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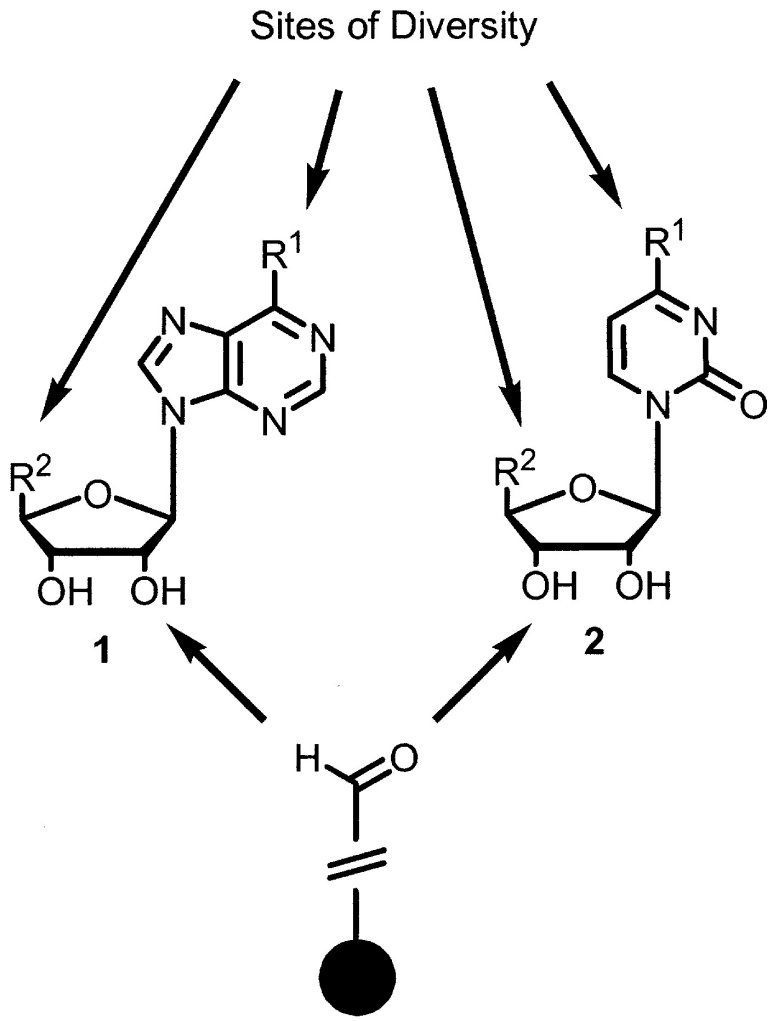


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# Solid-Phase Synthesis of Nucleoside Analogues

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The synthesis of a 25 000 member library of nucleoside analogues as discrete compounds in milligram quantities is described. The use of the Nanokan technology developed by IRORI (Discovery Partners International) together with macroporous solid support allowed us to develop a highly reliable and practical synthetic route for the high-throughput derivatization of both the pyrimidine and purine nucleoside scaffold. A 2′,3′-acetal linkage of the scaffolds to the solid support proved to be stable enough for the chemical transformations employed, yet labile enough for mild cleavage conditions to yield final products in high purity. The publication represents an example for combining synthetic organic chemistry on advanced scaffolds with the latest technologies of combinatorial chemistry in order to provide both industrial and academic institutions with compounds in high number and quality, thereby accelerating the search for novel biological targets and drug development.

## Introduction

Apart from being the genomic building blocks, nucleosides interact with roughly one-third of the protein classes in the human genome, including polymerases, kinases, reductases, motor proteins, membrane receptors, and structural proteins. Nucleosides are also rated as the central molecules of metabolism.

