-C bond (*e.g.*, Grignard reagents, etc.). Exemplary suitable nucleophilic substrates will have the general formula NR_1R_2 , R_1OH , or R_1SH , wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, and a substituted or unsubstituted heterocycle.

Alternatively, and especially where N-disubstituted amino-nitropyrimidine nucleosides are desired, synthesis may follow according to **Scheme 6** as depicted below. Here, the synthesis is substantially similar to the synthesis of Scheme 5, however, the nucleophilic substrate is a secondary amine (or set of secondary amines):

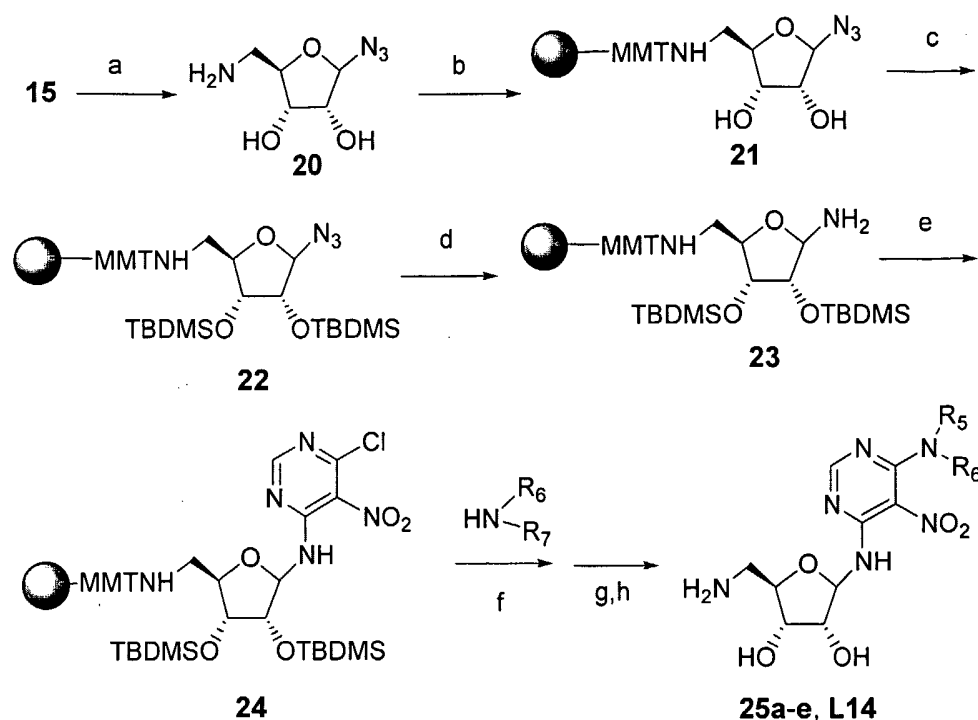


Scheme 6

Similarly, contemplated compounds and libraries may include a modified sugar portion, and especially contemplated modified sugar portions include amino sugars. Exemplary synthetic routes for 5'-amino sugars are depicted in **Schemes 7 and 8** below, wherein in Scheme 7 primary amines are employed as nucleophilic substrates, and wherein in Scheme 8 secondary amines are employed as nucleophilic substrates.

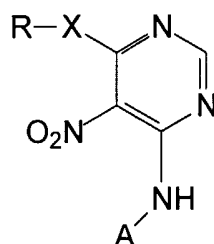


Scheme 7



Scheme 8

Consequently, a nucleoside library with at least two library compounds is contemplated in which one of the at least two library compounds has a structure according to Formula 4 with a first set of substituents A, X, and R, and wherein another one of the at least two library compounds has a structure according to Formula 4 with a second set of substituents A, X, and R

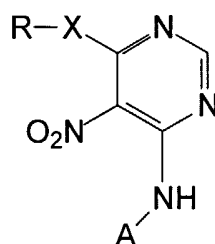


Formula 4

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected, X is chemical bond, NR', O, or S; wherein R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A, X, and R in the first set are the same as the substituents A, X, and R in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or a OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Thus, contemplated compounds may have a structure according to Formula 5



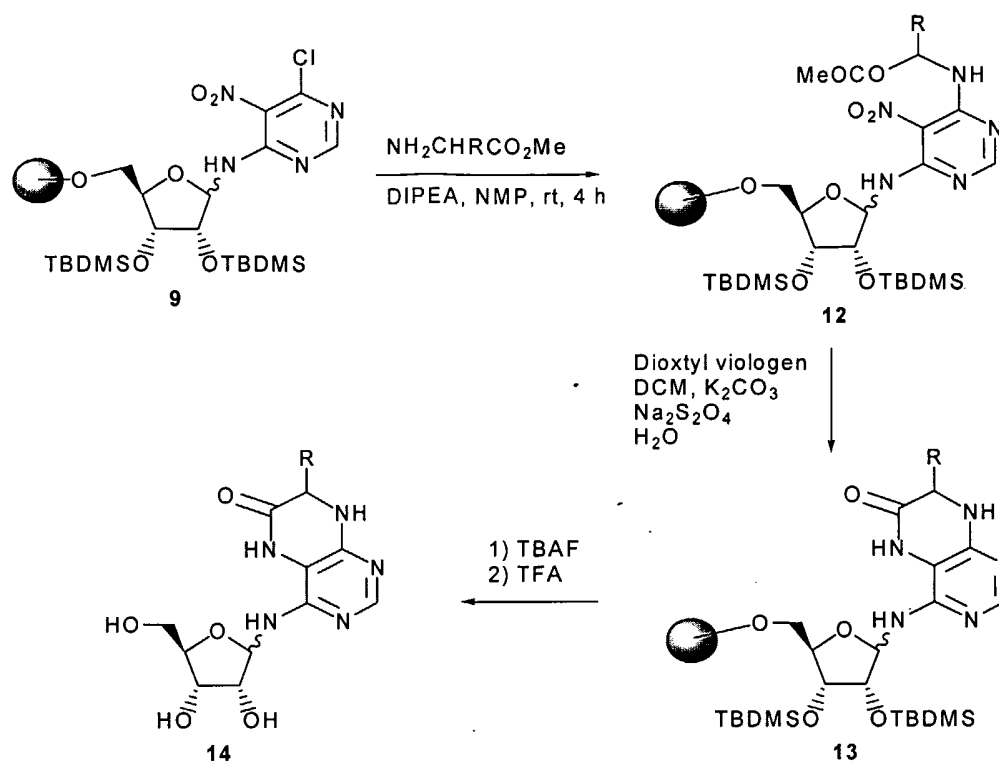
Formula 5

wherein A is a sugar, X is a chemical bond, NR', O, or S; wherein R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or a OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Piperazino-Pyrimidine Library And Compounds

The inventors still further discovered that a substituted piperazino-pyrimidine library may be synthesized using 5-nitro-4,6-dichloropyrimidine and an amino acid to generate a bicyclic heterocyclic base as depicted in **Scheme 9** below.



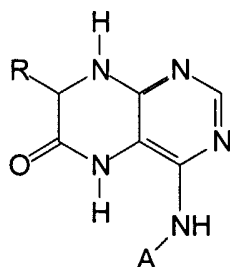
Here, the protected and solid phase bound compound 9 is synthesized as shown in Schemes 5 above and reacted (under conditions as indicated in Scheme 9 above) with an amino acid to form the corresponding substituted amino acid substituted nitropyrimidine C₁'-N-nucleoside (or nucleoside library where more than one amino acid or more than one sugar is employed). In a further step, the piperazino-pyrimidine heterocyclic base is formed via intramolecular cyclization (under conditions as indicated above), and the desired piperazino-pyrimidine nucleoside or nucleoside library is obtained via deprotection and cleavage of the sugar from the solid phase.

With respect to the sugar, the solid phase and the protection groups (including deprotection and cleavage of the sugar from the solid phase) the same considerations as described above apply. In further alternative aspects, it should be appreciated that various methods other than intramolecular cyclization using diethyl viologen as electron-transfer catalyst oxidation of are also suitable, and appropriate methods may include intramolecular cyclization using catalysts and/or activated acid groups.

Furthermore, it is contemplated that suitable amino acids will generally have the formula (NH₂)[CH(R)]_n(COCH₃), wherein n is between 1 and 3, and R is selected from the group

consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle. However, especially contemplated amino acids include naturally occurring amino acids (in D- and/or L-configuration). Furthermore, it should be
 5 recognized that where n is greater than 1, the corresponding bicyclic heterocyclic base will have a seven-membered, eight-membered or higher ring.

Consequently, a nucleoside library with at least two library compounds is contemplated in which one of the at least two library compounds has a structure according to Formula 6 with a first set of substituents A and R, and wherein another one of the at least two library compounds
 10 has a structure according to Formula 6 with a second set of substituents A and R

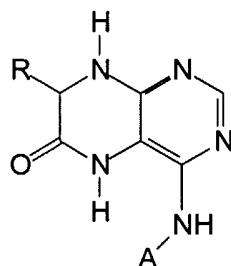


Formula 6

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected, R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or
 15 unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated
 20 aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or a OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Thus, contemplated compounds may have a structure according to Formula 7



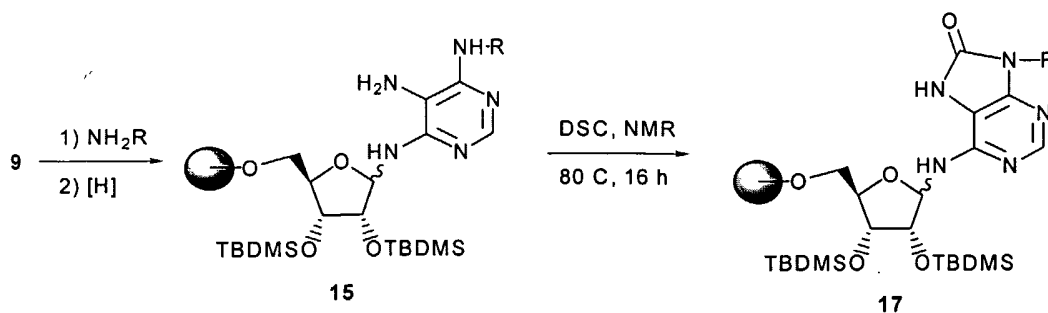
Formula 7

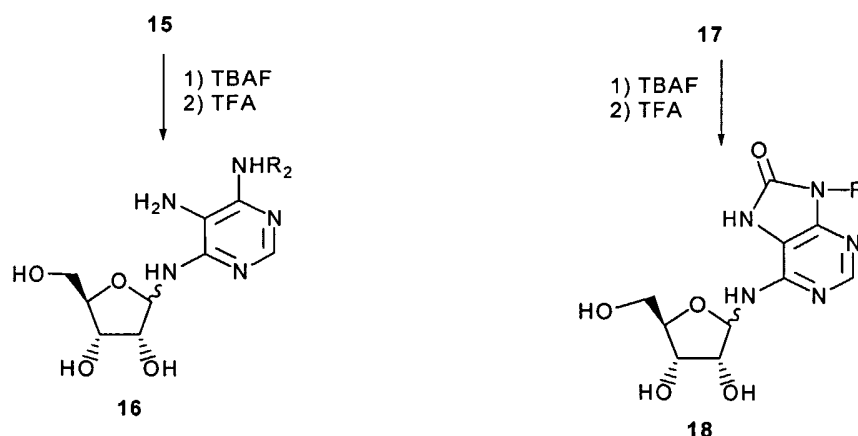
wherein A is a sugar, R is selected from the group consisting of hydrogen, a substituted
 5 or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted
 alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the
 ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated
 aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in
 10 place of a hydroxyl group, and/or a OR and/or R group (as defined above) in place of or in
 addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include
 substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated
 sugars may be in D- or L-configuration.

Imidazolidino-Pyrimidine Libraries And Compounds

15 In yet another preferred aspect of the inventive subject matter, a substituted imidazol-
 idino-pyrimidine library may be synthesized using 5-nitro-4,6-dichloropyrimidine as a starting
 material, which is first reacted with a first set of reagents and reduced to generate the
 corresponding substituted diamino pyrimidine, which is in a further step cyclized to a substituted
 imidazolidino-pyrimidine library as depicted in **Scheme 10** below.





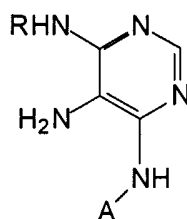
Scheme 10

Here, the protected and solid phase bound compound 9 is synthesized as shown in Scheme 5 above and reacted with a primary amine to form the corresponding substituted nitropyrimidine C₁'-N-nucleoside (or nucleoside library where more than one amino acid is employed). The so generated substituted nitropyrimidine C₁'-N-nucleoside (or nucleoside library) is then reduced in a hydrogenation reaction to form the corresponding substituted aminopyrimidine C₁'-N-nucleoside or nucleoside library, which is then in a further step cyclized to the desired piperazino-pyrimidine heterocyclic nucleoside or nucleoside library. Alternatively, cyclization may be omitted to obtain a substituted aminopyrimidine C₁'-N-nucleoside or nucleoside library after deprotection and cleavage of the sugar from the solid phase.

With respect to the sugar, the solid phase and the protection groups (including deprotection and cleavage of the sugar from the solid phase) the same considerations as described above apply.

Furthermore, it is contemplated that primary amines will generally have the formula RNH₂ wherein R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle. However, especially contemplated primary amines include those listed in the experimental section below.

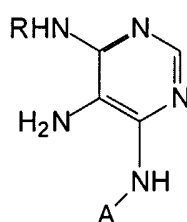
Consequently, a nucleoside library with at least two library compounds is contemplated in which one of the at least two library compounds has a structure according to Formula 8 with a first set of substituents A and R, and wherein another one of the at least two library compounds has a structure according to Formula 8 with a second set of substituents A and R

**Formula 8**

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected, R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Thus, contemplated compounds may have a structure according to Formula 9

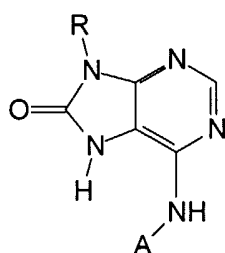
**Formula 9**

wherein A is a sugar, R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated

aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated
5 sugars may be in D- or L-configuration.

In still further contemplated aspects, nucleoside libraries prepared according to Scheme 10 above will include one of the at least two library compounds with a structure according to Formula 10 with a first set of substituents A and R, and another one of the at least two library compounds with a structure according to Formula 10 with a second set of substituents A and R

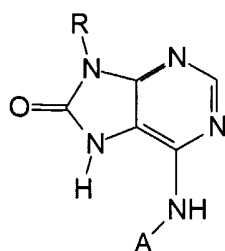


Formula 10

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected; R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted
15 or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in
20 place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

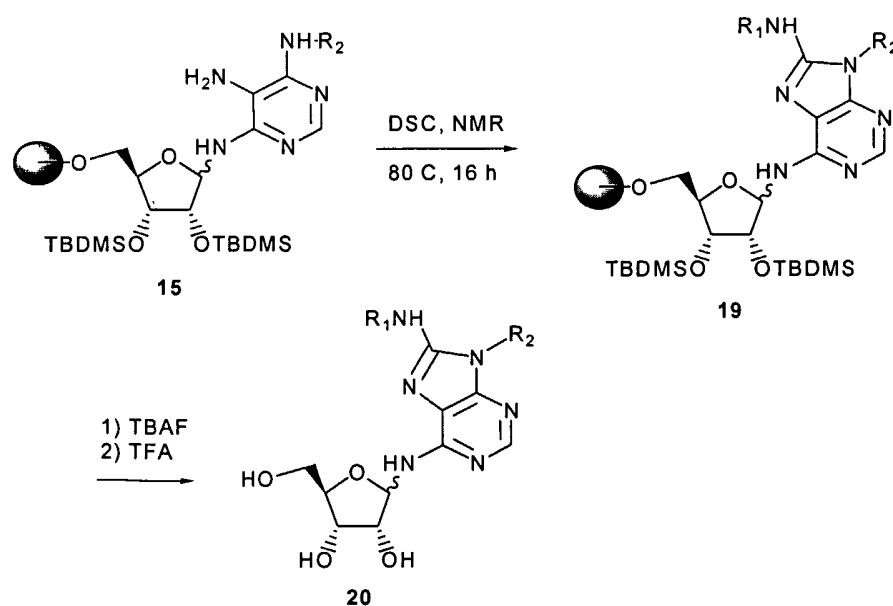
Thus, contemplated compounds may also have a structure according to Formula 11

**Formula 11**

wherein A is a sugar, and R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

In yet another aspect of the inventive subject matter, cyclization may be performed as depicted in **Scheme 11**.

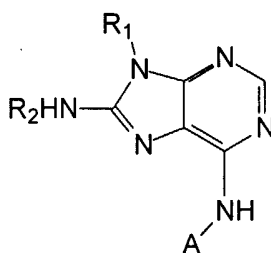


Scheme 11

Here, a substituted aminopyrimidine C₁'-N-nucleoside or nucleoside library (15) is prepared as described in Schemes 2A-2C above, and cyclization is performed as shown to obtain the desired disubstituted imidazole-pyrimidine C₁'-N-nucleoside or nucleoside library.

5 With respect to the sugar, the solid phase and the protection groups (including deprotection and cleavage of the sugar from the solid phase) the same considerations as described above apply.

Consequently, contemplated nucleoside libraries will include at least two library compounds in which one of the at least two library compounds has a structure according to
10 Formula 12 with a first set of substituents A, R₁, and R₂, and another one of the at least two library compounds with a structure according to Formula 12 with a second set of substituents A, R₁, and R₂



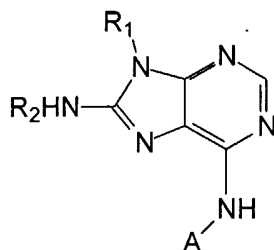
Formula 12

15 wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected, and R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and wherein not all of the substituents A, R₁, and R₂ in the first set are the same as
20 the substituents A, R₁, and R₂ in the second set.

In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C₅'-, C₂'- or C₃'-position. In especially contemplated aspects, the modification in the C₅'-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in
25 addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include

substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

Thus, contemplated compounds may also have a structure according to Formula 13



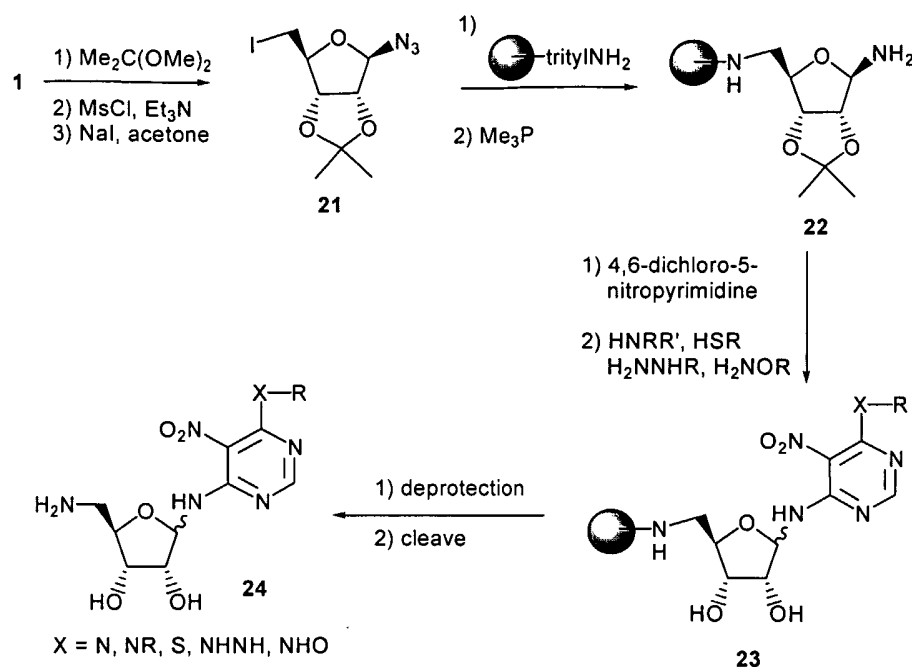
5

Formula 13

wherein A is a sugar, and R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

10 In particularly preferred aspects, the sugar comprises a ribofuranose, wherein the ribofuranose may further be modified at the C_{5'}-, C_{2'}- or C_{3'}-position. In especially contemplated aspects, the modification in the C_{5'}-position of the ribofuranose comprises an amino group in place of a hydroxyl group, and/or OR and/or R group (as defined above) in place of or in addition to the 2'- and 3'-hydroxyl group. Further particularly preferred alternative sugars include
15 substituted or unsubstituted arabinose, or a carbocyclic moiety, wherein all of the contemplated sugars may be in D- or L-configuration.