The binding motifs of these nucleosides are associated with a broad array of targets of therapeutic importance in biological systems. It was early recognized that introducing diversity into the carbohydrate or the base subunits of nucleosides represents promising strategies to identify specific receptor ligands, enzyme inhibitors, or nucleoside function modifiers.[1] Naturally occurring nucleoside analogues demonstrate selective activities, such as protein synthesis inhibitors (puromycin), glycosyl transferase inhibitors (tunicamycin), and methyl transferase inhibitors (sinefungin).

Synthetic analogues of nucleosides have been the cornerstone of antiviral therapy over the past 30 years.[2] Many nucleoside analogues exhibit antiproliferative,[3] antibiotic, and antifungal properties.[4] Ever since the discovery of extracellular purine and pyrimidine nucleosides as endogenous cell function modulators, the interest in adenosine receptors has continued to grow as a promising target of immense therapeutic potential.[5] The increasing resistance of pathogens,[6] the often severe side effects of nucleosides in chemotherapy,[7] and the lack of selective ligands for adenosine receptor subclasses despite extensive medicinal chemistry research[8] emphasizes the need for nucleoside analogues in high number and diversity. In addition, the availability of high-throughput screening capabilities together with the combinatorial synthesis of small organic molecule libraries[9] offers a unique opportunity to accelerate the discovery of novel pharmaceutical targets and leads, especially with biologically priviledged scaffolds, such as nucleosides in hand.

Although the solid-phase oligonucleotide synthesis is well established,[10] there are only a few reports on the solid-phase synthesis of mononucleoside analogues.[11] We have not come across any solid- or solution-phase-based mononucleoside library consisting of more than 500 members in the literature. Herein, the parallel synthesis of 25 000 nucleoside analogues as discrete compounds in 2−4 mg quantities is described.

## Results and Discussion

Several key considerations had to be taken into account in order to develop a strategy for the combinatorial solid-phase synthesis of nucleoside analogues with the general structures **1** and **2** (Scheme 1): (i) The main strategy was to introduce two sites of diversity on both the purine and the pyrimidine nucleoside scaffold bearing a myriad of functional groups. Thus, we were focusing on the derivatization of the 5′ position of the ribose subunit, as well as the C(6) position of the purine subunit and the C(4) position of the pyrimidine, respectively. The positions of diversification are chemically accessible and a wide range of biologically active nucleosides carry this substitution pattern. (ii) We chose to use low-cross-linked polystyrene based macroporous solid support[12] in order to enable chemical transformations possible even under conditions unsuitable for traditional gel-form solid supports, such as reactions in water and acetonitrile. (iii) The 2′,3′-hydroxyls of the ribose subunit offer the possibility of attaching the nucleosides to the solid support via an acetal linkage.[13] The chemical properties of a 2′,3′-acetal linkage allows for minimal protecting group manipulation throughout the library synthesis and cleavage under mild acidic conditions, which is essential to keep the glycosidic bond intact. The so-called preformed handle strategy provides an option to load the most advanced common intermediate onto the

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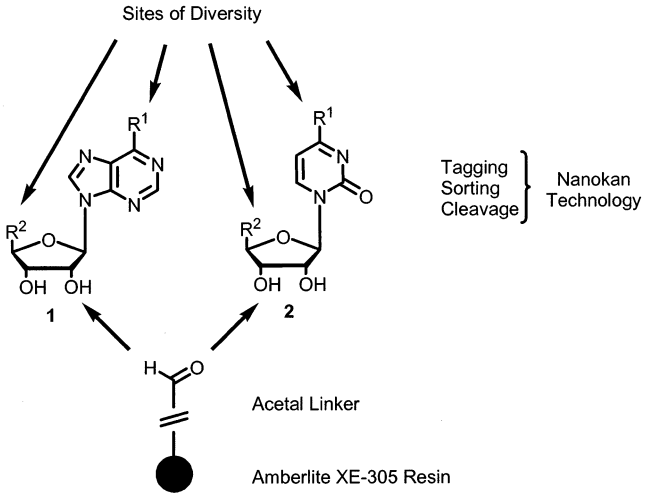
**Scheme 1.** General Strategy for the Solid-Supported Synthesis of Nucleoside Analogs




resin and to purify these intermediates prior to resin loading. Consequently, the number of steps on solid support are minimized, while the number of diversity generating steps on solid support are maximized. (iv) The Nanokan technology recently developed by IRORI (Discovery Partners International) provides a method to encapsulate up to 10 mg of resin aliquots in two-dimensional bar-coded microreactors.[14] Their automated directed sorting procedure allows tracing of quantities of several millimoles of the final compounds into discrete wells of microtiter plates. In addition, this technology enables facile quality control during the library synthesis as well as the premise for high-throughput purification. (v) A considerable challenge was to develop reliable, clean, and high-yielding derivatizations on solid support, ensuring exceptional purity of the final compounds upon cleavage. Mild and selective chemistry had to be employed to tolerate the sometimes fragile nature of the nucleoside scaffold.

The assembly of the resins containing the pyrimidine scaffold is depicted in Scheme 2. *p*-Hydroxybenzaldahyde **3** was reacted with ethyl-6-bromohexanoate **4** to afford aldehyde **5**, which was activated to the dimethoxyacetal **6**. Transketalization with uridine **7** gave the benzylidene **8**, which was mesylated at the 5′ position to **9** and substituted with azide to yield the 5′-azide **10**. The 5′-azido ester **10** was then saponified to the carboxylic acid **11**. Friedel−Crafts alkylation of unmodified Amberlite XE-305 **12** with *N*-(hydroxymethyl)phthalimide **13** (TFA = trifluoroacidic acid) and subsequent deprotection by hydrazinolysis yielded the aminomethyl-functionalized resin **14**.[15] The substantial aminomethyl substitution level of 1.5 mmol/g was determined by Fmoc quantitation following standard procedures.[16] The carboxylic acid **11** was then coupled to aminomethyl resin **14** using diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) activation to afford resin **15**.

1,2,4-Triazole **16** has proven to be highly successful as a leaving group for aromatic nucleophilic substitutions under mild conditions.[17] Uridines are readily activated with triazole **16** in the presence of phosphorus oxychloride ($POCl_3$) in basic media (TEA = triethylamine).[18] The 4-triazolo-activated solid supported pyrimidine **17** was loaded into IRORI nanokans (∼10 mg resin per kan) for library synthesis.