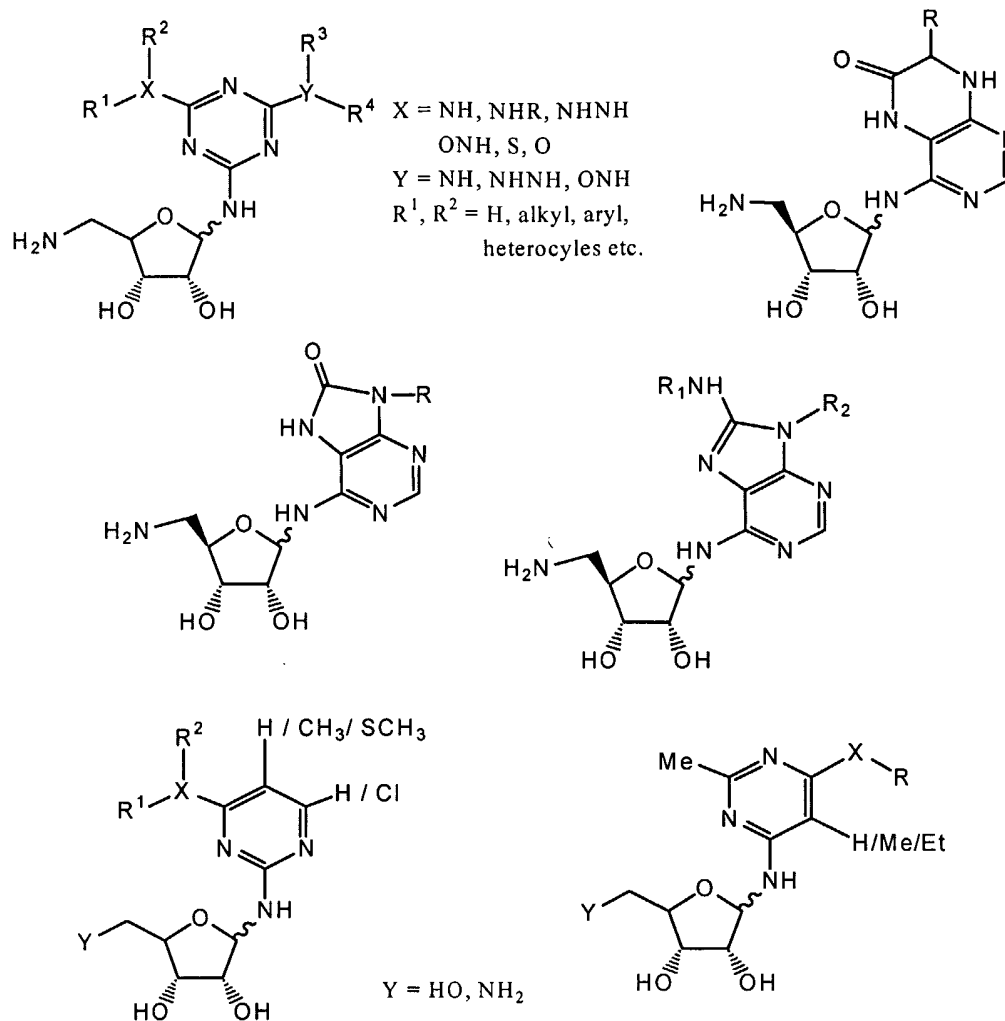
In still further especially preferred aspects of the inventive subject matter, C_{5'}-modified sugar portions are employed in contemplated libraries and compounds, and an exemplary synthetic route for a C_{5'}-amino sugar is shown in **Scheme 12** below.



Scheme 12

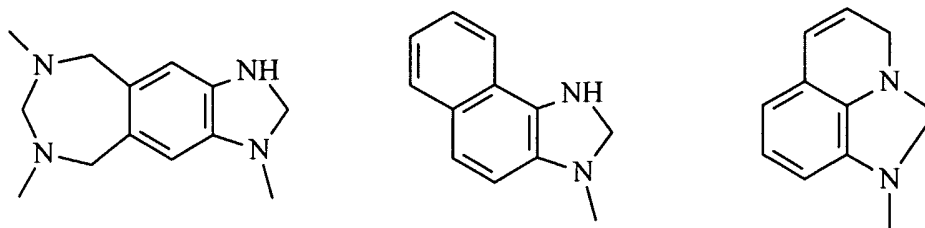
Here, a suitably protected 1'-azido-5'-iodo sugar is reacted with an amino trityl-modified solid phase, wherein the amino group of the solid phase replaces the leaving group on the sugar (*i.e.*, the iodine). Concurrent and/or subsequent reduction will then afford the corresponding 1'-amino sugar that is covalently bound to the solid phase via an NH group. In yet further reaction steps, the so prepared amino sugar can be coupled to a wide variety of heterocyclic bases, which may further be derivatized and/or combinatorialized to the corresponding C_{1'}-N-heterocyclic base nucleoside or nucleoside library (after optional deprotection and cleavage from the solid support).

Especially preferred heterocyclic bases, derivatization and/or combinatorialization include those described in the preceding schemes, wherein the same considerations as described above apply. It is particularly contemplated that in alternative aspects suitable sugars are not limited to ribofuranose sugars, and especially contemplated alternative sugars include substituted and unsubstituted arabinose, substituted and unsubstituted xylose, and substituted ribofuranose. Moreover, contemplated alternative sugars further include those described in the section entitled "Contemplated Sugars" above. Thus, exemplary contemplated nucleosides and/or nucleoside libraries (which may or may not include a solid phase on the C_{5'}-atom or other position in the sugar moiety) are considered with above contemplated amino-sugars as shown below.



Tricyclic Nucleoside Libraries

In a further aspect of the inventive subject matter, the inventors have discovered that nucleoside libraries may be produced, wherein the heterocyclic base is a tricyclic heterocyclic base that includes a benzimidazole moiety. The term "tricyclic" as used herein refers to any compound that includes a first, a second and a third ring, wherein the first ring is covalently bound to the second ring via at least two atoms in the first ring, and wherein the third ring is covalently bound to the first and/or second ring via at least two atoms in the first and/or second ring. Contemplated first, second, and third rings include at least 3 atoms, more typically 4-7 atoms, but may also contain more than 7 atoms, wherein contemplated atoms include C, N, O, S, Se, P, etc. Exemplary structures of tricyclic heterocyclic bases that include a benzimidazole moiety are outlined below.



While it is generally contemplated that tricyclic nucleosides may comprise various sugar portions, it is typically preferred that the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar may be in D- or L-configuration. Alternative contemplated sugar portions are described above in the section entitled "Contemplated Sugars".

Scheme 13 depicts an exemplary approach to generate various tricyclic nucleosides from the corresponding substituted benzimidazole nucleosides. Here, the carboxylic acid groups of benzimidazole-5,6-dicarboxylic acid are protected, and the resultant protected benzimidazole-5,6-dicarboxylic acid is then coupled to a suitable protected sugar (here: protected ribofuranose) to yield a protected benzimidazole nucleoside. The protected benzimidazole nucleoside may then be employed as starting material (27) for various tricyclic nucleoside libraries using various synthetic routes, and exemplary synthetic routes "A", "B", "C", and "D" are shown below.

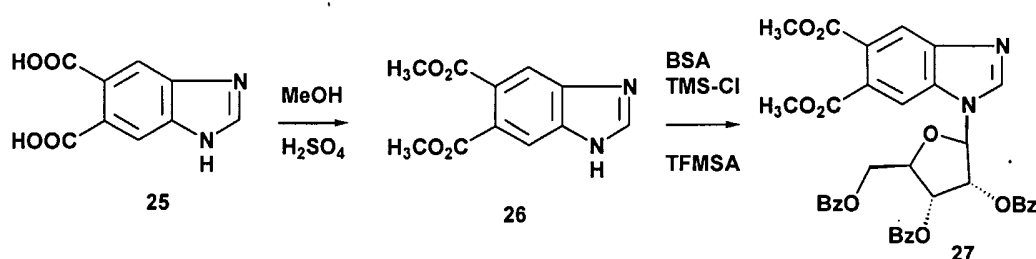
For example, a 1-β-D-Ribofuranosyl-(6,7-substituted)-6,7-dihydro-1H-imidazo[4,5-g]phthalazine-5,8-dione nucleoside library may be produced following a synthetic route as depicted in route "A" in Scheme 13. Here, the dicarboxylic compound is reacted with a substituted hydrazine to form a tricyclic nucleoside. Where a library of tricyclic nucleosides is desired, the starting material (*supra*) is partially deprotected and coupled to a solid phase, and aliquots of the resin are then reacted with a plurality of chemically distinct substituted hydrazines.

Alternatively, as shown in route "B", the starting material (*supra*) may be reacted with one or more primary or secondary amines (which may or may not be chemically distinct) to form a 1-β-D-Ribofuranosyl-1H-benzoimidazole-5,6-dicarboxylic Acid bis-substituted-amide (library). Libraries may advantageously be produced from intermediate 29 from route "A".

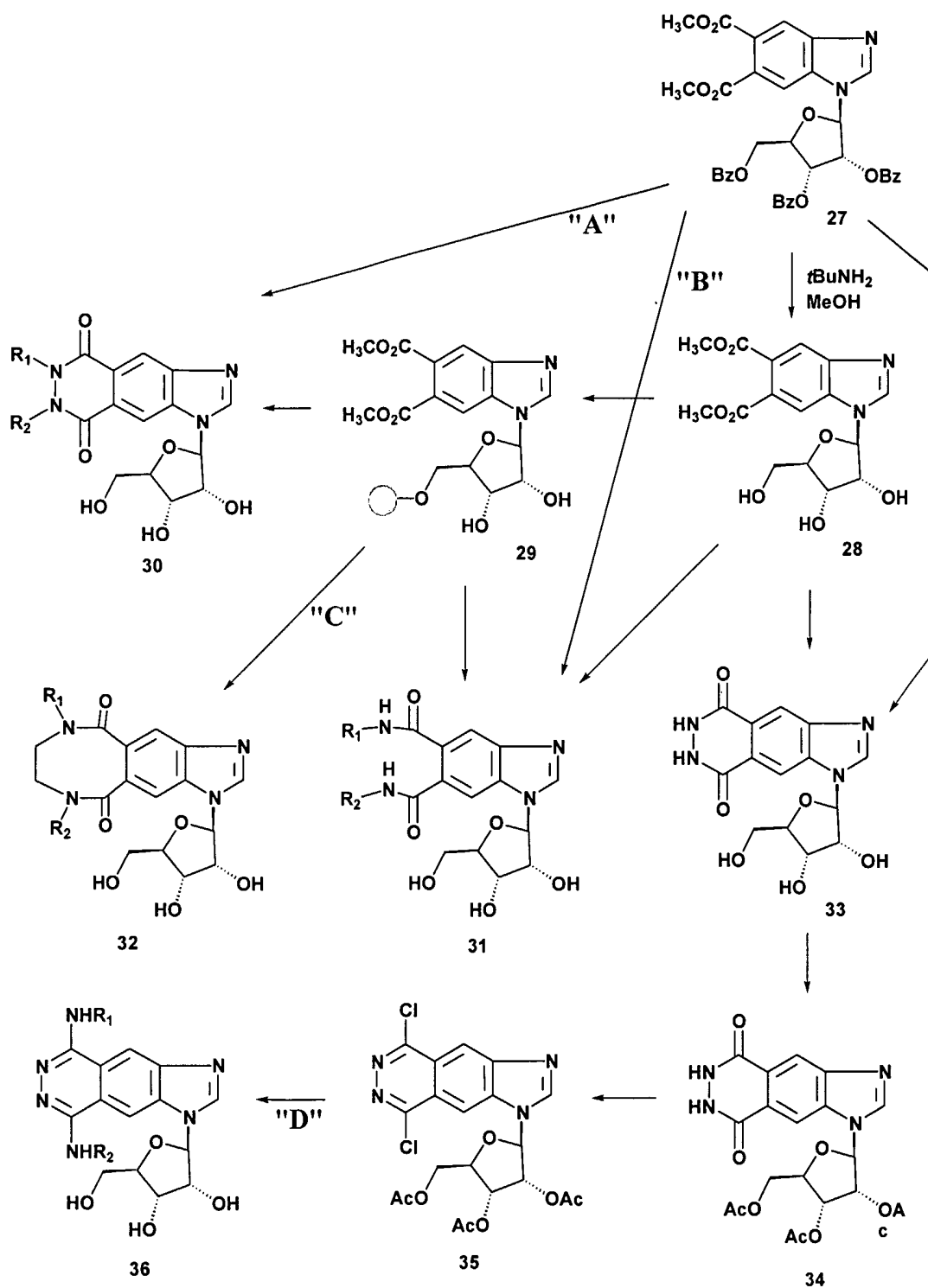
Furthermore, as depicted in route "C", the intermediate 29 may also be modified to produce a 'fat nucleoside' by reacting the intermediate with a substituted diamine to form a

substituted 6-β-D-Ribofuranosyl-4,6,11,14-tetraaza-tricyclo[7.6.0.0^{3,7}]pentadeca-1(9),2,4,7-tetraene-10,15-dione library.

In a still further contemplated route as shown in route "D", the starting material may be cyclized to a tricyclic dione nucleoside, which is subsequently protected at the sugar moiety. The so produced tricyclic dione nucleoside is then converted to the corresponding dichloro tricyclic nucleoside (1-(2',3',5'-Tri-*O*-acetyl-β-D-ribofuranosyl)-5,8-dichloro-6,7-dihydro-1H-imidazo[4,5-g]phthalazine) that serves as a substrate for one or more reactions with one or more primary or secondary amines to form a 5,8-disubstituted tricyclic nucleoside or 5,8-disubstituted tricyclic nucleoside library.



10



Scheme 13

While all of the above-described tricyclic nucleosides include a ribofuranose as the sugar portion, it should be appreciated that a particular chemical nature of the sugar is not limiting to the inventive subject matter. Consequently, it is contemplated that all known sugars and sugar analogs are deemed suitable for use in conjunction with the teachings presented herein (*supra*).

However, especially preferred sugars include ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and arabinose, wherein all of the contemplated sugars may be in D- or L-configuration.

Synthesis of contemplated tricyclic nucleosides will generally include a coupling reaction between a desired sugar and a heterocyclic base following protocols well known in the art (see *e.g.*, Experimental section below, or "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan; Gordon & Breach Science Pub; ISBN: 3718659212). With respect to the sugar portion it is contemplated that all, or almost all of the sugar portions are commercially available. Where a particular sugar is not commercially available, it is contemplated that such sugars may be synthesized using enzymatic (see *e.g.*, Enzymes in Carbohydrate Synthesis (Acs Symposium Series, No 466) by Mark D. Bednarski, Ethan S. Simon; Amer Chemical Society; ISBN: 0841220972) or non-enzymatic methods (Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization by Zoltan Gyorgydeak, Istvan F. Pelyvas, Istvan Pelyas, Zoltan Gyordydeak; Academic Pr; ISBN: 0125503601).

With respect to the tricyclic heterocyclic base it is contemplated that such bases are produced from appropriately substituted benzimidazole compounds, all or almost all of which are commercially available. Where a particular substituted benzimidazole compound is not commercially available, it should be appreciated that such compounds can be synthesized from commercially available precursors (*e.g.*, 5,6-dihalogenated benzimidazole) following procedures well known in the art without undue experimentation (see *e.g.*, Advanced Organic Chemistry: Structure and Mechanisms (Part A) by Francis A. Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306462435; or Advanced Organic Chemistry : Reactions and Synthesis (Part B) by Francis Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306434571, or Compendium of Organic Synthetic Methods, Volume 9, by Michael B. Smith, John Wiley & Sons; ISBN: 0471145793).

Formation of the tricyclic heterocyclic base from appropriately substituted benzimidazole compounds (*i.e.*, formation of the third ring) may also follow exemplary protocols as described in the experimental section (*infra*). Depending on the particular chemical nature of the substituent in the substituted benzimidazole compound, it should be appreciated that numerous diverse tricyclic nucleosides can be produced, and especially contemplated substituents include a

substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a hetero-cycle, halogens, nitriles, acroxylic acids, amines, amides, sulfhydryls, etc.

With respect to the substituted hydrazine in route "A", it is contemplated that all hydrazines are appropriate that have the general formula $RHN-NHR'$, wherein R and R' are independently selected from a hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted alkenyl, an unsubstituted alkenyl, a substituted alkynyl, an unsubstituted alkynyl, a substituted aryl, an unsubstituted aryl, a substituted alkaryl, an unsubstituted alkaryl, and a heterocycle. There are numerous such hydrazines commercially available, and it is contemplated that where a particular substituted hydrazine is not commercially available, such compounds can be synthesized from commercially available precursors following procedures well known in the art without undue experimentation (*supra*).

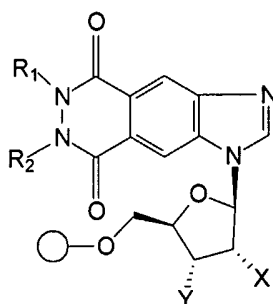
Similarly, with respect to the primary or secondary amines from route "B", it should be appreciated that all such compounds are suitable that have the general formula $R-NH_2$ or $RNHR'$, wherein R and R' are independently selected from a hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted alkenyl, an unsubstituted alkenyl, a substituted alkynyl, an unsubstituted alkynyl, a substituted aryl, an unsubstituted aryl, a substituted alkaryl, an unsubstituted alkaryl, and a heterocycle. Exemplary compounds are listed in the experimental section below. Moreover, many such amines are commercially available, and it is contemplated that where a particular amine is not commercially available, such compounds can be synthesized from commercially available precursors following procedures well known in the art without undue experimentation (*supra*).

Furthermore, with respect to contemplated substituted diamines in route "C", it should be recognized that various substituted diamines are appropriate, and especially preferred substituted diamines have a general formula $RHN-(CH_2)_n-NHR'$, with n between 1-4, and wherein R and R' are independently selected from a hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted alkenyl, an unsubstituted alkenyl, a substituted alkynyl, an unsubstituted alkynyl, a substituted aryl, an unsubstituted aryl, a substituted alkaryl, an unsubstituted alkaryl, and a heterocycle. Exemplary compounds are listed in the experimental section below. Moreover, many of such diamines are commercially available, and it is contemplated that where a particular diamine is not commercially available, such compounds can be synthesized from commercially

available precursors following procedures well known in the art without undue experimentation (*supra*).

With respect to the primary or secondary amines employed in route "D", it is contemplated that all primary and secondary amines are suitable, and exemplary suitable amines are listed in the experimental section below. Otherwise, the same considerations as the primary or secondary amines of route "B" apply.

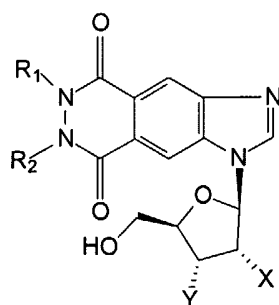
Thus, contemplated tricyclic nucleoside libraries may include at least two library compounds in which one of the at least two library compounds has a structure according to Formula 14 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 14 with a second set of substituents X, Y, R₁, and R₂



Formula 14

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; wherein ● comprises a solid phase; and wherein not all of the substituents X, Y, R₁, and R₂ in the first set are the same as the substituents X, Y, R₁, and R₂ in the second set.

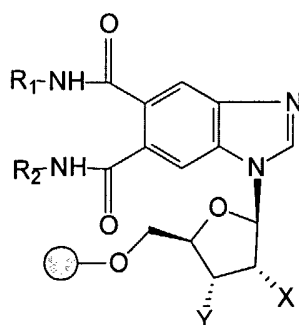
Thus, contemplated tricyclic nucleosides may have a structure according to Formula 15



Formula 15

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Further contemplated tricyclic nucleoside libraries may include at least two library compounds in which one of the at least two library compounds has a structure according to Formula 16 with a first set of substituents X, Y, R_1 , and R_2 , and wherein another one of the at least two library compounds has a structure according to Formula 16 with a second set of substituents X, Y, R_1 , and R_2



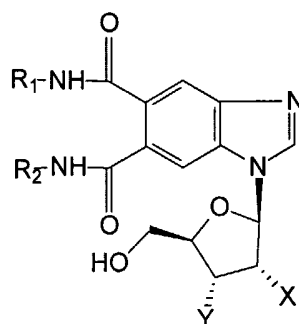
Formula 16

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

substituted alkynyl, an aryl, or a substituted aryl; wherein R_1 and R_2 together may form a ring; wherein $\bullet$ comprises a solid phase; and wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

Consequently, contemplated tricyclic nucleosides may have a structure according to

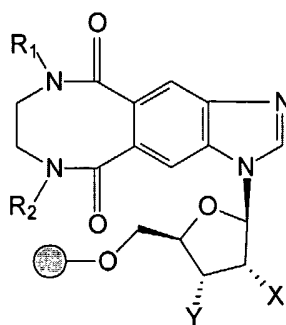
5 Formula 17



Formula 17

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein
 10 X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and wherein R_1 and R_2 together may form a ring.

Still further contemplated tricyclic nucleoside libraries may include at least two library
 15 compounds in which one of the at least two library compounds has a structure according to Formula 18 with a first set of substituents X, Y, R_1 , and R_2 , and wherein another one of the at least two library compounds has a structure according to Formula 18 with a second set of substituents X, Y, R_1 , and R_2

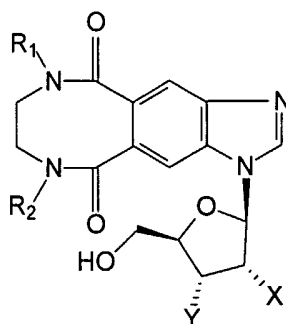


Formula 18

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; wherein $\bullet$ comprises a solid phase; and wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

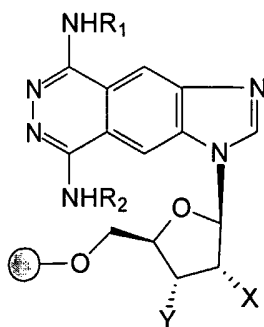
Consequently, contemplated tricyclic nucleosides may have a structure according to

Formula 19

**Formula 19**

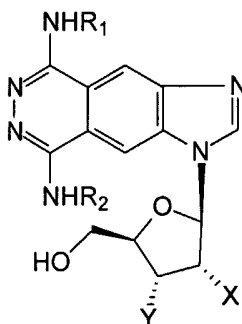
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Yet further contemplated tricyclic nucleoside libraries may include at least two library compounds in which one of the at least two library compounds has a structure according to Formula 20 with a first set of substituents X, Y, R_1 , and R_2 , and wherein another one of the at least two library compounds has a structure according to Formula 20 with a second set of substituents X, Y, R_1 , and R_2 .

**Formula 20**

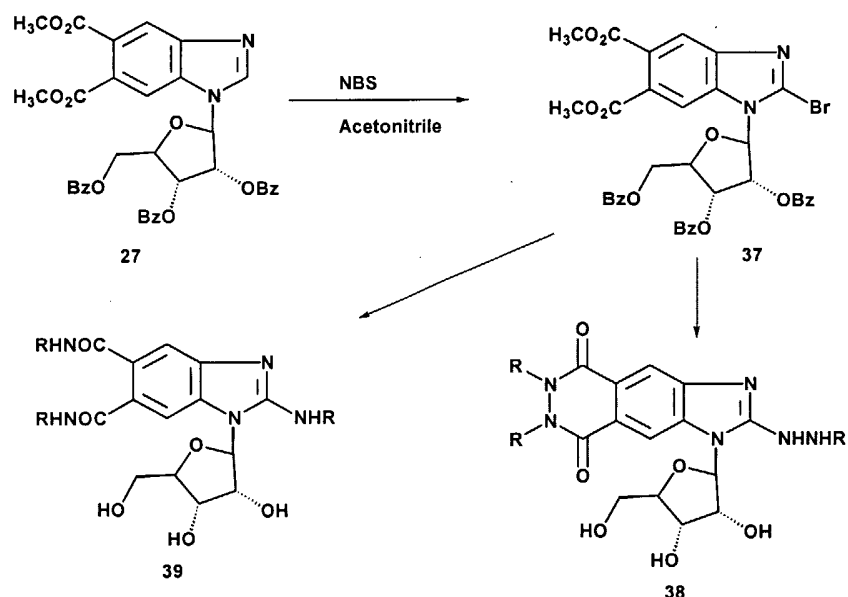
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; wherein $\bullet$ comprises a solid phase; and wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

Consequently, contemplated tricyclic nucleosides may have a structure according to Formula 21

**Formula 21**

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Alternatively, contemplated tricyclic nucleosides and libraries may be synthesized following a strategy as shown in **Scheme 14** below. Here, dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate is employed as the starting material (see compound 27 above), which is in a further step brominated in the 2-position of the heterocyclic base. In a still further reaction, a substituted (or a plurality of substituted) hydrazine(s) is reacted to form the corresponding 2-(substituted)hydrazine (substituted) tricyclic nucleoside 38. Alternatively, the brominated intermediate may be reacted with a (plurality of) primary and/or secondary amine(s) to yield a trisubstituted benzimidazole nucleoside (in which two substituents may form a ring). Of course, it should be recognized that the primary and/or secondary amines may be identical or chemically distinct.



Scheme 14

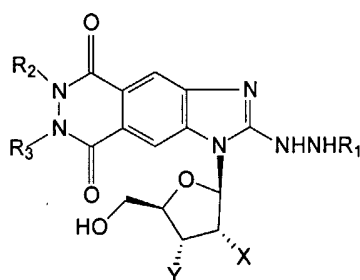
With respect to the sugar, and the heterocyclic base in such libraries and compounds, the same considerations as described above for tricyclic nucleoside libraries and compounds apply. Similarly, where the synthesis of such nucleosides and nucleoside libraries includes coupling of a sugar to a solid phase, suitable solid phases and coupling/decoupling are contemplated as described in the section entitled "Contemplated Solid Phases" above. A preferred position of a solid phase on contemplated sugars is the C_{5'}-position, however, other positions are also suitable. Furthermore, with respect to protection groups, the same considerations as described above apply.

Thus, with respect to the starting material it is generally preferred that the material is a nucleoside in which the heterocyclic base comprises a benzimidazole, and it is especially preferred that the starting material is dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)-benzimidazole-5,6-dicarboxylate. However, in alternative aspects, nucleosides with one or more substituents on a benzimidazole-containing heterocyclic base are also contemplated.

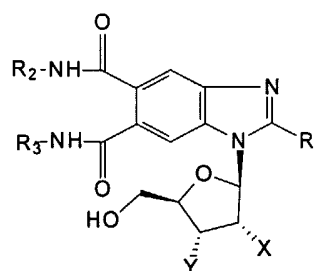
Where 2-substituted hydrazine tricyclic nucleosides are especially desired, it is contemplated that suitable reagents include hydrazine, which may include at least one substituent and will generally have a formula of $R'R''N-NR'R''$, wherein R' is typically hydrogen, or R'' , and wherein R'' is a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl. Exemplary hydrazines are listed in the experimental section below.

On the other hand, where synthesis of a trisubstituted benzimidazole nucleoside is especially preferred, it is contemplated that suitable reagents include primary and/or secondary amines to yield the desired trisubstituted benzimidazole nucleoside, and in particularly contemplated aspects, at least two of the substituents may form a ring. Contemplated primary and secondary amines will have the general formula $R-NR'H$, wherein R' may be hydrogen or R , wherein R may be is a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl. Exemplary hydrazines are listed in the experimental section below.

Therefore, contemplated compounds will have a structure according to Formula 22 or 23



Formula 22

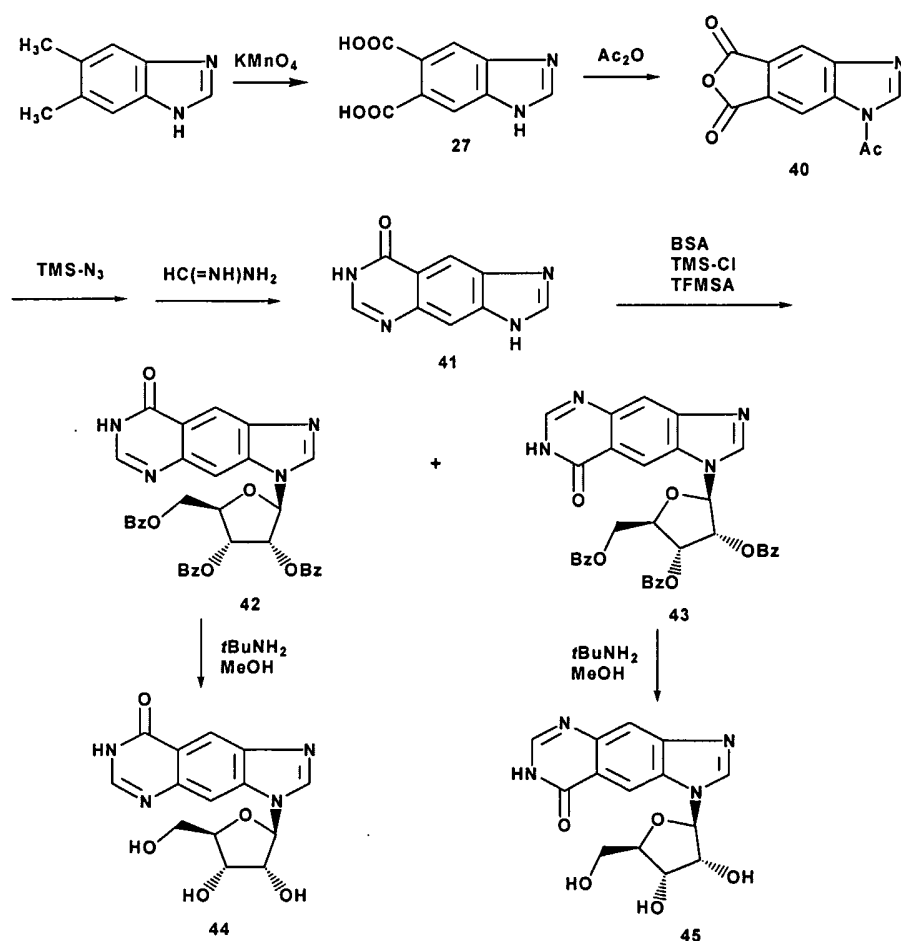


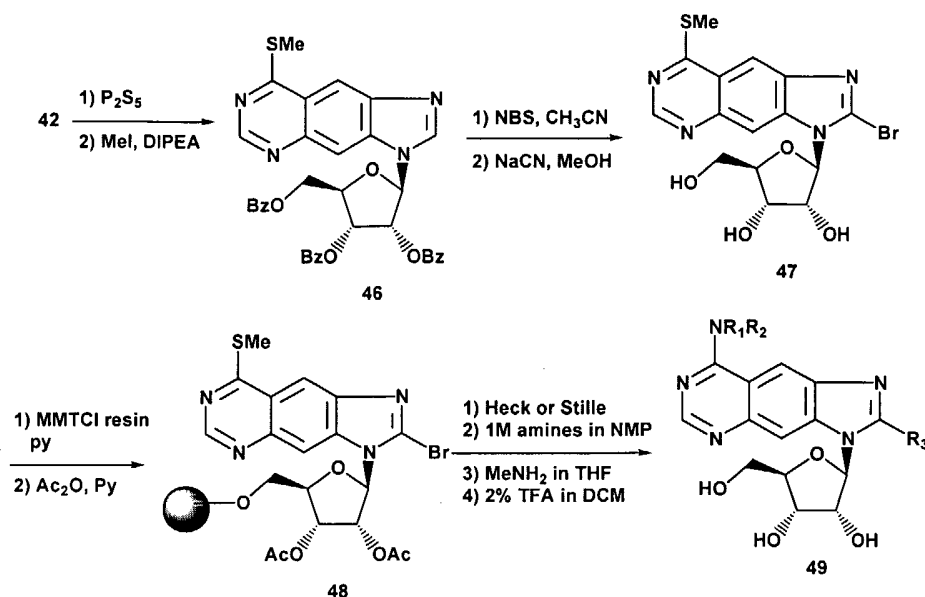
Formula 23

wherein R_1 , R_2 , and R_3 are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, and alkaryl; and wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a

substituted alkynyl, an aryl, or a substituted aryl. Furthermore, R_2 and R_3 in compounds of Formula 5B may form a ring (or may be a covalent bond between the nitrogen atoms).

In still further alternative aspects, tricyclic nucleoside libraries and compounds may be synthesized following a synthetic route as depicted in **Scheme 15** below. Here, 5,6-dimethyl benzimidazole is oxidized to the corresponding dicarboxylic acid, which is then further converted to the anhydride. Further reactions of the anhydride will yield the imidazo[4,5-g]quinazolin-8-(7H)-one as a heterocyclic base, which is subsequently coupled to a suitable protected sugar moiety to yield two isomeric forms (42/43) of a protected tricyclic nucleoside. Exchange of the keto group in the heterocyclic base with a leaving group (here: thiomethyl group) and bromination at the 2-position in the heterocyclic base with NBS will yield an intermediate that may then be coupled to a solid phase. The so generated resin is then subjected to a Heck or Stille reaction in the 2-position of the heterocyclic base with a suitable reagent, and further subjected to nucleophilic replacement of the $-SCH_3$ group with a second reagent (here: primary/secondary amine) to generate a library (and/or compounds) of tricyclic nucleosides, which may then be deprotected and cleaved of the solid support.



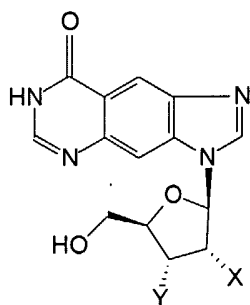
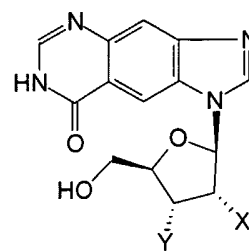


Scheme 15

With respect to the sugar, the protecting groups, and the solid phase (including suitable coupling/decoupling), it should be appreciated that the same considerations apply as described above and as described in the sections entitled "Contemplated Sugars" and "Contemplated Solid Phases". Furthermore, while a preferred position of a solid phase on contemplated sugars is the C_5' -position, other positions (*e.g.*, C_2' , or C_3') are also suitable.

Preferred starting materials are generally substituted benzimidazole moieties, and it is further preferred that such benzimidazole moieties have two vicinal carboxylic acid groups. However, numerous alternative benzimidazole moieties are also contemplated, and especially contemplated alternative benzimidazole moieties include those that include at least one substituent (functional group or hydrocarbon with or without heteroatom) on the 2-position. Coupling of contemplated heterocyclic bases may follow various protocols well known in the art (see *e.g.*, "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan; Gordon & Breach Science Pub; ISBN: 3718659212), or coupling of the heterocyclic base may be performed as described in the experimental section below.

Consequently, deprotection of the so produced nucleoside will yield tricyclic nucleosides according to Formulae 24 and 25

**Formula 24****Formula 25**

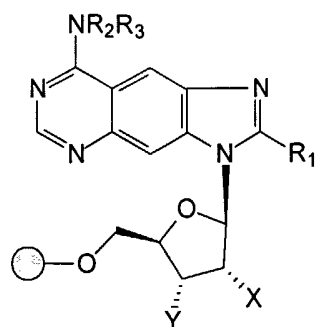
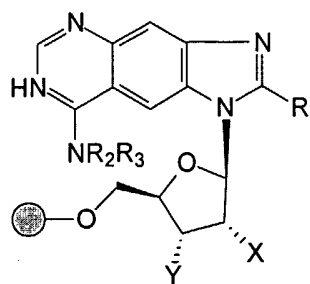
wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR,
SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl,
5 an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Alternatively, where the tricyclic nucleoside (*e.g.*, 42) is not deprotected, tricyclic
nucleoside libraries and compounds may be produced as shown above. With respect to the
reagent or reagents used in the Heck/Stille or Suzuki reaction, it is contemplated that all reagents
are suitable that will replace the halogen with concurrent formation of a carbon-carbon bond.

10 Particularly contemplated reagents are listed in the experimental section below.

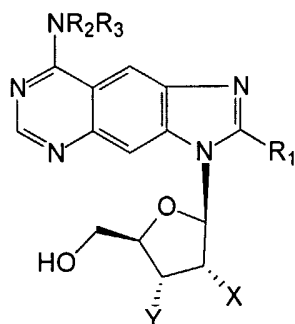
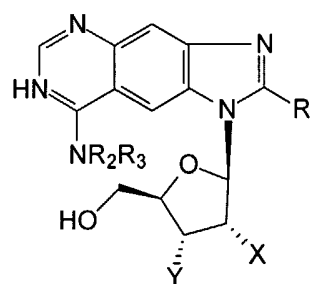
Similarly, it should be appreciated that with respect to the second reagent numerous
suitable reagents are contemplated. In fact, all reagents are considered suitable for use herein that
will replace the $-SCH_3$ group on the heterocyclic base with a substituent. However, particularly
preferred reagents include primary and secondary amines, and exemplary suitable reagents are
15 listed in the experimental section below. Furthermore, it should be recognized that the above
described reactions starting from nucleoside 42 may also be performed from nucleoside 43 to
yield the corresponding libraries and compounds.

Therefore, contemplated tricyclic nucleoside libraries may include at least two library
compounds in which one of the at least two library compounds has a structure according to
20 Formula 26 or 27 with a first set of substituents X, Y, R_1 , R_2 , and R_3 , and wherein another one of
the at least two library compounds has a structure according to Formula 26 or 27 with a second
set of substituents X, Y, R_1 , R_2 , and R_3

**Formula 26****Formula 27**

wherein R_1 , R_2 and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; wherein ● comprises a solid phase; and wherein not all of the substituents X , Y , R_1 , R_2 , and R_3 in the first set are the same as the substituents X , Y , R_1 , R_2 , and R_3 in the second set.

10. Consequently, contemplated tricyclic nucleosides may have a structure according to Formula 28 or 29

**Formula 28****Formula 29**

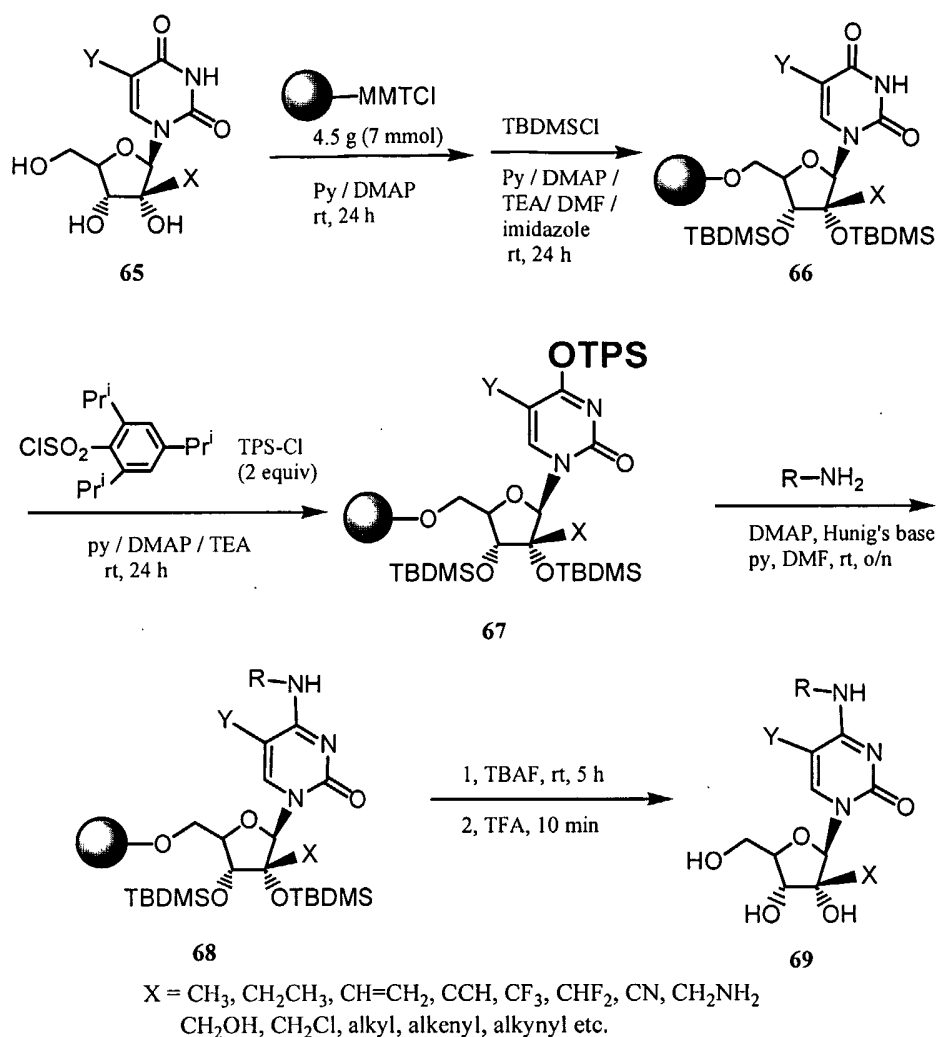
wherein R_1 , R_2 and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

2'-C-substituted Nucleosides

The inventors have still further discovered that nucleosides can be prepared in which the sugar portion in the nucleoside is modified with a substituent such that the 2'-position of the sugar is coupled to a carbon atom of the substituent of the 2'-position.

2'-Beta-C-Substituted-N⁴-Substituted Cytidine Library And Library Compounds

In a particularly preferred aspect of the inventive subject matter, a 2'-beta-C-substituted-N⁴-substituted cytidine library and corresponding library compounds are prepared following an exemplary synthetic strategy as depicted in **Scheme 16** below. Here, a 2'-beta-C-substituted-N⁴-substituted uridine is coupled to a solid phase and protected with suitable protecting groups (here: TBDMS). The so prepared resin is then reacted with TPS-Cl to replace a carbonyl oxygen on the heterocyclic base with a leaving group, which is in a still further reaction replaced by a nucleophilic reagent (preferably primary or secondary amine). Cleavage and deprotection of the nucleoside (or nucleoside library) will then afford the desired 2'-beta-C-substituted-N⁴-substituted cytidine library and corresponding library compounds.

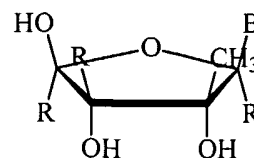
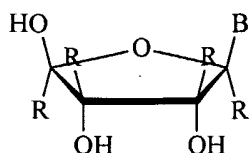


Solid-Phase Synthesis of 2'-beta-C-X- N4-Substituted Cytidine Library

Scheme 16

With respect to the 2'-beta-C-substituted ribofuranose, it should be appreciated that various alternative substituted sugars are also suitable, and particularly contemplated alternative substituted sugars include substituted ribofuranose and substituted arabinose in D- and L-configuration. An exemplary selection of suitable sugars includes one or more alkyl groups (or other substituents, including alkenyl, alkynyl, aryl, halogen, CF_3 , CHF_2 , CCl_3 , CHCl_2 , N_3 , NH_2 , etc.), which are covalently bound to sugar at the C'₁, C'₂, C'₃, C'₄, or C'₅ atom.

In such alkylated sugars, it is especially preferred that the sugar portion comprises a furanose (most preferably a D- or L-ribofuranose), and that at least one of the alkyl groups is a methyl group. Of course, it should be recognized that the alkyl group may or may not be substituted with one or more substituents. One exemplary class of preferred sugars is depicted below:



in which B is hydrogen, hydroxyl, or a heterocyclic base, R is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl (branched, linear, or cyclic), with R including between one and twenty carbon atoms.

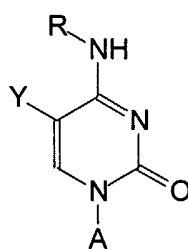
- 5 It should further be especially appreciated that the substituent in contemplated 2'-C-substituted sugars (or 3'-C-substituted sugars) may be oriented in the alpha or beta direction. Consequently, contemplated sugars and nucleosides may advantageously be coupled to a solid phase (preferably at the 5'-position).