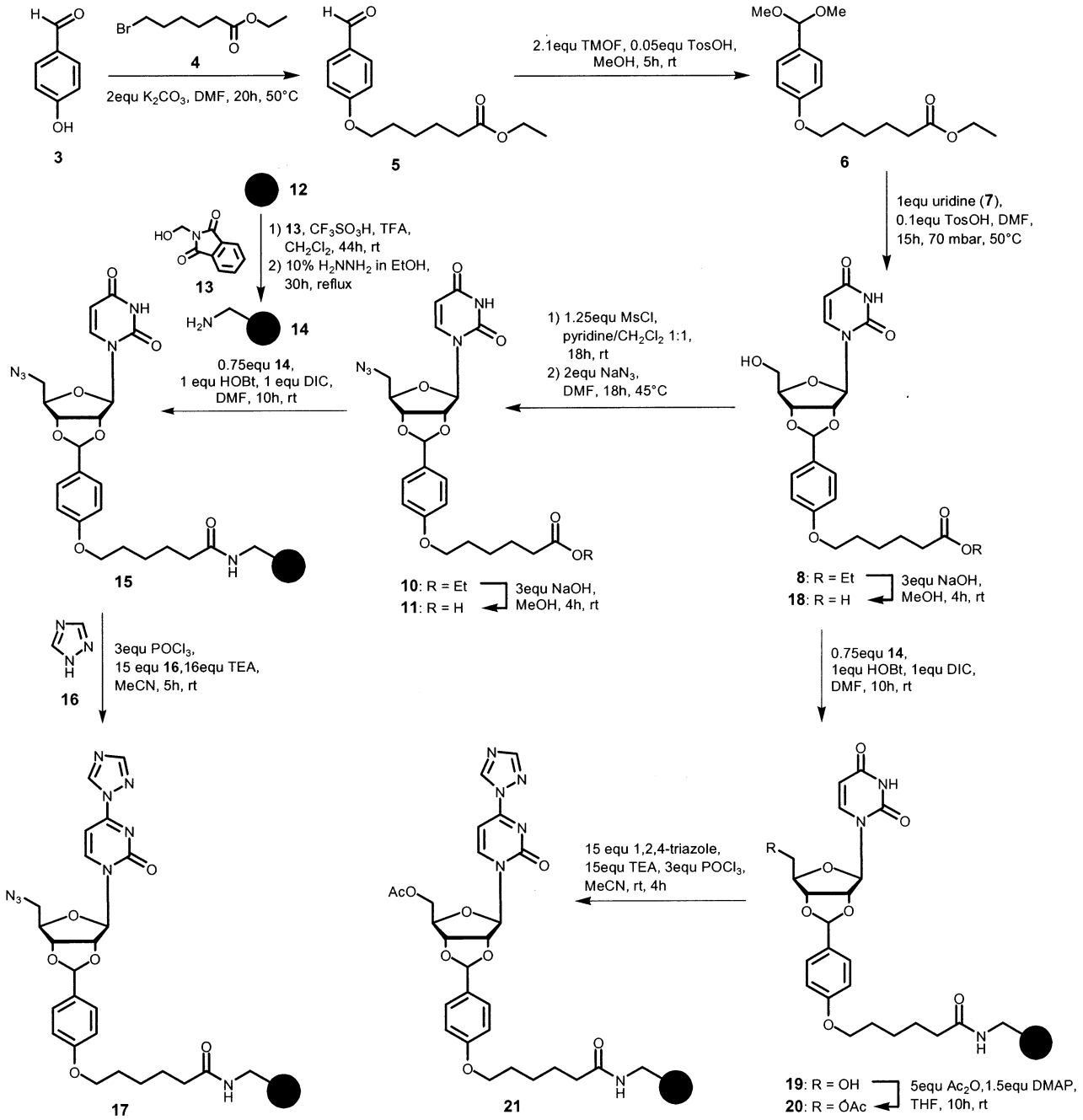
Alternatively, benzylidene **8** was saponified to the carboxylic acid **18** and loaded onto the aminomethyl resin **14** to give **19**. Protection of the 5′-hydroxy group with acetic anhydride ($Ac_2O$) in the presence of 4-(dimethylamino)-pyridine (DMAP) afforded the 5′-acetyl derivative **20**, which was activated to the 4-triazolo-5′-acetyl pyrimidine resin **21** and subsequently loaded into IRORI nanokans. Triazole-activation without prior protection of the 5′-hydroxy group led to various side products.

The synthesis of the resins containing the purine scaffold required a slightly different route (Scheme 3). 6-Chloroinosine **22** was selected as the nucleoside starting material. As a result of the high susceptibility of the C(6)-chloride for nucleophilic substitution, the ethyl ester **6** had to be transesterified with allyl alcohol **23** to the allyl ester **24**. Hence, after the transketalization of **18** with 6-chloroinosine **22**, the allyl ester **25** allowed for palladium-catalyzed saponification under neutral, water-free conditions[19] to yield the carboxylic acid derivative **26**. This step required a silica filtration of the catalyst byproducts. The coupling of **26** onto the aminomethyl functionalized macroporous resin **14** to give solid-supported purine **27** was carried out using *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) activation rather than HOBt and DIC, since HOBt partially displaces the chloride at the C(6) position of the purine (DIEA = diisopropylethylamine). Mesylation and subsequent substitution of the 5′ position with azide would also affect the C(6) position, thus support-bound 5′-azide **28** had to be generated from **27** using Mitsunobu conditions (DEAD = diethylazodicarboxylate) with diphenyl phosphoryl azide (DPPA).[20] Both **27** and **28** were loaded into IRORI nanokans for library synthesis. It is noteworthy that the entire solution-phase synthesis of **11** and **26** was accomplished without the need for a column chromatography purification step.

The first diversity generating step was accomplished by nucleophilic aromatic substitution of the Nanokan-encapsulated activated resins **17**, **21**, **27**, and **28** to afford products of the general structure **29**−**32** (Table 1). Of the various nucleophiles tried, only a certain fraction validated for both scaffolds. Generally, primary and secondary amines substituted quantitatively on both scaffolds at room temperature. Exceptions were strongly sterically hindered or weakly nucleophilic amines, which required heating to 50 °C. Aliphatic and aromatic thiols, alkoxides, and phenoxides tended to substitute well on the purine scaffold, but the corresponding products on the pyrimidine scaffold proved to be unstable to the acidic conditions for the cleavage of the final compounds off the resin. α-Nucleophiles, such as hydrazines and hydroxylamines, gave inconsistent and mostly moderate results for both scaffolds.

To vary hydrogen bonding characteristics, we attempted to substitute the activated species with water. This was unnecessary for the pyrimidine scaffold, since uridine-type resins **15** and **19** were readily available from our synthesis

**Scheme 2.** Synthesis of the Solid-Supported Pyrimidine Scaffolds



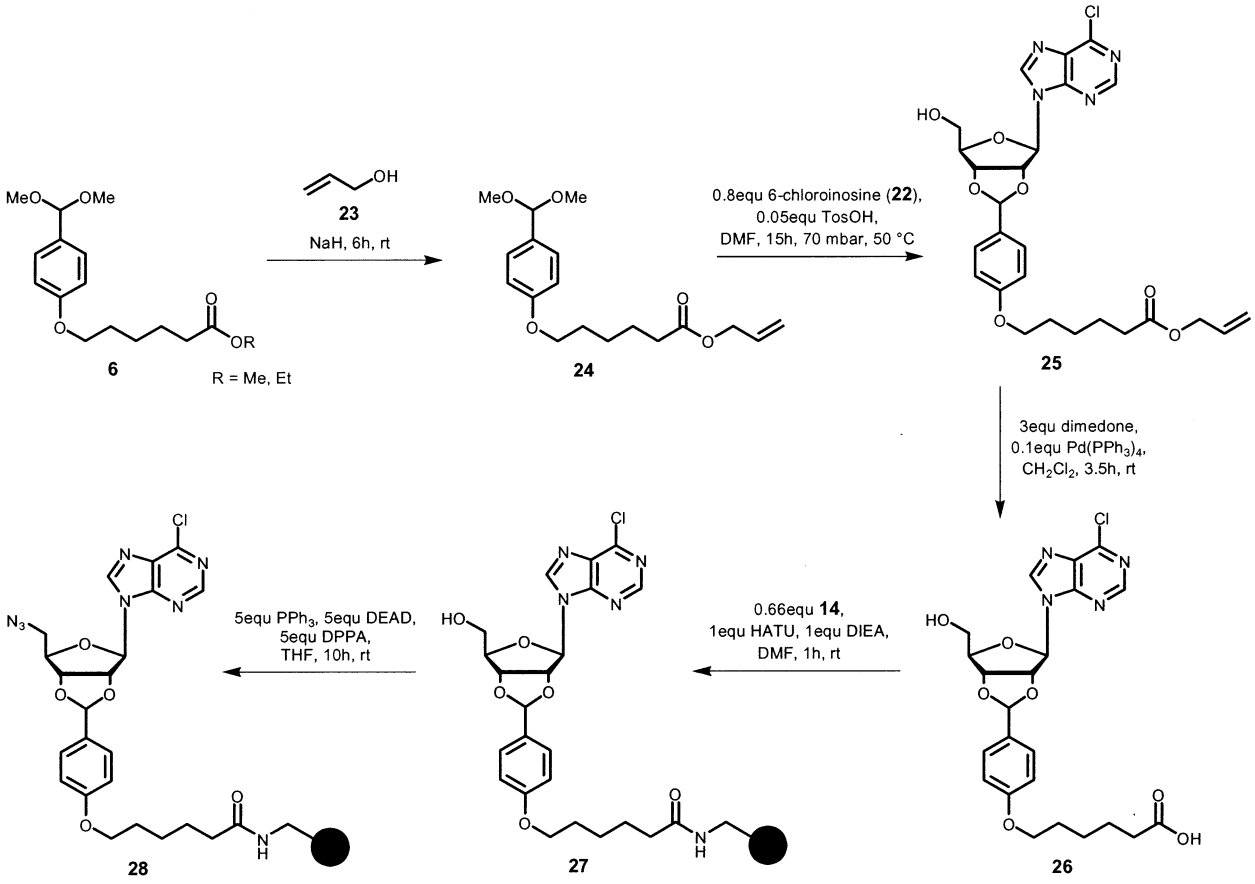

route. Concerning the purine scaffold, various conditions using hydroxide failed to give the desired product, but treatment with *N*,*N*-dimethyl hydroxylamine[21] afforded the inosine-type resins **33** and **34** in >90% purity (Scheme 4).