- 10 With respect to heterocyclic base, it should be appreciated that the exact chemical nature is not limiting to the inventive subject matter. Therefore, alternative heterocyclic bases may include various modifications in the uridine portion, and particularly contemplated modifications include various substituents on the 4- and/or 5-position (Particularly preferred substituents include halogens, alkyl, CF₃, NH₂, and NO₂). Furthermore, all known heterocyclic bases that include at least one carbonyl (keto) oxygen are contemplated suitable for use in conjunction with
- 15 the teachings presented herein. However, especially contemplated nucleosides include naturally occurring and synthetic bases, including purine bases, pyrimidine bases, and triazole bases, wherein all of such bases may further comprise one or more substituents. Exemplary suitable heterocyclic bases are depicted above in the section entitled "Contemplated Heterocyclic Bases".

- 20 With respect to suitable nucleophilic reagents it should be recognized that numerous reagents and compounds are suitable, and especially contemplated nucleophilic substrates include those having a nitrogen atom, and especially primary and/or secondary amines, and those having an oxygen or sulfur atom (*e.g.*, various alcohols and/or thiols). Moreover, suitable nucleophilic substrates also include reagents that form a C-C bond (*e.g.*, Grignard reagents, etc.). Exemplary suitable nucleophilic substrates will have the general formula NR₁R₂, R₁OH, or
- 25 R₁SH, wherein R₁ and R₂ are independently selected from the group consisting of a hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, and a substituted or unsubstituted heterocycle.

With respect to the protecting groups, the solid phase, and the coupling of the nucleoside to the solid phase, the same considerations as described above apply.

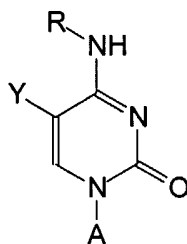
Consequently, a nucleoside library with at least two library compounds is contemplated in which one of the at least two library compounds has a structure according to Formula 30 with a first set of substituents A, Y, and R, and wherein another one of the at least two library compounds has a structure according to Formula 30 with a second set of substituents A, Y, and R



Formula 30

wherein A is a 2'-beta-C-substituted sugar (in D- or L-configuration) that is coupled to a solid phase, wherein the sugar is optionally protected, and wherein the substituent is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; Y is R or halogen, CF₃, NO₂, NH₃; and wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

Thus, contemplated compounds may have a structure according to Formula 31



Formula 31

wherein A is a 2'-beta-C-substituted sugar (in D- or L-configuration), wherein the substituent is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and Y is R or halogen, CF₃, NO₂, NH₃.

Uses of contemplated libraries and compounds

In one preferred aspect, it is contemplated that the libraries according to the inventive subject matter may be used to facilitate structure-activity analysis of nucleoside-type compounds. For example, where it is known that an enzyme employs a nucleoside as a substrate/co-substrate, and where an inhibitor or alternative substrate for the enzyme is desired, contemplated libraries will provide a researcher with rapid information on the impact of a particular substituent in a particular position of the library compound.

In a further example, it is contemplated that libraries according to the inventive subject matter will exhibit a significant source of revenue for a seller since in most cases purchase of a library of nucleosides, nucleoside analogs, nucleotides, and/or nucleotide analogs will be less costly to a user than individual synthesis of these compounds.

In yet another example, the library compounds may serve as *in vitro* and/or *in vivo* substrates or inhibitors with particularly desirable physicochemical and/or biological properties. Among other uses, the library compounds may act as inhibitors of DNA and/or RNA for various nucleoside-using enzymes, and especially polymerases, reverse transcriptases, and ligases. Therefore, contemplated nucleosides will exhibit particular usefulness as an *in vitro* and/or *in vivo* antiviral agent, antineoplastic agent, or immunomodulatory agent. Still further, it is contemplated that nucleosides according to the inventive subject matter may be incorporated into oligo- or polynucleotides, which will then exhibit altered hybridization characteristics with single or double stranded DNA *in vitro* and *in vivo*.

Particularly contemplated antiviral activities include at least partial reduction of viral titers of respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, Hanta virus (hemorrhagic fever),

human papilloma virus (HPV), and measles virus. Especially contemplated immunomodulatory activity includes at least partial reduction of clinical symptoms and signs in arthritis, psoriasis, inflammatory bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma, but also modulation of some portion of a mammal's immune system, and especially modulation of cytokine profiles of Type 1 and Type 2. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2, suppression of Type 1 and stimulation of Type 2, or suppression of Type 2 and stimulation of Type 1.

Where contemplated nucleosides are administered in a pharmacological composition, it is contemplated that suitable nucleosides can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated nucleosides can be administered orally as pharmacologically acceptable salts, or intravenously in physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated nucleosides may be modified to render them more soluble in water or another vehicle, which for example, may be easily accomplished by minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

In certain pharmaceutical dosage forms, prodrug forms of contemplated nucleosides may be formed for various purposes, including reduction of toxicity, increasing the organ- or target cell specificity, etc. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a target site within the host organism or patient (see above). One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a targeted site within the host organism or patient to maximize the intended effect of the compound.

In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of various diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Among other contemplated agents for combination with contemplated compounds, it is especially preferred that such agents include interferon, and particularly IFN-alpha or IFN-beta (or fragments thereof).

Examples

Experimental Procedures for Exemplary Libraries and Compounds

Triazine Nucleoside Analog Libraries (Scheme 1)

2',3'-O-Bis(t-butyldimethylsilyl)-5'-O-(monomethoxytrityl-polystyrene resin)- β -D-ribofuranosyl-1-azide (3). To a suspension of polystyrene monomethoxytrityl chloride resin (1.0 g, 1.73 mmol/g) in 4 mL of pyridine was added a solution of β -D-ribofuranosyl-1-azide (2) (0.60 g, 3.46 mmol) in 4 mL of pyridine, followed by the addition of 4-N,N-dimethylaminopyridine (DMAP) (0.122 g, 1.0 mmol). The reaction mixture was shaken well at room temperature for 48 h. The resin was filtered and washed sequentially with CH_2Cl_2 (3 X 25 mL), a mixture of CH_2Cl_2 -MeOH-N,N-diisopropylethylamine (8.5:1:0.5, 2 X 20 mL). The resultant resin was then dried under vacuum over KOH for 16 hours. The loading efficiency was 85% (1.46 mmol/g), calculated based on the starting material 2 recovered and the specified loading capacity of the resin. FT-IR (KBr) 2107.3 cm^{-1} (N_3 group). A small portion (50 mg) of the resin was treated with a 1.5% solution of TFA in CH_2Cl_2 for 60 seconds, filtered, and washed with CH_2Cl_2 (2 X 2 mL). The combined filtrate was concentrated providing the starting azido compound 2, which was confirmed by ^1H NMR (CD_3OD) δ 5.19 (s, 1H), 4.04 (dt, 1H, $J = 6.6, 4.8\text{ Hz}$), 3.97 (q, 1H), 3.81 (d, 1H, $J = 5.0\text{ Hz}$), 3.76 (dd, 1H, $J = 12.0, 3.0\text{ Hz}$), 3.56 (dd, 1H, $J = 12.0, 5.7\text{ Hz}$); MS (ESI) m/z 176 (M) $^+$.

To a suspension of the resultant resin (1.2 g), 5'-O-(monomethoxytrityl-polystyrene resin)- β -D-ribofuranosyl-1-azide, in 10 mL of anhydrous DMF were added excess amounts of t-butyldimethylsilyl chloride (TBDMS-Cl) (1.29 g, 8.65 mmol) and imidazole (1.17 g, 17.3 mmol). The reaction mixture was shaken well at room temperature for 16 h. The resin was
 5 filtered and washed sequentially with DMF (3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resin was then dried under vacuum over KOH for 16 h. FT-IR (KBr) 2109.9 cm⁻¹ (N₃ group). A small portion (0.10 g) of resin 3 was treated with a 1.5% solution of TFA in CH₂Cl₂ for 60 seconds, filtered, and washed with CH₂Cl₂ (2 X 2 mL). The combined filtrate was concentrated providing 2',3'-O-bis(t-butyldimethylsilyl)- β -D-ribofuranosyl-1-azide (30 mg),
 10 which was confirmed by ¹H NMR (CDCl₃) δ 5.13 (d, 1H, J = 1.2 Hz), 4.17 (dd, 1H, J = 7.2, 4.0 Hz), 4.05 (q, 1H), 3.88 (dd, 1H, J = 12.3, 2.7 Hz), 3.83 (dd, 1H, J = 3.9, 1.5 Hz), 3.60 (dd, 1H, J = 12.3, 3.6 Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.098 (s, 3H), 0.091 (s, 3H), 0.08 (s, 3H).

1'-(R, S)-Amino-2',3'-O-bis-(t-butyldimethylsilyl)-5'-O-(monomethoxytrityl-polystyrene resin)- β -D-ribofuranose 4. To a suspension of the azido resin 3 (1.1 g) in a mixture of THF and water (9:1, 7.5 mL) was added a solution of trimethylphosphine (PMe₃) in THF (2.5 mL, 1.0 M). The reaction mixture was shaken well at room temperature for 6 h. The resultant resin was filtered and then washed sequentially with THF-H₂O (1:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resin was then dried over KOH under
 20 vacuum for 16 h. FT-IR (KBr) 2109.9 cm⁻¹ (N₃ group) peak disappeared (see Figure 2).

N^{1'}-[(4,6-Dichloro)triazin-2-yl]-1'-(R, S)-Amino-2',3'-O-bis-(t-butyldimethylsilyl)-5'-O-(monomethoxytrityl-polystyrene resin)- β -D-ribofuranose 5. The amino resin 4 (1.0 g) was suspended in a solution of N,N-diisopropylethylamine in CH₂Cl₂ (5 mL, 20% v/v) and cooled to 0–5 °C. A solution of cyanuric chloride in CH₂Cl₂ (5 mL, 1.0 M) was added. The
 25 resultant suspension was shaken well at room temperature for 1 h and filtered using a sintered funnel. The resin was washed with CH₂Cl₂ (3 X 25 mL) and dried over KOH under vacuum for 16 h. A small portion (0.10 g) of resin 5 was treated with 1.5 mL of TFA solution in CH₂Cl₂ (1.5%) for 60 seconds, filtered, and washed with CH₂Cl₂ (2 X 2 mL). The combined filtrate was concentrated providing 30 mg of N^{1'}-[(4,6-dichloro)triazin-2-yl]-1'-(R, S)-amino-2',3'-O-bis-(t-butyldimethylsilyl)- β -D-ribofuranose, which was confirmed by ¹H NMR (CDCl₃) δ 7.32 (d, 0.6H, J = 8.7 Hz, ex. D₂O), 6.87 (d, 0.4H, J = 6.6 Hz, ex. D₂O), 5.84 (dd, 0.55H, J = 5.4, 8.7

Hz), 5.52 (d, 0.45H, J = 6.9 Hz), 4.26 (m, 1H), 4.09 (m, 1H), 3.93-3.60 (m, 3H), 3.83 (dd, 1H, J = 1.5, 3.9 Hz), 0.94, 0.92, 0.89, 0.87 (4s, 18H), 0.10-0.06 (ms, 12H).

N^{1'}-[(4-N-Alkylamino-6-N,N-dialkylamino)triazin-2-yl]-1'-(R, S)-amino-2',3'-O-bis-(t-butyldimethylsilyl)-5'-O-(monomethoxytrityl-polystyrene resin)-β-D-ribofuranose 6. To a suspension of resin 5 (50 mg) in a solution of N,N-diisopropylethylamine in NMP (0.75 mL, 20% v/v) was added a solution of a primary amine in NMP (0.75 mL, 1 M). The reaction mixture was shaken well at room temperature for 2 h. The resin was then washed sequentially with NMP (3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). A suspension of the resultant resin (0.05 g) in a solution of N,N-diisopropylethylamine in NMP (0.75 mL, 20% v/v) was treated with a solution of a secondary amine in NMP (0.75 mL, 1 M). The reaction mixture was shaken well at 80 °C for 6 h. The resin was then washed with NMP (3 X 10 mL) and CH₂Cl₂ (3 X 10 mL). The fully protected and substituted resin was obtained after being dried over KOH under vacuum for 16 h.

N^{1'}-[(4-N-Alkyl-amino-6-N,N-dialkylamino)triazin-2-yl]-1'-(R, S)-amino-β-D-ribofuranose 7. Resin 6 (0.05 g) was suspended in a solution of tetrabutylammonium fluoride in THF (1.5 mL, 1 M) and shaken well at room temperature for 16 h. The resin was filtered and treated with a DMF-AcOH-H₂O mixture (8:1:1, 1.5 mL) for 10 minutes to remove the excess amount of tetrabutylammonium salt. The resin was filtered and washed sequentially with DMF-H₂O mixture (9:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 20 mL). After being dried over KOH under vacuum for 16 h, the resultant resin (50 mg) was suspended in 1.5 mL of TFA solution in CH₂Cl₂ (1.5%) and shaken well at room temperature for 60 seconds. The resin was filtered and further washed with MeOH (2 X 1 mL). The combined filtrate was concentrated under high vacuum to provide compound 7 as the corresponding trifluoroacetate salt.

Synthesis of Exocyclic Nucleoside Libraries L1–12 (Scheme 2)

First amine substitution: Approximately 70 mg of starting dichloro triazine resin 5 was dispensed in each of the 96 reaction wells using a dispensing spatula and funnel. A pre-cooled solution (–20 °C) of N,N-diisopropylethylamine in NMP (20% v/v, 0.75 mL) was added to each well with a repetitive pipette, followed by the addition of 12 primary amines (building block set A) (0.75 mL, 1.0 M in NMP, pre-cooled to –20° C) in the respective columns. The reaction block was covered and shaken at room temperature for 2 h. The reaction mixture was filtered,

and the resin was washed sequentially with DMF (X 3), a mixture of MeOH and CH₂Cl₂ (X 3), and finally with CH₂Cl₂ (X 2), and then dried under nitrogen.

Second amine substitution: To the resultant mono-chloro triazine resin was added a solution of N,N-diisopropylethylamine in NMP (20%, 0.75 mL), followed by the addition of 8
5 secondary amines (building block set B) in NMP (0.75 mL, 1.0 M) in the respective rows. The reaction block was covered and shaken at 80 °C for 5 h. The reaction mixtures were filtered, and the resins were washed sequentially with DMF (X 3), a mixture of MeOH and CH₂Cl₂ (X 3), and finally with CH₂Cl₂ (X 2), and then dried under nitrogen.

Deprotection: A solution of tetrabutylammonium fluoride (TBAF) in THF (1.5 mL, 1.0
10 M) was added to the resin. The reaction block was shaken at room temperature overnight. After being emptied and washed with DMF, the resins were washed with 10% acetic acid in DMF three times to remove the excess amount of tetrabutylammonium salt, then washed as usual with DMF (X 3), a mixture of MeOH and CH₂Cl₂ (X 3), and finally with CH₂Cl₂ (X 2), and then dried under nitrogen.

Cleavage from the resin: A solution of trifluoroacetic acid in CH₂Cl₂ (1.5%) was added
15 to the resin in each well, and then the reaction block was shaken for 2 min. The 96 reaction wells were filtered into the 96 pre-labeled and pre-weighed vials in the 96-well format. The resins were washed with 1 mL of MeOH and filtered into the corresponding 96 wells. Toluene (0.25 mL) was added to each well, and the resultant solutions were concentrated under vacuum to
20 dryness using Savant SpeedVac with vacuum evaporator.

Synthesis of 5'-Amino Exocyclic Nucleoside Libraries - I (Scheme 3)

Synthesis of Libraries **57**. The iodo compound **21** was treated with 50% TFA in dichloromethane for 5 hours. The reaction mixture was worked up with water and the organic phase was concentrated. The residue was purified by chromatography on a silica gel column to
25 provide pure azido compound **50**. The compound **50** (1.5 equiv) was treated with 1 equiv of MMT-amino resin in a mixture of DMAP, pyridine and DMF for 24 hours. The resin was filtered and thoroughly washed with DMF, pyridine, and methylene chloride. The resultant resin **51** was converted to resins **52**, **53**, and **54** utilizing the same procedures as described above for resin **2**, **3**, **4**, and **5**, respectively (Scheme1). Resin **54** was converted to resins **55** and **56**, further

deprotected and cleaved from resin to provide final libraries **57** by the same procedures as described above for the preparation of resins **6** and **7**, as well as final libraries **8**.

Synthesis of 2'-modified Exocyclic Nucleoside Libraries L1–12 (Scheme 4)

Synthesis of Libraries **64**. Compounds **58** (X = CH₃, CH=CH₂, CF₃, ethynyl) were prepared based on literature procedures (R. E. Harry-O'Kuru, J. M. Smith, M. S. Wolfe, J. Org. Chem. 1997, 62, 1754-1759; R. E. Harry-O'Kuru, E. A. Kryjak, M. S. Wolfe, Nucleosides Nucleotides 1997, 16 (7-9), 1457-1460; M. S. Wolfe, R. E. Harry-O'Kuru, Tetrahedron Letters, 1995, 36, 7611-7614; N. S. Li, X. Q. Tang, J. A. Piccirilli, organic Letters, 2001, 3, 1025-1028). Other 2'-substituted ribose derivatives are synthesized similarly. Compound **58** was treated with SnCl₄ (0.05 equiv) and NaN₃ in DMF followed by NaCN in MeOH to provide the azido compound **59**. Compound **59** was attached on the MMT-Cl resin and then converted to resins **61**, **62**, **63** and further deprotected / cleaved to final libraries **64** utilizing the same procedures as described above for the preparation of resins **3**, **5**, **6**, and **7** as well as libraries **6** (see Schemes 1 and 2).

Clitocine Mimic Library - I (Scheme 5)

The synthesis for Scheme 5 is substantially similar to synthesis of Scheme 6 below. However, instead of secondary amines, various primary amines, alcohols, and thiols were employed.

Clitocine Mimic Library - II (Scheme 6)

N''-[(5-Nitro-6-chloro)pyrimidin-4-yl]-1'-(R, S)-amino-2',3'-O-bis-(*t*-butyldimethylsilyl)-5'-O-(monomethoxytrityl-polystyrene resin)-β-D-ribofuranose 9. Resin **4** (1.0 g), prepared as described above, was suspended in a solution of *N,N*-diisopropylethylamine in NMP (8 mL, 20% v/v) and treated with 4,6-dichloro-5-nitropyrimidine (1.0 g, 5.18 mmol). The reaction mixture was shaken well at room temperature for 4 h. The resultant brown suspension was filtered, and the resin was washed with NMP (3 X 25 mL) and CH₂Cl₂ (3 X 25 mL). After being dried under vacuum over P₂O₅ for 16 h, resin **9** was obtained.

N''-[(5-Nitro-*N*-alkyl or *N,N*-dialkyl or *N*-cycloalkyl)pyrimidin-4-yl]-1'-(R, S)-amino-β-D-ribofuranose 11. To a suspension of resin **9** (0.05 g) in a solution of *N,N*-diisopropylethylamine in NMP (0.75 mL, 20% v/v) was added a solution of isopropylamine in

NMP (0.75 mL, 1 M). The suspension was shaken well at room temperature for 16 h. The resin was filtered and washed sequentially with MeOH (3 X 10 mL), CH₂Cl₂ (3 X 10 mL), an NMP-H₂O mixture (3:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resultant resin, 10 (50 mg) was suspended in a solution of tetrabutylammonium fluoride (1.5 mL, 1 M) in THF and shaken well at room temperature for 16 h. The resin was filtered and washed sequentially with THF (3 X 10 mL), MeOH (3 X 10 mL), an NMP-H₂O mixture (3:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resin was treated with a mixture of DMF-H₂O-AcOH (8:1:1, 2 mL) and shaken well for 15 minutes to remove the excess amount of tetrabutylammonium salt. The resin was filtered and washed with MeOH (3 X 10 mL), an NMP-H₂O mixture (3:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resultant clean resin was treated with a solution of TFA in CH₂Cl₂ (1.5 mL, 1.5%) for 60 seconds. The resin was filtered and washed with MeOH (2 X 2.5 mL). The combined filtrate was concentrated to provide product 11 (15-20 mg) as the corresponding trifluoroacetate salt. ¹H NMR (CD₃OD) δ 8.09, 8.07 (ss, 1H), 6.10 (d, 0.55H, *J* = 4.8 Hz), 5.92 (d, 0.45H, *J* = 3 Hz), 4.24 (m, 1H), 4.15 (m, 0.55H), 4.09 (m, 0.45H), 3.98 (m, 1H), 3.68 (m, 2H), 1.30 (dd, 6H, *J* = 2.7, 6.6Hz).

Substitution: Approximately 70 mg of starting resin **9** was dispensed in each of the 96 reaction wells using a dispensing spatula and funnel. A solution of *N,N*-diisopropylethylamine in NMP (20%, 0.75 mL) was added to each well, followed by the addition of 82 amines (building block set C) in NMP (0.75 mL, 1.0 M). The reaction block was covered and shaken at room temperature for 16 h. The reaction mixtures were filtered, and the resins were washed sequentially with DMF (X 3), a mixture of MeOH and CH₂Cl₂ (X 3), and finally with CH₂Cl₂ (X 2), and then dried under nitrogen.

Deprotection: A solution of tetrabutylammonium fluoride in THF (1.5 mL, 1.0 M) was added to the resin, and the reaction block was shaken at room temperature overnight. The resins were filtered and washed with DMF. A mixture of DMF-AcOH-H₂O (7:2:1, 1.5 mL) was added to the resins, which were shaken at room temperature for 1 h to remove the excess amount of tetrabutylammonium salt. The resins were filtered and washed sequentially with DMF (X3), a mixture of MeOH and CH₂Cl₂ (X 3), and finally with CH₂Cl₂ (X 2), and then dried under nitrogen.