One of the most direct routes of generating diversity from an azido functionality employs a 1,3-dipolar cycloaddition with substituted alkynes.[22] However, even the solution-phase reactions are usually slow. Nevertheless, we were able to obtain the 5′-triazole products **35**−**38** as a mixture of regioisomers in satisfactory yield and purity by employing high alkyne concentration (20% alkyne in toluene), high temperature, and prolonged reaction times (Table 2). Occasionally, the high-temperature sensitivity of some alkynes required a second subjection. In general, monosubstituted and carboxy-substituted alkynes validated.

Alternatively, the azides **29** and **31** were cleanly reduced to the corresponding amines **39** and **40** using stannous chloride and thiophenol (PhSH).[23] The free amines **39** and **40** were then treated with various acylation reagents (HOBt/DIC activated carboxylic acids, isocyanates, isothiocyanates, aryl sulfonyl chlorides) to give amides, ureas, thioureas, and aryl sulfonamides of the general structures **41**−**48** (Scheme 5).

Substituted amidines and guanidines are highly interesting and desirable pharmacophores.[24] Solution-phase synthetic routes to these functionalities are usually hampered by tedious isolation and purification procedures as a result of their polar nature. Working on solid support can enormously facilitate their isolation, which in the case of guanidines has resulted in various novel synthetic strategies.[25] The Staudinger

**Scheme 3.** Synthesis of the Solid-Supported Purine Scaffolds

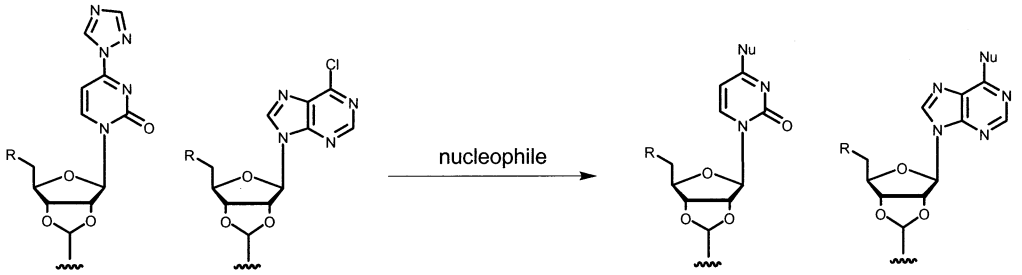



reaction[25e] provides a direct and elegant way to both functionalities (Scheme 6). The transformation of the azides **29** and **31** to their phospho-aza-ylide derivatives **49** and **50** with triphenylphosphine is spontaneous and quantitative. Intermediate resins **49** an **50** turned out to be stable enough to be stored for several months at room temperature. In fact, their hydrolysis to the free amines **39** and **40** required acid or base promotion, elevated temperature (50 °C), and overnight reaction times.[26] Treatment of phosphinamines **49** and **50** with isocyanates gave carbodiimides **51** and **52**. Alternatively, treatment with acid chlorides at elevated temperature in basic media resulted in the formation of imino chlorides **53** and **54**. Affording another step of diversity, both intermediates were then quenched with excess amine to yield the guanidines **55** and **56** and the amidines **57** and **58**, respectively. To suppress the formation of ureas and amides as hydrolysis byproducts of the reactive intermediates **51**−**54**, dry conditions, minimum reaction times, and minimal washing steps are required.

The 5′-hydroxy group opens routes to different sets of functionalities. The following transformations of the 5′-hydroxy group met the standards required for solid-phase library production. They are clean, in many cases quantitative, and provide a handle for broad diversification. First, a hydrazinolysis[27] step on the resin containing the 5′-acetoxy-pyrimidine scaffold (**30**) was necessary to deprotect the 5′-hydroxy functionality (**59**, Scheme 7). Both scaffolds **59** and **32** were readily converted into the 5′-mesylates **60** and **61** using mesyl chloride in pyridine.[28] Although especially primary amines cleanly displaced the pyrimidine mesylate **60** at room temperature to give 5′-amines **62**, the purine resins **61** reacted very slowly and sluggishly, even at higher temperature. Alternative ways to install amino substituents at the 5′ position of the purine scaffold (**63**) had to be explored. Chlorination of the 5′ position of **59** and **32** using triphenylphosphine and carbontetrachloride[29] led to 5′-chlorides **64** and **65**. In this case, secondary amines displaced faster than primary amines at high temperature, and the purine scaffold gave the cleaner results. Thus, we decided to use mesylation on the pyrimidine and chlorination on the purine scaffold for the synthesis of substituted 5′-amino nucleosides **62** and **63**. Yet another route to substituted 5′ amines is reductive amination. After oxidation of the 5′-alcohols **59** and **32** to the corresponding aldehydes **66** and **67** using Dess−Martin periodinane,[30] treatment with primary amines in the presence of sodium triacetoxyborohydride resulted in monosubstituted 5′-amines **62** and **63**. Other established oxidation protocols failed to produce clean aldehydes.[31] In general, the oxidation/reductive amination route gave inferior purities of the final compounds, as compared to the activation/nucleophilic displacement routes described above.

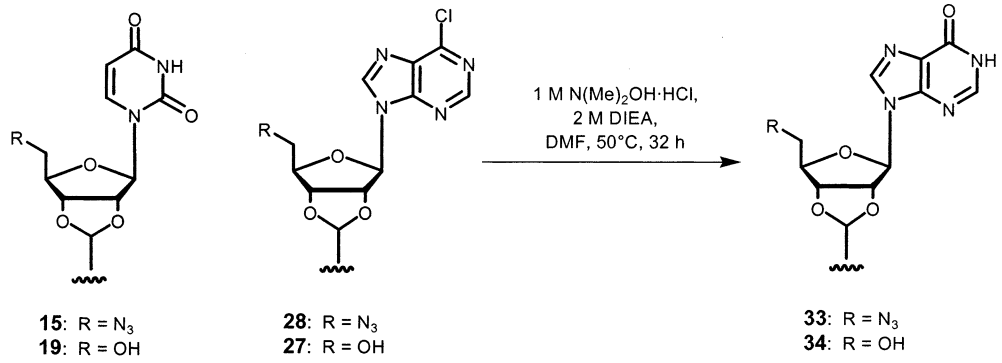
Attempts to cleanly oxidize the 5′-aldehydes **66** and **67** to the 5′-carboxylic acids **68** and **69** (Scheme 8) using *m*-chloroperbenzoic acid[32] or sodium chlorite ($NaClO_2$)[33] failed. The direct oxidation of the 5′-alcohols **59** and **32** through the recently developed 2,2,6,6-tetramethylpiperidinyloxyl