Cleavage from the resin: A solution of trifluoroacetic acid in CH₂Cl₂ (1.5%) was added to the resin in each well, and the reaction block was shaken for 2 minutes. The 96 reaction wells

were filtered into the 96 pre-labeled and pre-weighed vials in the 96-well format. The resins were washed with 1 mL of MeOH and filtered into the corresponding 96 wells. Toluene (0.25 mL) was added to each well, and the resultant solutions were concentrated under vacuum using Savant SpeedVac with vacuum evaporator to dryness.

5 *5'-Amino Clitocine Mimic Library - I (Scheme 7)*

2',3'-Isopropylidene-1'-azido-D-ribofuranose (12). To a solution of azido-sugar 2 (40.0 g, 228.5 mmol) in 400 mL of acetone was added 2 mL of concentrated H₂SO₄. The reaction mixture was stirred at room temperature for 6 h and neutralized with a saturated sodium bicarbonate solution (100 mL). The volatile was evaporated, and the residue was extracted with
10 CH₂Cl₂ (600 mL). The organic layer was dried over anhydrous MgSO₄ and concentrated to give product 12; ¹H NMR (CDCl₃) δ 5.54 (s, 1H), 4.77 (d, 1H, *J* = 6.0 Hz), 4.53 (d, 1H, *J* = 6.0 Hz), 4.41 (t, 1H, *J* = 3.6, 3.9 Hz), 3.74 (m, 2H), 2.29 (bs, 1H, D₂O ex), 1.45 (s, 3H), 1.32 (s, 3H).

5'-Bromo-5'-deoxy-2',3'-isopropylidene-1'-azido-D-ribofuranose (13). To a solution of compound 12 (32.0 g, 148.8 mmol) in 340 mL of CH₂Cl₂ was slowly added Ph₃PBr₂ (62.8 g,
15 148.8 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was allowed to warm to room temperature under stirring and continued to be stirred for 16 h. The reaction mixture was quenched with a saturated and cold sodium bicarbonate solution (100 mL) and diluted with CH₂Cl₂ (300 mL). The organic layer was separated and washed with water (300 mL) and brine (300 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated. The resultant
20 residue was purified by flash chromatography on a silica gel column providing 34.0 g of product 13 (82.2%); ¹H NMR (CDCl₃) δ 5.58 (s, 1H), 4.79 (d, 1H, *J* = 6.0 Hz), 4.50 (d, 1H, *J* = 6.0 Hz), 4.48 (ddd, 1H, *J* = 10.2, 5.4, 1.1 Hz), 3.45 (ddt, 2H, *J* = 10.2, 5.4, 1.1 Hz), 1.49 (s, 3H), 1.32 (s, 3H).

5'-(*N*-Phthalimido)-5'-deoxy-2',3'-isopropylidene-1'-azido-D-ribofuranose (14). To
25 a solution of compound 13 (34.0 g, 122.3 mmol) in 250 mL of NMP was added potassium phthalimide (45.25 g, 244.6 mmol). The resultant reaction mixture was heated at 80 °C for 16 h and then diluted with 500 mL of ice water. The suspension was stirred at room temperature for 3 h. The solid was filtered and thoroughly washed with water (3 X 500 mL) to give 34.0 g of
30 compound 14 (80.8%); ¹H NMR (CDCl₃) δ 7.87 (ddd, 2H, *J* = 39.9, 5.4, 3.3 Hz), 7.74 (ddd, 2H, *J* = 39.9, 5.4, 3.0 Hz), 5.57 (s, 1H), 4.78 (d, 1H, *J* = 6.0 Hz), 4.57 (t, 2H, *J* = 5.9, 6.9 Hz), 3.92 (m, 2H), 1.44 (s, 3H), 1.28 (s, 3H).

5'-Amino-5'-deoxy-2',3'-isopropylidene-1'-azido-D-ribofuranose (15). To a suspension of compound 14 (5.8 g, 16.86 mmol) in 100 mL of methanol was added anhydrous hydrazine (1.04 mL, 33.72 mmol). The reaction mixture was stirred at room temperature for 16 h. The precipitate was filtered and washed with methanol (3 X 25 mL). The combined filtrate
5 was concentrated, and the residue was triturated with CH₂Cl₂ (100 mL). The filtrate was concentrated, and the residue was purified by flash chromatography on a silica gel column, which was pretreated with triethylamine, to provide pure 3.0 g of product 15 (83.1%). ¹H NMR (CD₃OD) δ 5.55 (s, 1H), 4.67 (dd, 1H, *J* = 0.9, 6.0 Hz), 4.50 (d, 1H, *J* = 6.0 Hz), 4.2 (t, 1H, *J* = 7.8 Hz), 2.77 (d, 2H, *J* = 7.8 Hz), 1.44 (s, 3H), 1.29 (s, 3H).

2',3'-Isopropylidene-5'-N-(monomethoxytrityl-polystyrene resin)-5'-amino-5'-deoxy-β-D-ribofuranosyl-1-azide 16. To a suspension of polystyrene monomethoxytrityl chloride resin (1.0 g, 1.73 mmol/g) in pyridine (4 mL) was added a solution of compound 15 (0.4 g, 1.87 mmol) in pyridine (4 mL) and 4-*N,N*-dimethylaminopyridine (0.122 g, 1.0 mmol). The reaction mixture was shaken well at room temperature for 48 h. The resin was filtered and
15 washed with CH₂Cl₂ (3 X 25 mL), and then a mixture of CH₂Cl₂-MeOH-*N,N*-diisopropylethylamine (8.5:1:0.5, 2 X 20 mL). The product resin was obtained after being dried over KOH under vacuum for 16 h. Loading efficiency was 84%, calculated based on the recovered starting material (1.52 mmol alcohol loaded). FT-IR (KBr) of resin: 2111.9 cm⁻¹ (N₃ group). A small portion (50 mg) of the resin was treated with 1.5 mL of TFA solution in CH₂Cl₂
20 (1.5%) for 60 seconds, filtered, and washed with CH₂Cl₂. The filtrate was concentrated to give the starting azido compound 15, which was confirmed by ¹H NMR.

2',3'-Isopropylidene-5'-N-(monomethoxytrityl-polystyrene resin)-1',5'-diamino-5'-deoxy-β-D-ribofuranose 17. To a suspension of azido resin 16 (1.1 g) in a mixture of THF and water (7.5 mL, 9:1) was added a solution of trimethylphosphine in THF (2.5 mL, 1 M). The
25 mixture was shaken well at room temperature for 6 h. The resin was filtered and then washed sequentially with a mixture of THF and H₂O (1:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). After being dried over KOH under vacuum for 16 h, resin 17 was obtained. FT-IR (KBr): 2111.9 cm⁻¹ (N₃ group) peak disappeared.

1'-N-[(5-Nitro-6-chloro)pyrimidin-4-yl]-1'-(R, S)-amino-2',3'-isopropylidene-5'-N-(monomethoxytrityl-polystyrene resin)-1',5'-diamino-5'-deoxy-β-D-ribofuranose 18. Resin
30 17 (1.0 g) was suspended in a solution of *N,N*-diisopropylethylamine in NMP (8 mL, 20% v/v)

and then treated with 4,6-dichloro-5-nitropyrimidine (1.0 g, 5.18 mmol). The reaction mixture was shaken well at room temperature for 4 h. The resultant brown suspension was filtered, and the resin was washed with NMP (3 X 25 mL) and CH₂Cl₂ (3 X 25 mL). After being dried under vacuum over P₂O₅ for 16 h, resin 18 was obtained.

1'-*N*-[(5-Nitro-*N*-alkyl or *N,N*-dialkyl or *N*-cycloalkyl)pyrimidin-4-yl]- 1'-(*R*, *S*), 5'-
diamino-5'-deoxy- β -D-ribofuranose 19. Resin 18 (50 mg) was suspended in a solution of *N,N*-
diisopropylethylamine in NMP (0.75 mL, 20% v/v), and an NMP solution of an amine (0.75 mL,
1 M) was then added. The suspension was shaken well at room temperature for 16 h. The resin
was filtered and washed sequentially with MeOH (3 X 10 mL), CH₂Cl₂ (3 X 10 mL), an NMP-
H₂O mixture (3:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resultant
resin was then treated with a mixture of TFA-H₂O (9:1, 2 mL) and kept at room temperature for
1 h. The reaction mixture was filtered, and the resin washed with MeOH (2 X 5 mL). The
combined filtrate was concentrated, and the residue was co-evaporated with toluene (2 X 5 mL)
to provide the title compound (15-20 mg) as the corresponding trifluoroacetate salt.

15 *5'-Amino Clitocine Mimic Library - II (Scheme 8)*

5'-Amino-5'-deoxy-1'-azido-D-ribofuranose (20). A solution of isopropylidene derivative 15 (0.50 g, 2.5 mmol) in a mixture of TFA-H₂O (9:1, 2 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated, and the residue was co-evaporated with toluene (2 X 5 mL) to provide 0.43 g of product 20 in a quantitative yield as the corresponding trifluoroacetate salt; ¹H NMR (CDCl₃) δ 5.33 (s, 1H), 4.10 (ddd, 1H, *J* = 2.7, 7.8, 9.6 Hz), 4.01 (dd, 1H, *J* = 4.2, 7.8 Hz), 3.87 (dd, 1H, *J* = 0.9, 4.2 Hz), 3.01 (dd, 2H, *J* = 9.6, 13.2 Hz).

5'-N-(Monomethoxytritylpolystyrene resin)-5'-amino-5'-deoxy-β-D-ribofuranosyl-1-azide 21. To a suspension of polystyrene monomethoxytrityl chloride resin (1.0 g, 1.73 mmol/g) in pyridine (4 mL) was added a solution of the trifluoroacetate salt of β-D-ribofuranosyl-1-azide (20) (0.40 g, 1.87 mmol) in pyridine (4 mL), followed by the addition of 4-*N,N*-dimethylaminopyridine (0.122 g, 1.0 mmol). The reaction mixture was shaken well at room temperature for 48 h. The resin was filtered and washed with CH₂Cl₂ (3 X 25 mL), a mixture of CH₂Cl₂-MeOH-*N,N*-diisopropylethylamine (8.5:1:0.5, 2 X 20 mL). The product resin 21 was obtained after dried over KOH under vacuum for 16 h. Loading efficiency was 86%, calculated based on the recovery of the starting material (1.57 mmol amino 20 loaded). FT-IR (KBr) 2107.7

cm⁻¹ (N₃ group). A small portion (50 mg) of resin 21 was treated with 1.5 mL of TFA solution in CH₂H₂ (1.5%) for 60 seconds. The resultant resin was filtered and washed with CH₂Cl₂ (25 mL). The filtrate was concentrated to provide the starting azido compound 20, which was confirmed by ¹H NMR.

5 **2',3'-O-Bis-(*t*-butyldimethylsilyl)-5'-*N*-(monomethoxytrityl-polystyrene resin)-5'-amino-5'-deoxy-β-D-ribofuranosyl-1-azide 22.** To a suspension of resin 21 (1.2 g) in 10 mL of DMF were added *t*-butyldimethylsilyl chloride (1.29 g, 8.65 mmol) and imidazole (1.17 g, 17.3 mmol). The reaction mixture was shaken well at room temperature for 16 h. The resin was filtered and washed sequentially with DMF (3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X
10 10 mL). Resin 22 was obtained after being dried over KOH under vacuum for 16 h. A small portion (0.10 g) of resin 22 was treated with a solution of TFA in CH₂Cl₂ (1.5%) for 60 seconds, filtered, and washed with CH₂Cl₂ (2 X 5 mL). The combined filtrate was concentrated to give the 2',3'-O-bis-(*t*-butyldimethylsilyl)-5'-amino-5'-deoxy-β-D-ribofuranosyl-1-azide (30 mg) as the corresponding trifluoroacetate salt, which was confirmed by ¹H NMR and MS.

15 **2',3'-O-Bis-(*t*-butyldimethylsilyl)-5'-*N*-(monomethoxytrityl-polystyrene resin)-1',5'-diamino-5'-deoxy-β-D-ribofuranose 23.** To a suspension of resin 22 (1.1 g) in a mixture of THF and H₂O (9:1, 7.5 mL) was added a solution of trimethylphosphine in THF (2.5 mL, 1 M). The resultant mixture was shaken well at room temperature for 6 h. The resin was filtered and then washed with a THF and H₂O mixture (1:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3
20 X 10 mL). After being dried over KOH under vacuum for 16 h, resin 23 was obtained. FT-IR (KBr) 2107.7 cm⁻¹ (N₃ group) peak disappeared.

1'-*N*-[(5-Nitro-6-chloro)pyrimidin-4-yl]-1'-(R, S)-amino-2',3'-(*t*-butyldimethylsilyl)-5'-*N*-(monomethoxytrityl-polystyrene resin)-1',5'-diamino-5'-deoxy-β-D-ribofuranose 24.
To a suspension of resin 23 (1.0 g) in a solution of *N,N*-diisopropylethylamine in NMP (8 mL,
25 20% v/v) was added 4,6-dichloro-5-nitropyrimidine (1.0 g, 5.18 mmol). The reaction mixture was shaken well at room temperature for 4 h. The brown suspension was filtered, and the resin was washed with NMP (3 X 25 mL) and CH₂Cl₂ (3 X 25 mL), and dried under vacuum over P₂O₅ for 16 h to provide resin 24.

1'-*N*-[(5-Nitro-*N*-alkyl or *N,N*-dialkyl or *N*-cycloalkyl)pyrimidin-4-yl]-5'-*N*-(monomethoxytrityl-polystyrene resin)-1'-(R, S),5'-diamino-5'-deoxy-β-D-ribofuranose 25.
30 To a suspension of resin 24 (50 mg) in a solution of *N,N*-diisopropylethylamine in NMP (0.75

mL, 20% v/v) was added an amine solution in NMP (0.75 mL, 1 M). The suspension was shaken well at room temperature for 16 h. The resin was filtered and washed sequentially with MeOH (3 X 10 mL), CH₂Cl₂ (3 X 10 mL), an NMP-H₂O mixture (3:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 10 mL). The resin was then treated with a DMF-AcOH-H₂O mixture (8:1:1, 1.5 mL) for 10 minutes and filtered. The resin was washed with a DMF-H₂O mixture (9:1, 3 X 10 mL), MeOH (3 X 10 mL), and CH₂Cl₂ (3 X 20 mL). After being dried over KOH under vacuum for 16 h, a suspension of the resultant resin (50 mg) in 1.5 mL of TFA solution in CH₂Cl₂ (1.5%) was shaken well at room temperature for 60 seconds and filtered. The resin was further washed with MeOH (2 X 1 mL), and the combined filtrate was concentrated to give product 25 as the corresponding trifluoroacetate salt.

Synthesis of 5'-Deoxy-5'-amino Clitocine Library L14. Library L14 was synthesized from resin 24 and 96 amines by similar procedures as described for the synthesis of libraries L1–L12 and L13.

Tricyclic Nucleoside Libraries - I (Scheme 13)

Dimethyl benzimidazole-5,6-dicarboxylate (26). To a solution of 0.55 g of benzimidazole-5,6-dicarboxylic acid (25) in 60 ml of anhydrous methanol was added 1 ml of concentrated sulfuric acid. The mixture was refluxed for 72 hours. The reaction was cooled to room temperature and sodium bicarbonate was added to neutralize this solution to pH 7. The solid was filtered and washed with methanol. The filtrate was evaporated to dryness to give crude product as white a solid, which was purified by silica gel column (chloroform-methanol, 20:1) to give pure product as a white solid product 26.

Dimethyl 1-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (27). A suspension of 1'-*O*-acetyl-2',3',5'-tri-*O*-benzoyl-β-D-ribofuranose (1 g) and dimethyl benzimidazole-5,6-dicarboxylate (26) (0.47 g) in 10 ml of anhydrous dichloroethane was heated to 80 °C and treated with 1.75 ml of bis(trimethylsilyl)acetamide. After stirring for 1 hour at 80 °C, 1.45 ml of trimethylsilyl triflate was added to the clear solution and stirring continued for 2.5 hours at this temperature. The reaction mixture was diluted with chloroform and washed with saturated sodium bicarbonate and water. After drying over sodium sulfate and filtration, the solvent was evaporated to dryness in vacuo. The residue was purified by silica gel column

(chloroform) to give pure product as a foam, which was recrystallized from methanol to give colorless crystals **27**.

Dimethyl 1- β -D-ribofuranosylbenzimidazole-5,6-dicarboxylate (**28**). To a solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**27**) in methanol was added *tert*-butylamine (5 equiv) and stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified by silica gel column (chloroform-methanol, 15:1) to give pure product as a white solid product **28**.

Dimethyl 1-(5'-*O*-(4-methoxytrityl resin)- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**29**). A mixture of dimethyl 1- β -D-ribofuranosylbenzimidazole-5,6-dicarboxylate (**28**) (2 equiv) and 4-methoxytrityl chloride resin (1 equiv) in anhydrous pyridine (8-10 ml/g resin) was shaken at room temperature for 2 days, then this resin was filtered and washed with anhydrous pyridine and anhydrous diethyl ether several times. After drying in vacuo, yellow resin **29** was obtained.

1- β -D-Ribofuranosyl-(6,7-substituted)-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine-5,8-dione (**30**). A mixture of dimethyl 1-(5'-*O*-(4-methoxytrityl resin)- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**29**) in hydrazines (hydrazine, methylhydrazine, etc.) was refluxed overnight. Then the resin was filtered and washed with methanol several times. This resin was cleaved by 1.5% TFA in dichloromethane to give the corresponding product **30**.

A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**27**) in 20% hydrazines (hydrazine, methylhydrazine, etc.) in ethanol was refluxed for 24 hours. The reaction mixture was cooled and the precipitate was filtered and washed with ethanol to give product **30**.

6- β -D-Ribofuranosyl-4,6,11,14-tetraaza-tricyclo[7.6.0.0^{3,7}]pentadeca-1(9),2,4,7-tetraene-10,15-dione (**32**). A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**27**) in an excess amount of ethylenediamine was heated at 115 °C overnight and then the diamine was evaporated in vacuo. The residue was coevaporated with ethanol three times and then dissolved in hot ethanol and cooled to 0 °C. The resultant precipitate was filtered and washed with ethanol to give cyclic product **32** as a yellow solid.

1- β -D-Ribofuranosyl-1H-benzoimidazole-5,6-dicarboxylic Acid Bis-substituted-amide (31). A mixture of dimethyl 1-(5'-*O*-(4-methoxytrityl resin)- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (29) in amines (or in ethanol solution) was refluxed for 1-2 days. Then the resin was filtered and washed with methanol several times. This resin was cleaved by 1.5% TFA in dichloromethane to give the corresponding product 31.

A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (27) in amines (or in ethanol solution) was refluxed for 24 hours. The reaction mixture was evaporated to dryness in vacuo and the residue was purified by silica gel column to give the corresponding products 31.

1- β -D-Ribofuranosyl-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine-5,8-dione (33). A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (27) in 20% hydrazines in ethanol was refluxed for 24 hours. The reaction mixture was cooled and the precipitate was filtered and washed with ethanol to give product 33.

1-(2',3',5'-Tri-*O*-acetyl- β -D-ribofuranosyl)-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine-5,8-dione (34). To a suspension of 0.67 g of 1- β -D-ribofuranosyl-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine-5,8-dione (33) (2 mmol) and 18.3 mg of DMAP (0.15 mmol) in a mixture of 25 ml of anhydrous acetonitrile and 1.1 ml of triethylamine (7.9 mmol) was added 0.68 ml of acetic anhydride (7.2 mmol) at room temperature. After stirring for 1.5 hours, 0.25 ml of methanol was added to the mixture and stirring was continued for an additional 5 min. The reaction mixture was filtered and the solid was washed with acetonitrile. The filtrate was evaporated to dryness in vacuo. The resultant residue was recrystallized from methanol to give product 34 as a white solid.

1-(2',3',5'-Tri-*O*-acetyl- β -D-ribofuranosyl)-5,8-dichloro-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine (35). To a suspension of 1-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-6,7-dihydro-1H-imidazo[4,5-*g*]phthalazine-5,8-dione (34) and 0.2 g of tetraethylammonium iodide (Et₄NI) in 10 ml of anhydrous acetonitrile was added 0.08 ml of *N,N*-dimethylaniline and 0.33 ml of POCl₃ with stirring at room temperature. The resultant mixture was refluxed for 1 hour, and then the solvent was removed in vacuo. The residue was dissolved in chloroform and the chloroform solution was shaken with crushed ice for 10 min and washed with cold water, 5% NaHCO₃ and cold water until this water layer reached pH 7, dried over MgSO₄. The residue after removing

solvent in vacuo was applied to silica gel column (chloroform-methanol, 30:1) to give pure product **35**.

1- β -D-Ribofuranosyl-5,8-disubstituted amino-6,7-dihydro-1H-imidazo[4,5-g]phthalazine (**36**). A solution of 1-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-5,8-dichloro-6,7-dihydro-1H-imidazo[4,5-g]phthalazine (**35**) in DMF solution of amines was heated at 80-100°C for 24 hours, then solvent was removed in vacuo. The residue was dissolved in saturated ammonia methanol and stirred at room temperature overnight. After removal of solvent, the residue was purified by silica gel column to give the corresponding products **36**.

Tricyclic Nucleoside Libraries - II (Scheme 14)

Benzimidazole-5,6-dicarboxylic Acid (**27**). To a 1000 ml three-necked, round-bottomed flask equipped with a condenser and a thermometer was added 140 ml of a 1:1 (v/v) mixture of water and tert-butyl alcohol followed by 8.0 g of 5,6-dimethylbenzimidazole. Stirring of this heterogeneous mixture at room temperature for 30 min gave a homogeneous, slightly brown solution, to which was added dropwise a hot solution (86.5 g dissolved in 600 ml of water) prepared separately at 68-70 °C, and the rate of addition of the KMnO₄ solution and heating were regulated so as to keep the temperature at this level. The heat was turned off, and stirring was continued overnight. 30 g of anhydrous Na₂SO₃ were added in five portions to consume the excess unreacted KMnO₄ while the temperature of reaction mixture was maintained at 78-80 °C by heating. The hot mixture was stirred for 30 min and filtered. The MnO₂ cake was washed with 100 ml of boiling water. The combined filtrate were concentrated to approximately 300 ml at 40-45°C in vacuo and then diluted to 600 ml with distilled water. To the solution cooled at 0-2 °C was added 120 ml of cold acetic acid-H₂O (2:1) (v/v). The white precipitate was filtered and washed with cold water. After drying in vacuo over P₂O₅, product **27** was obtained as a white powder.

Dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)-2-bromo-benzimidazole-5,6-dicarboxylate (**37**). A mixture of 6.78 g of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)benzimidazole-5,6-dicarboxylate (**27**) (10 mmol) and 3.58 g of NBS (20 mmol) in 120 ml of anhydrous acetonitrile was refluxed for 2 hours. The reaction mixture was concentrated in vacuo to dryness, and the residue was purified by silica gel column (chloroform) to give pure product **37** as a foam.

1- β -D-Ribofuranosyl-6,7-disubstituted-2-(N'-substituted-hydrazino)-6,7-dihydro-1H-imidazo[4,5-g]phthalazine-5,8-dione (**38**). A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)-2-bromobenzimidazole-5,6-dicarboxylate (**37**) (210 mg) in 6 ml of 20% hydrazine in ethanol was stirred at room temperature for 24 hours. The precipitate was filtered and washed with ethanol to give yellowish solid product **38**. Different hydrazines gave other derivatives by using the same procedure.

1- β -D-Ribofuranosyl-2-substituted amino-1H-benzoimidazole-5,6-dicarboxylic Acid Bis-substituted amide (**39**). A solution of dimethyl 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)-2-bromobenzimidazole-5,6-dicarboxylate (**37**) in amines (or in ethanol solution) was refluxed for 24 hours. The reaction mixture was evaporated to dryness in vacuo and the residue was purified by silica gel column to give the corresponding product **39**.

Tricyclic Nucleoside Libraries - III (Scheme 15)

1-Acetylbenzimidazole-5,6-dicarboxylic Anhydride (**40**). A suspension of benzimidazole-5,6-dicarboxylic acid (**27**) (1 g) in 10 ml of acetic anhydride was stirred at 145-150 °C for 4 hours with exclusion of moisture. After cooling to 5 °C, the white precipitate was collected by filtration, washed with anhydrous ether, and dried overnight at 2 °C to give 1.03 g of product **40** as a brown solid.

Imidazo[4,5-g]quinazolin-8-(7H)-one (*lin*-Benzohypoxanthine) (**41**). To a suspension of 1-acetylbenzimidazole-5,6-dicarboxylic Anhydride (**40**) (5 g) in 300 ml of anhydrous acetonitrile was added 12 ml of trimethylsilane azide at room temperature with the exclusion of moisture. The mixture was stirred vigorously while the temperature of the oil bath was raised gradually to 90-95 °C. When the temperature reached ~60 °C, this reaction mixture became clear. This reaction mixture was refluxed for 4 hours, the solution was cooled in an ice-bath and 15 ml of water was added dropwise. Removal of the solvent at reduced pressure provided the reaction product.

The dried crude mixture of two isomers was dissolved in 100 ml of anhydrous DMF, then 7.5 g of formamidine acetate was added and the reaction mixture was heated for 3 hours at 155 °C. The reaction mixture was cooled to 50 °C, and the precipitate was collected by filtration and washed with 100 ml of water. Drying at 100 °C in vacuo over P₂O₅ gave product **41** as a gray powder.

1- and 3-(2',3',5'-Tri-*O*-benzoyl- β -D-ribofuranosyl)imidazo[4,5-*g*]quinazolin-8-(7H)-one (**42/43**). A suspension of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (1.1 g) and imidazo[4,5-*g*]quinazolin-8-(7H)-one (*lin*-Benzohypoxanthine) (**41**) (0.37 g) in 10 of anhydrous dichloroethane was heated to 80 °C and treated with 1.75 ml of bis(trimethylsilyl)-acetamide.

5 After stirring for 1 hour at 80 °C, 1.45 ml of trimethylsilyl triflate was added to the clear solution and stirring continued for 2.5 hours at this temperature. This reaction mixture was diluted with chloroform and washed with saturated sodium bicarbonate and water respectively. After drying over sodium sulfate and filtration, the solvent was evaporated to dryness in vacuo. The residue was purified by silica gel column (chloroform and chloroform-methanol, 25:1) to give isomeric
10 products **42** and **43**.

1- β -D-Ribofuranosylimidazo[4,5-*g*]quinazolin-8-(7H)-one (**44**). To a solution of 1-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazo[4,5-*g*]quinazolin-8-(7H)-one (**42**) in methanol was added *tert*-butylamine (6 equiv) and stirred at room temperature for 24 hours. The solvent was removed in vacuo, and the residue was recrystallized from chloroform/methanol to
15 give the corresponding product **44**.

3- β -D-Ribofuranosylimidazo[4,5-*g*]quinazolin-8-(7H)-one (**45**). To a solution of 3-(2',3',5'-tri-*O*-benzoyl- β -D-ribofuranosyl)imidazo[4,5-*g*]quinazolin-8-(7H)-one (**43**) in methanol was added *tert*-butylamine (6 equiv) and stirred at room temperature for 24 hours. The solvent was removed in vacuo, and the residue was recrystallized from chloroform/methanol to
20 give the corresponding product **45**.

Synthesis of Compound **46**. A mixture of tricyclic nucleoside **42** (2 g, 3.2 mmol) and phosphorous penta sulphide (3.8 g, 10 mmol) in pyridine (100 ml) was heated for 12 h at 100 °C. After completion, the reaction mixture was poured into water and extracted with ethylacetate, dried over anhydrous MgSO₄ and evaporated. The crude material was dissolved in methanol.
25 Methyl iodide (10 ml) and diisopropylethylamine (1 ml) were added and mixture was heated at 80 °C for 1 h. After the reaction solvent was evaporated to dryness and purified by silica gel column chromatography using 3 % methanol in chloroform as an eluent. (1.7 g, 82%)

Synthesis of Compound **47**. S-Methyl tricyclic nucleoside **46** (1 g, 1.5 mmol) was dissolved in acetonitrile (25 ml). N-Bromosuccinimide (316 mg, 1.8 mmol) was added in to
30 reaction mixture and stirred at room temperature for 4 h. After consumption of the starting

material, mixture was treated with saturated NaHCO_3 solution and extracted with ethylacetate. The organic phase was dried over anhydrous MgSO_4 and evaporated. Purification on flash silica gel column chromatography using 8% methanol in chloroform afforded 800 mg (72%) of product. Bromo-S-methyl-tricyclic nucleoside (740 mg, 1 mmol) was dissolved in methanol 20 ml. Sodium cyanide (450 mg, 9 mmol) was added and the reaction mixture was stirred at room temperature for 36 h. The reaction mixture was directly adsorbed on silica gel and evaporated to dryness. Dried silica gel was loaded on the silica gel column and the pure compound **47** was obtained using 8% methanol in chloroform as an eluent. (356 mg, 83%).

Solid phase synthesis of tricyclic-nucleoside libraries: Bromo-S-methyl-tricyclic nucleoside **47** (700 mg, 1.64 mmol) was dissolved in dry pyridine (15 ml). MMTrCl resin (700 mg, 1.3 mmol) was added and the mixture was shaken well at room temperature. After 36 hours, the mixture was reacted with 15 ml methanol for 30 min. The resin was thoroughly washed three times with MeOH, DMF, MeOH, CHCl_3 and dried. The resin was redissolved in anhydrous pyridine and 2ml of acetic anhydride was added. After shaking at room temperature for 12 h, resin **48** was washed three times with MeOH, DMF, MeOH, CHCl_3 and dried.

Heck or Stille Reaction: To each sealed reaction vessel containing ~50 mg of the loaded resin **48** was added a freshly prepared 1.5 mL of 1.5 M solution of CuI and triphenylphosphine and $\text{Pd}(\text{OAc})_2$ in anhydrous DMF. After the addition of 0.5 mL of 1 M tributylphenyltin (or other suitable reagent, *supra*) in DMF, the reaction vessels were shaken at 80 °C for 3 days. The resin was washed three times with DMF, MeOH, and DCM.

Reactions with amines: After the Heck or Stille reaction was completed, 1.7 mL of 2.0 M amines (*supra*) in toluene and N-methylpyrrolidone (1:1) was added to each reaction vessel. The reaction vessels were shaken at 80°C for 24 h. The reaction solution was removed (empty step on synthesizer).

Deprotection with 2.0 M MeNH_2 in MeOH. To each reaction vessel was added 1.7 mL of 2.0 M methyl amine in methanol. The vessels were shaken at room temperature overnight (12-16 h), and washed three times with DMF, MeOH, and DCM.

Cleavage with 1% TFA in DCE. To each reaction vessel was added 1.0 mL of 1% TFA in DCE. The vessels were shaken at room temperature for 5 min and 0.5 mL of MeOH was added. The vessels were shaken for 5 min again. The reaction vessels were opened and 150 mg

basic resin (Amberlite IRA-93, supplied by ICN, washed with MeOH) was added to each of the vessels, which were then shaken for 5 min. The solution was pushed down into the receiving vials. The reaction vessels were washed with 0.5 mL of MeOH/DCM (1:1) to provide final libraries **49**, which were characterized by LC-MS spectrometry having 60-95% purity.

5 *2'-beta-C-substituted-N4-substituted Cytidine Libraries (Scheme 16)*

Compounds **65** (X = CH₃, CH=CH₂, CF₃, ethynyl; and Y = H, CH₃) were prepared based on literature procedures (R. E. Harry-O'Kuru, J. M. Smith, M. S. Wolfe, J. Org. Chem. 1997, 62, 1754-1759; R. E. Harry-O'Kuru, E. A. Kryjak, M. S. Wolfe, Nucleosides Nucleotides 1997, 16 (7-9), 1457-1460; N. S. Li, X. Q. Tang, J. A. Piccirilli, organic Letters, 2001, 3, 1025-1028). The compounds **65** with different X and Y groups are made by the similar procedures. A solution of 2'-O-methyluridine (**65**) (2.17 g) in 25 ml of pyridine was added to a shakable funnel containing 4.05 g of 4-methoxytrityl chloride resin (Novabiochem, loading capacity, 1.73 mmol/g). 4-N,N-Dimethylaminopyridine (DMAP) was added to the solution. The reaction mixture was shaken at room temperature for 2 days. The mixture was filtered and the resin was washed 4 times with
15 pyridine-DMF (1:1) and 4 times with dichloromethane.

The resultant uridine-substituted resin was swelled in 20 ml of pyridine, 10 ml of dichloromethane and 3.0 ml of triethylamine. t-Butyldimethylsilylchloride (5.27 g, 5 eq.) and imidazole (2.38 g, 5 eq) were added to the mixture followed by 5 ml of DMF to improve the solubility. The mixture was shaken at room temperature for 24 hours and filtered. The resin was
20 washed 4 times with pyridine-DMF (1:1) and 3 times with dichloromethane, and dried under vacuum to provide dried resin **66** loaded with protectedcytidine.

A mixture of resin **66**, DMAP (100 mg), dichloromethane (30 ml) and triethylamine (6.8 ml) was shaken at room temperature for 30 minutes. 2,4,6-tris(isopropyl)benzenesulfonyl chloride (TIP-Cl, 4.24 g, 2 eq) was added to the mixture. The resultant mixture was shaken at
25 room temperature for 24 hours. 2 ml of methanol was added to consume the excess amount of TIP-Cl, shaken and filtered. The resin was washed 5 times with pyridine-DMF (1:1) and 3 times with dichloromethane, and dried under vacuum to provide 7.2 g of resin **67** which was confirmed by MAS NMR spectrometry and ready for the parallel array synthesis of nucleoside library **69**.

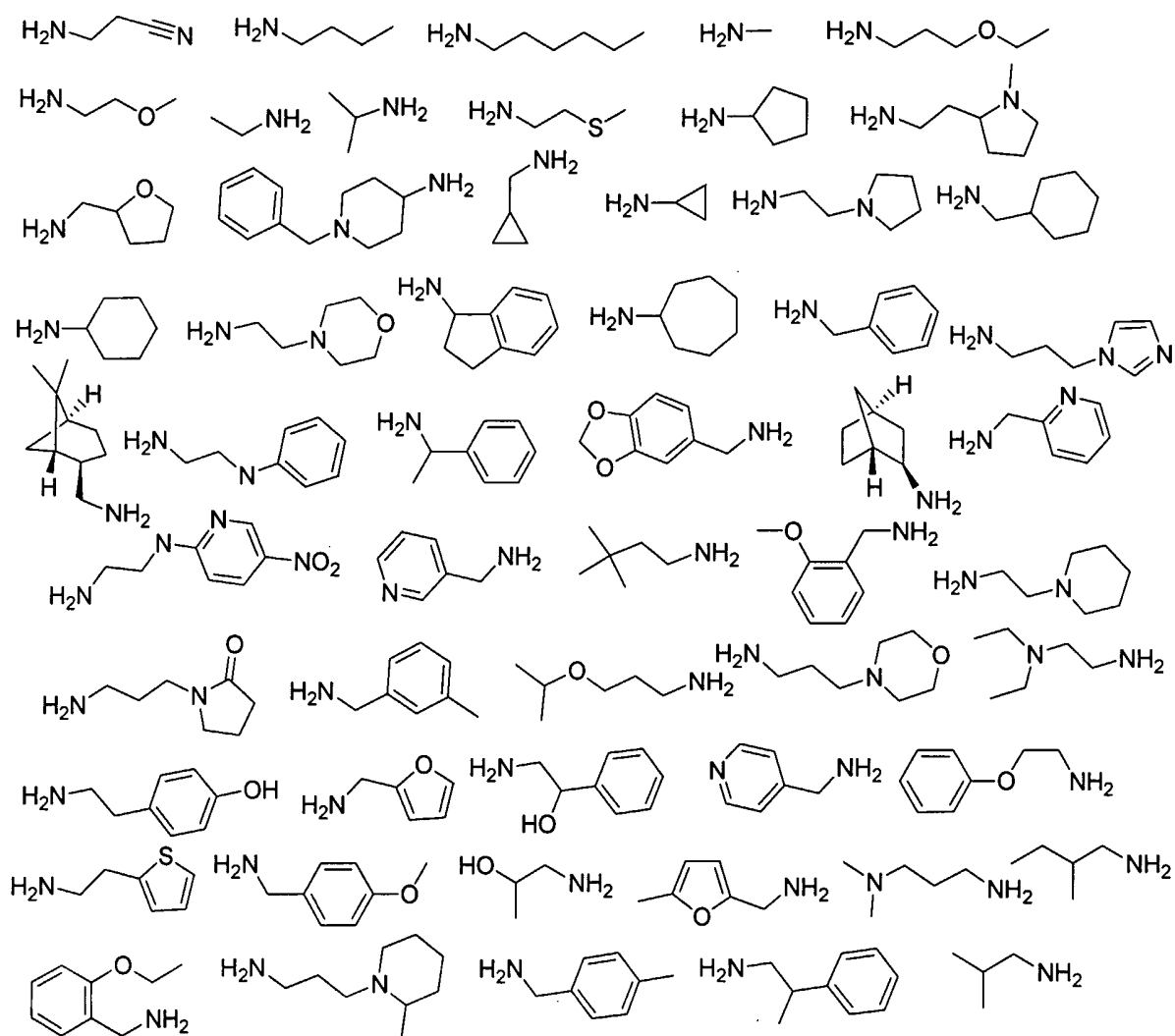
50 mg of resin **67** was added to each of the 96 wells on the ACT parallel synthesizer. 1 ml of base (0.3 M DMAP in pyridine containing diisopropylethylamine) and 0.65 ml of each of the 96 amines (1 M in DMF) were added to each of the 96 reaction vessels. The sealed reaction vessels in the reaction block were shaken at room temperature 6 hours. The solvent was filtered
5 off by vacuum. The resins were washed 3 times with DMF, 3 times with DCM-MeOH, and 3 times with dichloromethane to give a library of 96 resins **68**.

1 ml of DMF and 1 ml of tetrabutylammonium fluoride in THF (1 M) were added to each of the 96 reaction vessels. The reaction block was shaken at room temperature for 5 hours, filtered and washed 3 times with DMF, 3 times with 40% water in methanol, and 3 times with
10 dichloromethane.

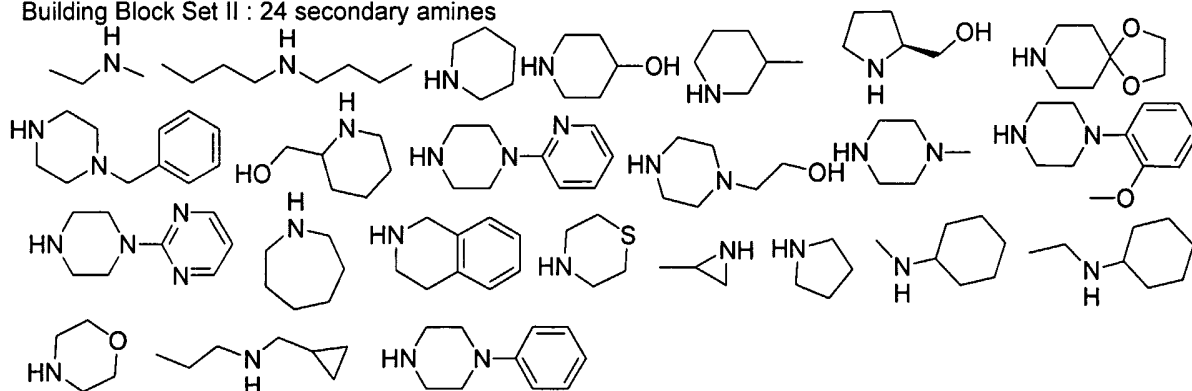
To the 96 reaction vessels containing resins, was added 1.5 ml of 2% trifluoroacetic acid solution in dichloroethane. After shaking for 2 minutes, the filtrates were collected to 96 different vials. The resins were further washed with methanol and the filtrates were combined to the corresponding 96 vials. The solutions of the 96 samples were dried to provide 96 nucleosides
15 **69** in 20 – 30 mg. The samples were analyzed by TLC and LC-MS spectrometry. LC-MS analysis of these samples confirmed the integrity and purity. Sample purity of the samples ranges from 70-100% purity.

Exemplary Building Blocks for contemplated Triazine and Nitropyrimidine Libraries

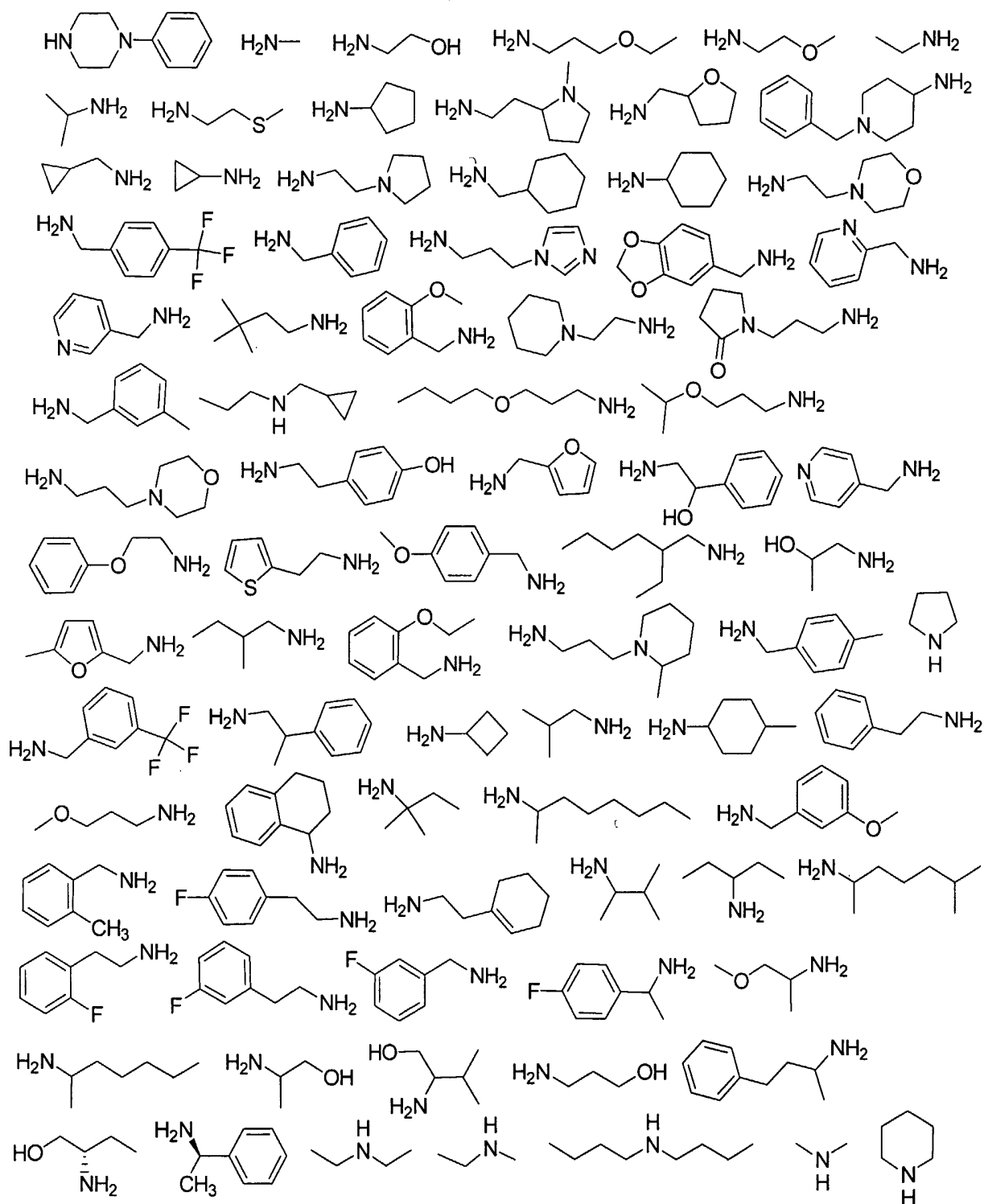
Building Block Set I : 56 primary amines



Building Block Set II : 24 secondary amines



Building Block Set III (82 amines)



Further Contemplated Exemplary Amino Building Blocks for Contemplated Libraries

1-(Benzyl)benzylamine, 2-phenyl-n-propylamine, m-trifluorobenzylamine, 2,2-diphenylethylamine, cyclobutylamine, methylcyclohexylamine, 2-methylpropylamine, allylcyclopentanylamine, N-methyl-4-piperidinylmethylamine, 4-hydroxypiperidine, 3-hydroxypiperidine, 1-benzylpiperazine, p-methoxybenzylamine, N,N-bis(isopropyl)-aminoethylamine, 2-ethylhexylamine, 5-methyl-2-furanosylmethylamine, N,N-dimethylaminopropylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methylbutylamine, o-ethoxybenzylamine, 3-(2-methyl-N-piperidinylpropylamine, 1-(2-aminoethyl)pyrrolidine, 2-morpholinylethylamine, N4-hydroxyethylpiperazine, N-methylethylenediamine, 3-morpholinylpropylamine, pyridinyl-2-ethylamine, butylamine, hexylamine, methylamine, 2-hydroxyethylamine, N,N-dimethylethylenediamine, 3-methoxypropylamine, 2-methoxyethylamine, ethylamine, 2-isopropylamine, methylethylamine, 2-methylthioethylamine, di-n-butylamine, dimethylamine, allylamine, cyclopantylamine, 2-(N-methyl-pyrrolidin-2-yl)ethylamine, tetrahydrofuranosyl-2-methylamine, piperidine, N-benzyl-4-aminopiperidine, aminomethylcyclopropane, cyclopropylamine, 3-methylpiperizine, 4-piperidin-1-ylpiperidine, cyclohexylamine, piperazine, 4-pyridin-2-ylpiperazine, 1-methylpiperazine, N-(2-methoxyphenyl)-piperazine, N-pyrimidin-2-ylpiperazine, cycloheptylamine, p-trifluorobenzylamine, benzylamine, 3-imidazol-1-ylpropylamine, exo-2-aminonorborane, N-phenylethylene-diamine, 1-methylbenzylamine, 3,4-(1,3-dioxolanyl)benzylamine, pyridin-2-ylmethylamine, pyridin-3-ylmethylamine, pyridin-4-ylmethylamine, thiophen-2-ylmethylamine, 3,3-dimethylbutylamine, o-methoxybenzylamine, 1-(3-aminopropyl)-pyrrolidin-2-one, N-methylethylenediamine, m-methylbenzylamine, 3-methylbutylamine, 2-methylbutylamine, heptylamine, 3-butoxypropylamine, 3-isopropoxypropylamine, 2-morpholin-4-ylpropylamine, N1,N1-diethylethylenediamine, 2-ethylthioethylamine, 4-(2-aminoethyl)phenol, furfurylamine, 4-aminomethylpiperidine, 2-(2-aminoethyl)-pyridine, 2-phenoxyethylamine, 2-aminoethylthiophene, p-methoxybenzylamine, 2-(N,N-dimethylamino)ethylamine, 1-amino-2-propanol, 5-methylfurfurylamine, 3-(dimethylamino)propylamine, o-methoxybenzylamine, 1-(3-aminopropyl)-2-pipecoline, hydrazine, 4-hydroxypiperidine, ethylenediamine, 1,4-diaminobutane, N-methylpropylamine, trans-1,4-diaminocyclohexane, 2,2,2-trifluoroethylamine, 3-chloropropylamine, 3-ethoxypropylamine, aminoacetaldehyde dimethyl acetal, 3-amino-1,2-propanediol, 1,3-diamino-2-hydroxypropane, 1-aminopyrrolidine, 2-(2-aminoethyl)-1-methylpyrrolidine, 3-methylpiperidine, 2-piperidine methanol, 3-piperidine methanol, 1-

aminohomopiperidine, homopiperazine, 4-aminomorpholine, 3-bromobenzylamine, piperonylamine, 1,2,3,4-tetrahydroisoquinoline, L-proline methyl ester, 1-(2-pyridyl)piperazine, 4-(2-aminoethyl)morpholine, 1-(2-aminoethyl)piperidine, 3-aminopropionitrile, 3-(aminomethyl)pyridine, 2-(aminomethyl)pyridine, thiomorpholine, 1,4-dioxo-8-azaspiro(4,5)-
5 decane, 2-hydroxyethylamine, 1-(2-aminoethyl)pyrrolidine, aminomethylcyclohexane, 2-hydroxymethylpyrrolidine, 3-amino-1,2-propanediol acetone ketal, N-(2-hydroxyethyl)piperazine, N-phenylethylenediamine, 4-amino-2,2,6,6-tetramethylpiperidine, N-(4-nitrophenyl)ethylenediamine, 1,2-diphenylethylamine, 1-(N,N-dimethylamino)-2-propylamine, 2-phenylpropylamine, 2-methylcyclopropylamine, 2-methylaziridine,
10 aminomethylcyclopropane, 1-aminomethyl-2-methylcyclopropane, buten-3-ylamine, 3-methyl-buten-2-ylamine, 3-methyl-buten-3-ylamine, 4-aminomethyl-1-cyclohexene, 3-phenylallylamine, 2,2-dimethylethylenediamine, 3-ethylhexylamine, 3-(N,N-dimethylamino)-2,2-dimethylpropylamine, 2-methyl-N-aminopropylpiperidine as well as other related aliphatic and aromatic primary and secondary amines are good nucleophiles to react with leaving groups on
15 the scaffolds.

Exemplary Building Blocks for C-C Bond Formation on Heterocyclic Bases

For Heck Reaction: 2-ethynylpyridine, 5-phenyl-1-pentyne, 4-(tert-butyl)phenylacetylene, phenylacetylene, 3-dibutylamino-1-propyne, phenyl propargyl ether, 5-chloro-1-pentyne, 3-diethylamino-1-propyne, 4-phenyl-1-butyne, 1-heptyne, 1-dimethylamino-2-propyne, 1-pentyne, 2-methyl-1-hexene, (triethylsilyl)acetylene, 3-phenyl-1-propyne, methyl
20 propargyl ether, 3-cyclopentyl-1-propyne, 1-ethynylcyclohexene, 3-butyne-1-ol, styrene, vinylcyclohexane, 2-(tributylstannyl)furan, 2-(tributylstannyl)thiophene, tetraphenyltin, 3-cyclohexyl-1-propyne, 4-methoxyphenylacetylene, 4-(trifluoromethyl)phenylacetylene, 4-fluorophenylacetylene, 4-pentyn-1-ol, 4-methylphenylacetylene, 1-ethynylcyclopentanol, 3-methyl-1-propyne, 5-cyano-1-pentyne, cyclohexylethyne, 1-ethynylcyclohexene, 5-cyano-1-pentyne, 1-dimethylamino-2-propyne, N-methyl-N-propargylbenzylamine, 2-methyl-1-buten-3-yne, cyclopentylethyne, 4-nitrophenylacetylene, phenyl propargylsulfide, 4-methyl-1-pentyne, propargyl ethylsulfide, 2-prop-2-ynoxybenzothiazole, 4-ethoxy-1-prop-2-ynyl-1,5-dihydro-2H-pyrrol-2-one, 6-methyl-5-(2-propynyl)-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone and related
25 end-alkenes and alkynes.
30

For Stille Reaction: tetraethyltin, 2-(tributylstannyl)pyridine, tributylstannyl-4-t-butylbenzene, ethynyltri-n-butyltin, vinyltri-n-butyltin, allyltri-n-butyltin, phenylethynyltri-n-butyltin, phenyltri-n-butyltin, (2-methoxy-2-cyclohexen-1-yl)tributyltin, 5,6-dihydro-2-(tributylstannyl)-4H-pyran, tri-n-butyl(2-furanyl)tin, tri-n-butyl(2-thienyl)tin,
 5 tributyl(phenylethenyl)tin, 4-fluoro-(tri-n-butylstannyl)benzene, 5-fluoro-2-methoxy(tri-n-butylstannyl)benzene, 1-methyl-2-(tributylstannyl)-1H-pyrrole, 5-methyl-2-tributylstannylthiophene, 2-tributylstannylthiazole, 2-tributylstannylpyrrazine, tributyl[3-(trifluoromethyl)phenyl]stannane and other related organic tin reagents.

For Suzuki Reaction: phenylboronic acid, 4-tolylboronic acid, 2-thiopheneboronic acid,
 10 thiophene-3-boronic acid, furan-2-boronic acid, cyclopentylboronic acid, 4-methylfuran-2-boronic acid, 3-hydroxyphenylboronic acid, 5-methylfuran-2-boronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, (5-formyl-3-furanyl)boronic acid, furan-3-boronic acid and other related organic boronic acids.

Typical Library Quality for exemplary Libraries L1-12 of Scheme 2

15

Library No	Percentage of Products 80-100%	Percentage of Products >60%*	Library No	Percentage of Products 80-100%	Percentage of Products >60%*
L1 (T4)	70.8%	92.7%	L7 (T10)	81.2%	91.7%
L2 (T5)	65.7%	88.5%	L8 (T15)	81.3%	100%
L3 (T6)	74.0%	96.9%	L9 (T11)	76.0%	86.5%
L4 (T7)	76.0%	90.6%	L10 (T12)	76.0%	81.3%
L5 (T8)	84.3%	95.8%	L11 (T13)	80.3%	85.4%
L6 (T9)	92.7%	97.9%	L12 (T14)	75.0%	82.3%

* 96 compounds for each plate except II of 82 compounds

** Percentage of the library members with more than 60% purity is defined as the successful rate of the library.

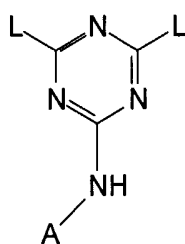
Thus, specific embodiments and applications of unusual nucleoside libraries and
 20 compounds have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted

except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced
5 elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

CLAIMS

What is claimed is:

1. A compound having a structure A-M-B, wherein A comprises a sugar, M comprises an intermediary atom other than carbon, and B comprises a heterocyclic base, wherein M is covalently bound to a carbon atom of the sugar and further covalently bound to the heterocyclic base.
2. The compound of claim 1 wherein B further comprises at least one electrophilic center and at least one leaving group.
3. The compound of claim 1 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.
4. The compound of claim 1 wherein the heterocyclic base has a structure selected from the group consisting of a five-membered ring, a six-membered ring, and a fused aromatic system that comprises at least one of a nitrogen atom, a sulfur atom, an oxygen atom, and a phosphorus atom.
5. The compound of claim 2 having a structure according to Formula 3

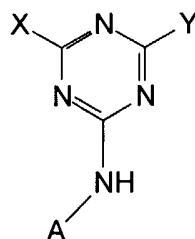


Formula 3

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected; and

L is a leaving group.

6. The compound of claim 1 having a structure according to Formula 2



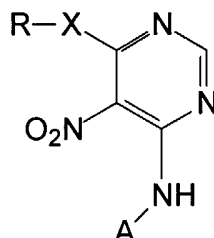
Formula 2

wherein A is a sugar, wherein the sugar is optionally protected;

X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR; and

wherein R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

7. The compound of claim 1 having a structure according to Formula 5

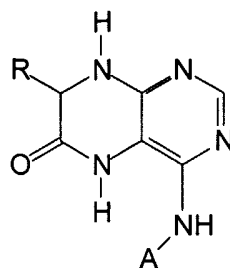


Formula 5

wherein A is a sugar; X is NR', O, or S; and

wherein R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

8. The compound of claim 1 having a structure according to Formula 7

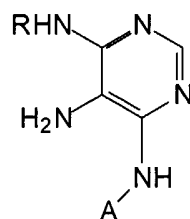


Formula 7

wherein A is a sugar; and

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

9. The compound of claim 1 having a structure according to Formula 9

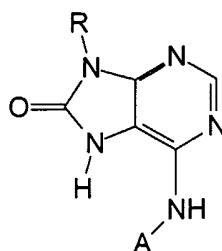


Formula 9

wherein A is a sugar; and

wherein R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

10. The compound of claim 1 having a structure according to Formula 11

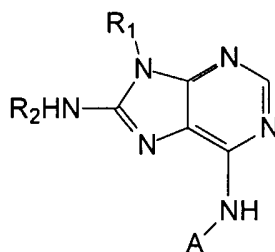


Formula 11

wherein A is a sugar; and

wherein R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

11. The compound of claim 1 having a structure according to Formula 13



Formula 13

wherein A is a sugar; and

R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

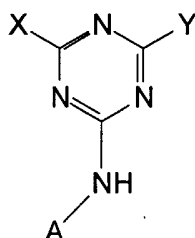
12. A nucleoside library comprising:

a first library compound and a second library compound, wherein each of the first and second library compounds has a structure A-M-B;

wherein A comprises a sugar, M comprises an intermediary atom other than carbon, and B comprises a heterocyclic base, wherein M is covalently bound to a carbon atom of the sugar and further covalently bound to the heterocyclic base; and

wherein the first library compound and the second library compound are chemically distinct.

13. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 1 with a first set of substituents A, X, and Y, wherein the second library compound has a structure according to Formula 1 with a second set of substituents A, X, and Y



Formula 1

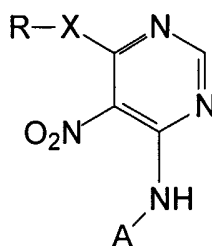
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR;

R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, X, and Y in the first set are the same as the substituents A, X, and Y in the second set.

14. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 4 with a first set of substituents A, X, and R, and wherein the second library compound has a structure according to Formula 4 with a second set of substituents A, X, and R



Formula 4

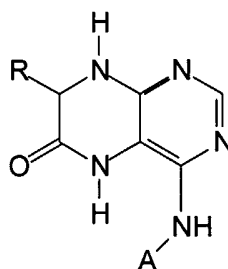
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

X is NR', O, or S;

R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, X, and R in the first set are the same as the substituents A, X, and R in the second set.

15. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 6 with a first set of substituents A and R, and wherein the second library compound has a structure according to Formula 6 with a second set of substituents A and R



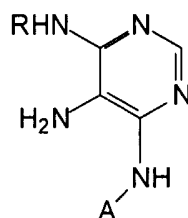
Formula 6

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

16. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 8 with a first set of substituents A and R, and wherein the second library compound has a structure according to Formula 8 with a second set of substituents A and R



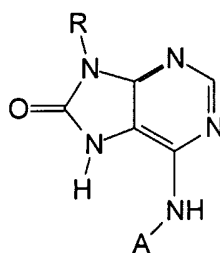
Formula 8

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

17. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 10 with a first set of substituents A and R, and the second library compound has a structure according to Formula 10 with a second set of substituents A and R



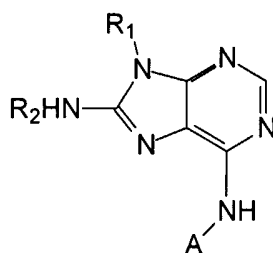
Formula 10

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

18. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 12 with a first set of substituents A, R₁, and R₂, and the second library compound has a structure according to Formula 12 with a second set of substituents A, R₁, and R₂



Formula 12

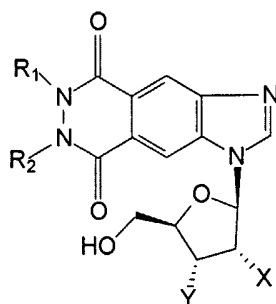
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted

or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, R₁, and R₂ in the first set are the same as the substituents A, R₁, and R₂ in the second set.

19. A nucleoside having a sugar covalently bound to a tricyclic heterocyclic base comprising a benzimidazole moiety.
20. The nucleoside of claim 19 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.
21. The nucleoside of claim 19 having a structure according to Formula 15

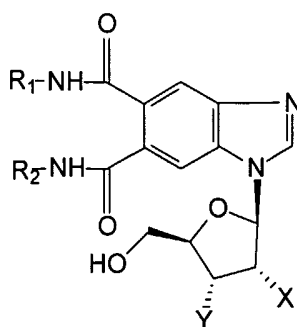


Formula 15

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

22. The nucleoside of claim 19 having a structure according to Formula 17



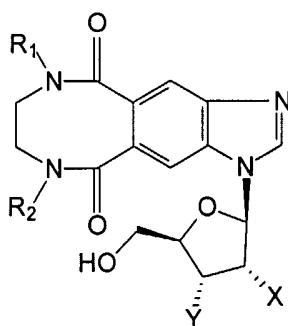
Formula 17

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

wherein R_1 and R_2 together form a ring.

23. The nucleoside of claim 19 having a structure according to Formula 19

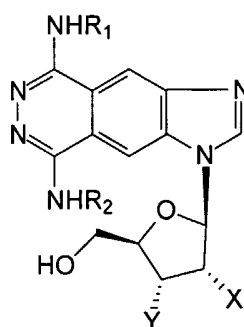


Formula 19

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

24. The nucleoside of claim 19 having a structure according to Formula 21

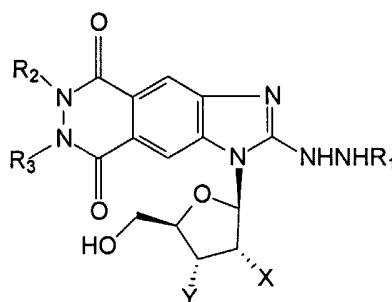


Formula 21

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

25. The nucleoside of claim 19 having a structure according to Formula 22

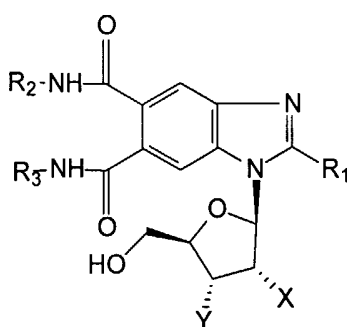


Formula 22

wherein R_1 , R_2 , and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

26. The nucleoside of claim 19 having a structure according to Formula 23



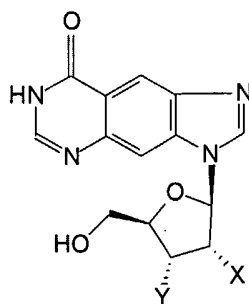
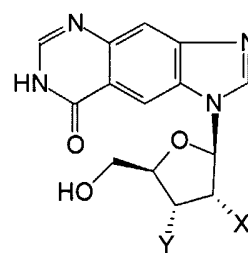
Formula 23

wherein R_1 , R_2 , and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

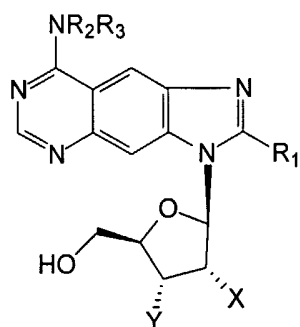
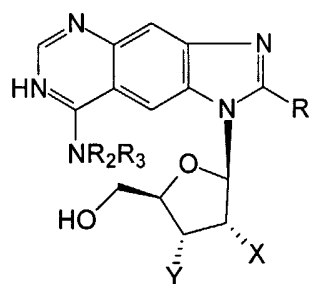
wherein R_2 and R_3 optionally form a ring, or form a covalent bond between the nitrogen atoms.

27. The nucleoside of claim 19 having a structure according to Formula 24 or 25

**Formula 24****Formula 25**

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

28. The nucleoside of claim 19 having a structure according to Formula 28 or 29

**Formula 28****Formula 29**

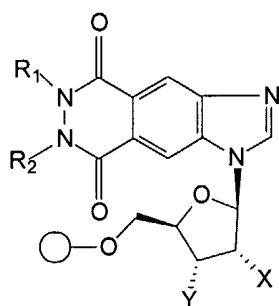
wherein R₁, R₂ and R₃ are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

29. A nucleoside library comprising a first library compound and a second library compound, wherein each of the first and second library compounds has a sugar covalently bound to a

tricyclic heterocyclic base that comprises a benzimidazole moiety, and wherein the first and second library compounds are chemically distinct.

30. The nucleoside library of claim 29 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.
31. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 14 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 14 with a second set of substituents X, Y, R₁, and R₂



Formula 14

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

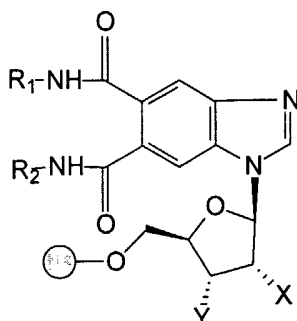
X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, and R₂ in the first set are the same as the substituents X, Y, R₁, and R₂ in the second set.

32. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according

to Formula 16 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 16 with a second set of substituents X, Y, R₁, and R₂



Formula 16

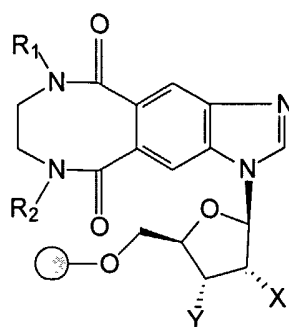
wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle, and wherein R₁ and R₂ together may form a ring;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, and R₂ in the first set are the same as the substituents X, Y, R₁, and R₂ in the second set.

33. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 18 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 18 with a second set of substituents X, Y, R₁, and R₂



Formula 18

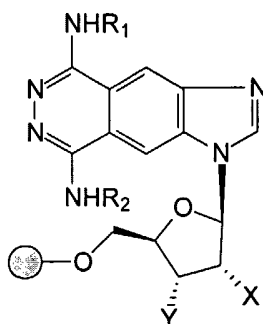
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

34. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 20 with a first set of substituents X, Y, R_1 , and R_2 , and wherein another one of the at least two library compounds has a structure according to Formula 20 with a second set of substituents X, Y, R_1 , and R_2



Formula 20

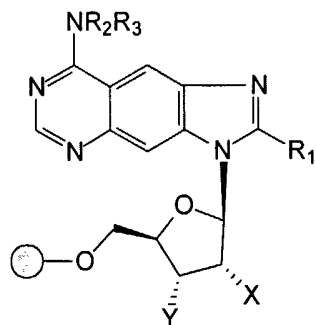
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

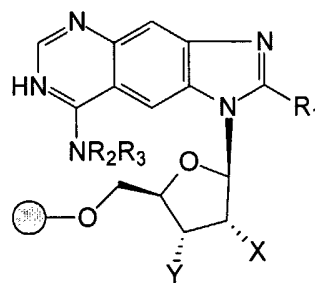
● comprises a solid phase; and

wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

35. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 26 or 27 with a first set of substituents X, Y, R_1 , R_2 , and R_3 , and wherein another one of the at least two library compounds has a structure according to Formula 26 or 27 with a second set of substituents X, Y, R_1 , R_2 , and R_3



Formula 26



Formula 27

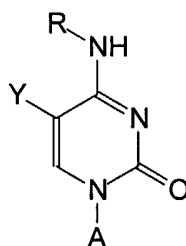
wherein R_1 , R_2 and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

- comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, R₂, and R₃ in the first set are the same as the substituents X, Y, R₁, R₂, and R₃ in the second set.

36. A nucleoside library comprising at least two library compounds in which one of the at least two library compounds has a structure according to Formula 30 with a first set of substituents A, Y, and R, and wherein another one of the at least two library compounds has a structure according to Formula 30 with a second set of substituents A, Y, and R



Formula 30

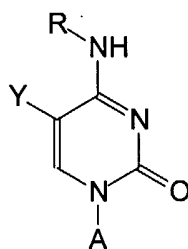
wherein A is a 2'-beta-C-substituted sugar that is coupled to a solid phase, wherein the sugar is optionally protected, and wherein the substituent is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

Y is R or halogen, CF₃, NO₂, NH₃; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

37. A nucleoside according to Formula 31

**Formula 31**

wherein A is a 2'-beta-C-substituted sugar, and wherein the substituent in the sugar is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

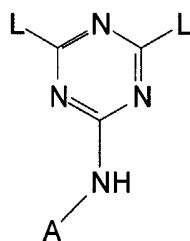
R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein Y is R or halogen, CF₃, NO₂, NH₃.

AMENDED CLAIMS

**[Received by the International Bureau on 20 May 2003 (20.05.03):
original claims 1-37 replaced by amended claims 1-37]**

1. A compound having a structure A-M-B, wherein A comprises a ribofuranose or a substituted ribofuranose, M comprises a nitrogen atom, and B comprises a heterocyclic base, wherein M is covalently bound to a C1'-position of a carbon atom of the ribofuranose or substituted ribofuranose and further covalently bound to the heterocyclic base.
2. The compound of claim 1 wherein B further comprises at least one electrophilic center and at least one leaving group.
3. The compound of claim 1 wherein the ribofuranose or the substituted ribofuranose is in a D-configuration or in an L-configuration.
4. The compound of claim 1 wherein the heterocyclic base has a structure selected from the group consisting of a five-membered ring, a six-membered ring, and a fused aromatic system that comprises at least one of a nitrogen atom, a sulfur atom, an oxygen atom, and a phosphorus atom.
5. The compound of claim 2 having a structure according to Formula 3

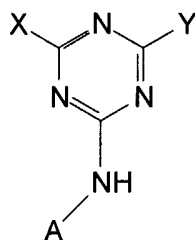


Formula 3

wherein A is optionally protected; and

L is a leaving group.

6. The compound of claim 1 having a structure according to Formula 2



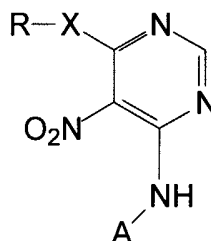
Formula 2

wherein A is optionally protected;

X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR; and

wherein R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

7. The compound of claim 1 having a structure according to Formula 5

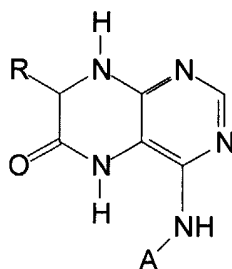


Formula 5

wherein X is NR', O, or S; and

wherein R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

8. The compound of claim 1 having a structure according to Formula 7

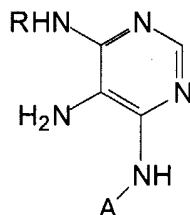


Formula 7

wherein A is optionally protected; and

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

9. The compound of claim 1 having a structure according to Formula 9

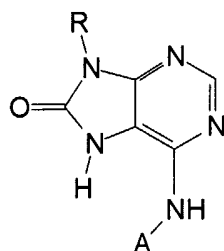


Formula 9

wherein A is optionally protected; and

wherein R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

10. The compound of claim 1 having a structure according to Formula 11

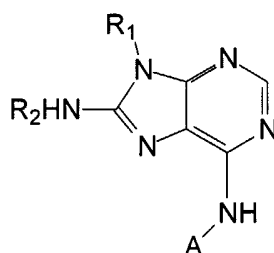


Formula 11

wherein A is optionally protected; and

wherein R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

11. The compound of claim 1 having a structure according to Formula 13

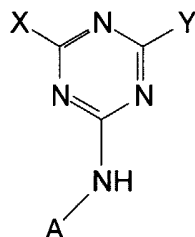


Formula 13

wherein A is optionally protected; and

R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle.

12. A nucleoside library having a complexity of at least 20 distinct compounds, comprising:
- a first library compound and a second library compound, wherein each of the first and second library compounds has a structure A-M-B;
- wherein A comprises a sugar, M comprises an intermediary atom other than carbon, and B comprises a heterocyclic base, wherein M is covalently bound to a carbon atom of the sugar and further covalently bound to the heterocyclic base; and
- wherein the first library compound and the second library compound are chemically distinct.
13. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 1 with a first set of substituents A, X, and Y, wherein the second library compound has a structure according to Formula 1 with a second set of substituents A, X, and Y



Formula 1

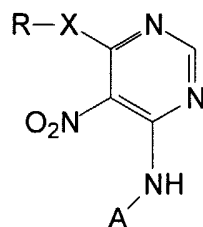
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

X and Y are independently R, OR, NRR', NHNHR, ONHR, or SR;

R and R' are independently hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, X, and Y in the first set are the same as the substituents A, X, and Y in the second set.

14. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 4 with a first set of substituents A, X, and R, and wherein the second library compound has a structure according to Formula 4 with a second set of substituents A, X, and R



Formula 4

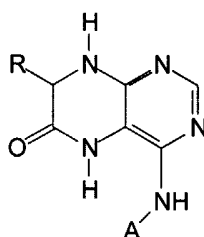
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

X is NR', O, or S;

R and R' are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, X, and R in the first set are the same as the substituents A, X, and R in the second set.

15. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 6 with a first set of substituents A and R, and wherein the second library compound has a structure according to Formula 6 with a second set of substituents A and R



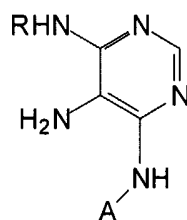
Formula 6

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

16. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 8 with a first set of substituents A and R, and wherein the second library compound has a structure according to Formula 8 with a second set of substituents A and R



Formula 8

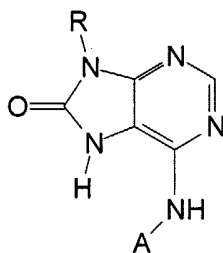
wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

17. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 10 with a first set of substituents A and R, and the second

library compound has a structure according to Formula 10 with a second set of substituents A and R



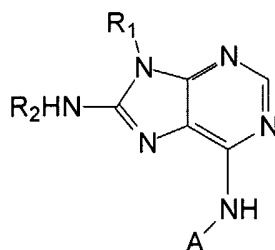
Formula 10

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

18. The nucleoside library of claim 12 wherein the first library compound has a structure according to Formula 12 with a first set of substituents A, R₁, and R₂, and the second library compound has a structure according to Formula 12 with a second set of substituents A, R₁, and R₂



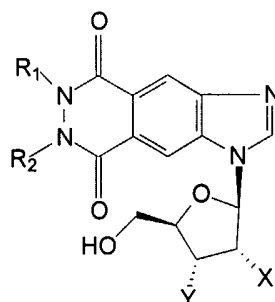
Formula 12

wherein A is a sugar that is coupled to a solid phase, wherein the sugar is optionally protected;

R₁ and R₂ are independently selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle; and

wherein not all of the substituents A, R₁, and R₂ in the first set are the same as the substituents A, R₁, and R₂ in the second set.

19. A nucleoside having a sugar covalently bound to a tricyclic heterocyclic base comprising a benzimidazole moiety, wherein the sugar is not a ribofuranose or a dideoxyribofuranose.
20. The nucleoside of claim 19 wherein the sugar is selected from the group consisting of a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.
21. A nucleoside having a structure according to Formula 15

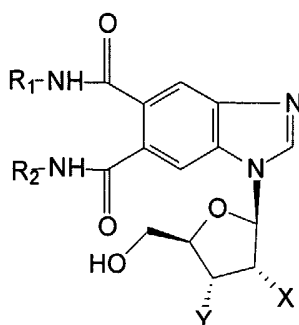


Formula 15

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

22. A nucleoside having a structure according to Formula 17



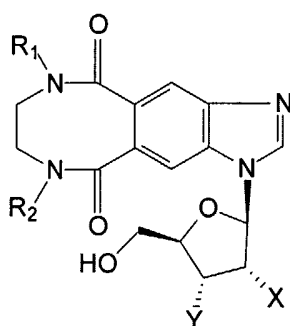
Formula 17

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

wherein R_1 and R_2 together form a ring.

23. A nucleoside having a structure according to Formula 19

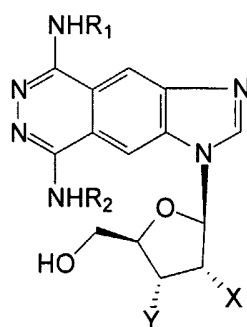


Formula 19

wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

24. A nucleoside having a structure according to Formula 21

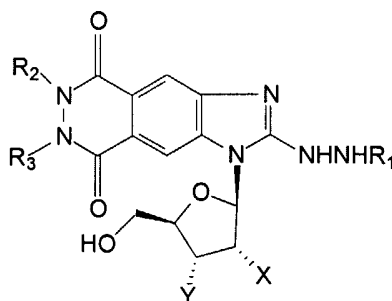


Formula 21

wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

25. A nucleoside having a structure according to Formula 22

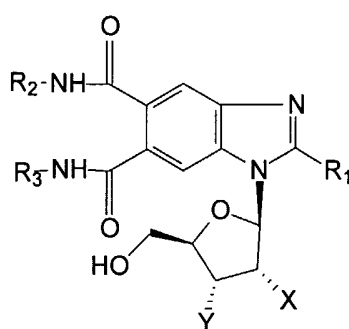


Formula 22

wherein R_1 , R_2 , and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

26. A nucleoside having a structure according to Formula 23



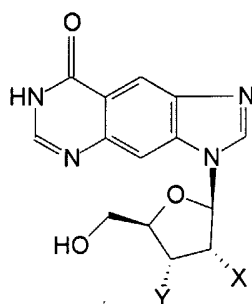
Formula 23

wherein R_1 , R_2 , and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

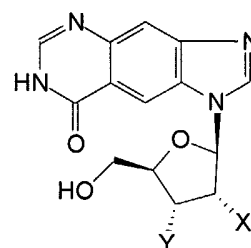
wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

wherein R_2 and R_3 optionally form a ring, or form a covalent bond between the nitrogen atoms.

27. The nucleoside of claim 19 having a structure according to Formula 24 or 25



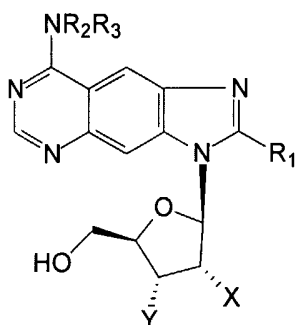
Formula 24



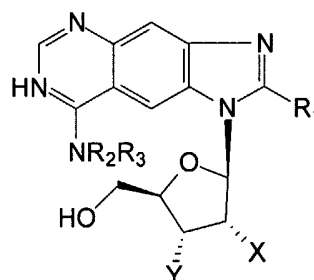
Formula 25

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

28. The nucleoside of claim 19 having a structure according to Formula 28 or 29



Formula 28

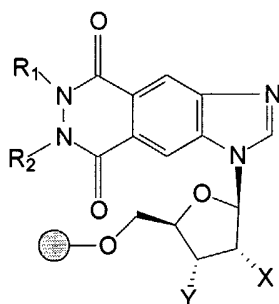


Formula 29

wherein R₁, R₂ and R₃ are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle; and

wherein X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

29. A nucleoside library having a complexity of at least 20 distinct compounds comprising a first library compound and a second library compound, wherein each of the first and second library compounds has a sugar covalently bound to a tricyclic heterocyclic base that comprises a benzimidazole moiety, and wherein the first and second library compounds are chemically distinct.
30. The nucleoside library of claim 29 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.
31. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 14 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 14 with a second set of substituents X, Y, R₁, and R₂.



Formula 14

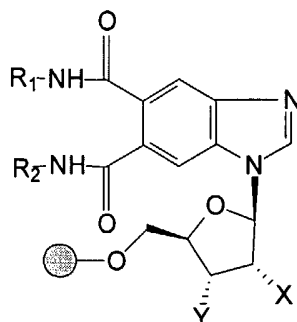
wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, and R₂ in the first set are the same as the substituents X, Y, R₁, and R₂ in the second set.

32. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 16 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 16 with a second set of substituents X, Y, R₁, and R₂



Formula 16

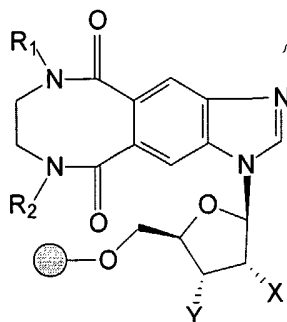
wherein R₁ and R₂ are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle, and wherein R₁ and R₂ together may form a ring;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, and R₂ in the first set are the same as the substituents X, Y, R₁, and R₂ in the second set.

33. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 18 with a first set of substituents X, Y, R₁, and R₂, and wherein another one of the at least two library compounds has a structure according to Formula 18 with a second set of substituents X, Y, R₁, and R₂



Formula 18

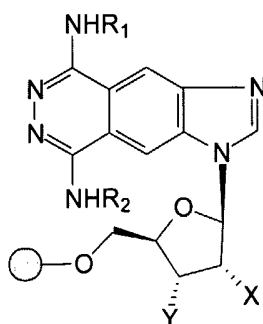
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X , Y , R_1 , and R_2 in the first set are the same as the substituents X , Y , R_1 , and R_2 in the second set.

34. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 20 with a first set of substituents X , Y , R_1 , and R_2 , and wherein another one of the at least two library compounds has a structure according to Formula 20 with a second set of substituents X , Y , R_1 , and R_2



Formula 20

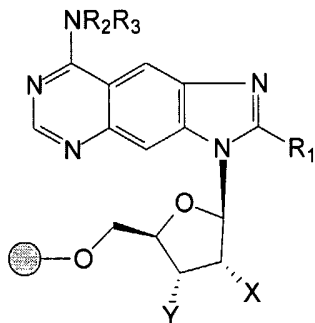
wherein R_1 and R_2 are independently selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

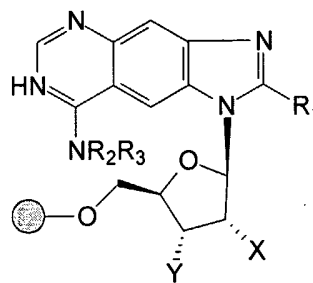
● comprises a solid phase; and

wherein not all of the substituents X, Y, R_1 , and R_2 in the first set are the same as the substituents X, Y, R_1 , and R_2 in the second set.

35. The nucleoside library of claim 29 wherein the library includes at least two library compounds in which one of the at least two library compounds has a structure according to Formula 26 or 27 with a first set of substituents X, Y, R_1 , R_2 , and R_3 , and wherein another one of the at least two library compounds has a structure according to Formula 26 or 27 with a second set of substituents X, Y, R_1 , R_2 , and R_3



Formula 26



Formula 27

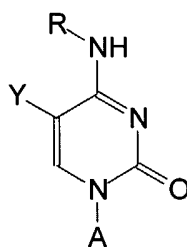
wherein R_1 , R_2 and R_3 are independently selected from the group consisting of hydrogen, a substituted alkyl, an unsubstituted alkyl, a substituted aryl, an unsubstituted aryl, and a heterocycle;

X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

● comprises a solid phase; and

wherein not all of the substituents X, Y, R₁, R₂, and R₃ in the first set are the same as the substituents X, Y, R₁, R₂, and R₃ in the second set.

36. A nucleoside library having a complexity of at least 20 distinct compounds comprising at least two library compounds in which one of the at least two library compounds has a structure according to Formula 30 with a first set of substituents A, Y, and R, and wherein another one of the at least two library compounds has a structure according to Formula 30 with a second set of substituents A, Y, and R



Formula 30

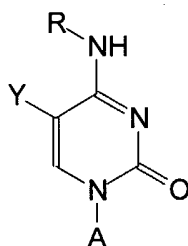
wherein A is a 2'-beta-C-substituted sugar that is coupled to a solid phase, wherein the sugar is optionally protected, and wherein the substituent is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

Y is R or halogen, CF₃, NO₂, NH₃; and

wherein not all of the substituents A and R in the first set are the same as the substituents A and R in the second set.

37. A nucleoside according to Formula 31



Formula 31

wherein A is a 2'-beta-C-substituted sugar, and wherein the substituent in the sugar is selected from the group consisting of a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

R is selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkynyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocycle;

with the proviso that where the sugar has a 2'-alpha substituent that is covalently coupled to the 2'-position via an oxygen atom, or where Y and R are H, then the 2'-beta-C-substituent is not methyl; and

wherein Y is R, halogen, CF₃, NO₂, or NH₃.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/40415

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 19/00; A01N 43/04; A61K, 31/70

US CL : 536/26.1, 26.11, 26.12, 26.13, 27.21, 27.6, 27.62, 28.5; 514/45, 46, 47, 48, 49

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)

U.S. : 536/26.1, 26.11, 26.12, 26.13, 27.21, 27.6, 27.62, 28.5; 514/45, 46, 47, 48, 49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	ADAM, Michael J. et al. "Synthesis of Carbohydrate Conjugates. Chemical Modification of Monosaccharides via 2,4,6-Trichloro-1,3,5-triazine". Carbohydrate Research, 1985, Vol. 144, pages 23-31.	1-4, 6, 12 ----- 5, 13
X --- Y	MONTGOMERY, John A. et al. "Isonucleosides. I. Preparation of Methyl 2-Deoxy-2-(purin-9-yl)arabinofuranosides and Methyl 3-Deoxy-3-(purin-9-yl)xylofuranosides". Journal of Organic Chemistry, 1975, Vol. 40, No. 13, pages 1923-1927.	1-4, 7, 9, 12 ----- 14, 16
X --- Y	KEYSER, Gene E. "Synthesis of lin-Benzoinosine, lin-Benzoxanthosine, and lin-Benzoguanosine". Journal of Organic Chemistry, 1979, Vol. 44, No. 17, pages 2989-2994.	19-20, 27-30 ----- 35
X --- Y	OROZCO, Modesto et al. "A Quantum Chemical Study of the Enzymatic Deamination of Benzoadenine Derivatives". European Journal of Biochemistry, 1990, Vol. 188, pages 155-163.	19-20, 28-30 ----- 35



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search

06 March 2003 (06.03.2003)

Date of mailing of the international search report

24 FEB 2003

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

PCT/US02/40415

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	ZHANG, Jianzhong et al. "Inhibition of HIV Integrase by Novel Nucleotides Bearing Tricyclic Bases". Bioorganic & Medicinal Chemistry Letters, 1998, Vol. 8, pages 1887-1890.	19-20, 28-30 ----- 35
A	US 4,086,416 (ACTON et al.) 25 April 1978 (25.04.1978).	10-11, 17-18
X --- Y	WO 01/90121 A2 (NOVIRIO PHARMACEUTICALS LIMITED) 29 November 2001 (29.11.2001), entire document.	37 ----- 36
X --- Y	WO 01/92282 A2 (NOVIRIO PHARMACEUTICALS LIMITED) 6 December 2001 (06.12.2001), entire document.	37 ----- 36
X, P --- Y, P	WO 02/18404 A2 (F. HOFFMANN-LA ROCHE AG) 7 March 2002 (07.03.2002), entire document.	37 ----- 36
X, P --- Y, P	WO 02/057425 A2 (MERCK & CO., INC.) 25 July 2002 (25.07.2002), entire document.	37 ----- 36