**Table 1.** Nucleophile Scope for the Nucleophilic Aromatic Substitution of Resin-Bound, Activated Pyrimidine and Purine Nucleosides




| nucleophile | | concn, M | temp, °C | time, h | solvent | purity, % | comment |
|---|---|---|---|---|---|---|---|
| $NaN_3$ | Py | 0.4 | 50 | 48 | NMP | 70 | slow |
| | Pu | 0.4 | rt | 24 | NMP | >95 | fast |
| $Et_4NCN$ | Py | 0.2 | 50 | 3 | $CH_3CN$ | <10 | decay |
| | Pu | 0.2 | 50 | 3 | $CH_3CN$ | 80 | side products |
| $NH_3$ | Py | 1.0 | 50 | 24 | $^n$BuOH/NMP 1:1 | >95 | fast |
| | Pu | 1.0 | 50 | 48 | $^n$BuOH/NMP 1:1 | 80 | slow |
| amines | Py | 0.4 | 50 | 24 | NMP | >95 | sterics |
| | Pu | 0.4 | 50 | 24 | NMP | >95 | basicity |
| thiols | Py | 0.4 | 50 | 24 | $^n$BuOH | <10 | decay |
| | Pu | 0.4 | 50 | 24 | $^n$BuOH | >90 | |
| alkoxides | Py | 0.4 | 50 | 24 | alcohol | <10 | decay |
| | Pu | 0.4 | 50 | 24 | alcohol | >90 | |
| hydrazines | Py | 0.4 | 50 | 24 | DMF | 0−>95 | inconsistent |
| | Pu | 0.4 | 50 | 24 | DMF | 0−>95 | inconsistent |
| hydroxy- amines | Py | 0.4 | 50 | 24 | DMF | 0−>95 | inconsistent |
| | Pu | 0.4 | 50 | 24 | DMF | 0−>95 | inconsistent |

**Scheme 4.** Uridine- and Inosine-Type Resins

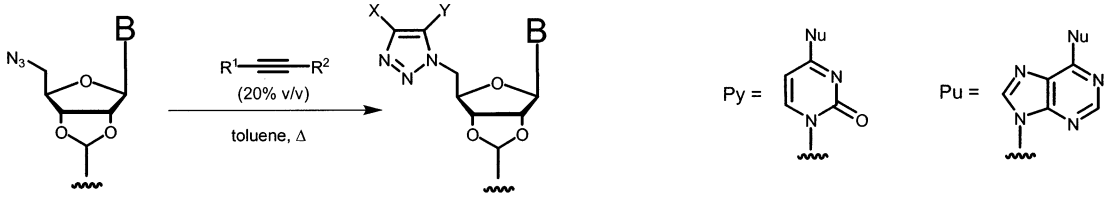



(TEMPO)-catalyzed oxidation employing bisacetoxyiodobenzene (BAIB) as the stoichiometric oxidant[34] resulted in a remarkably clean conversion to the corresponding carboxylic acids **68** and **69**. Amide bond formation with primary and secondary amines using HOBt/DIC activation led to uronamides of the general structures **70** and **71**.

Finally, carbonylation of resins **59** and **32** using carbonyldiimidazole (CDI)[35] gave intermediates **72** and **73**, which were quenched with primary or secondary amines to yield carbamates **74** and **75** (Scheme 9). In general, when secondary amines were employed, the reaction needed higher temperature in order to be driven to completion. Quenching with alcohols resulted in the formation of carbonates **76** and **77**, although in lower yield and purity.

The ultimate step after all of the above-mentioned reaction schemes is the cleavage of the resin-bound nucleoside analogues **78** and **79** to give the final products of the general structures **80** and **81** (Scheme 9). The employed acetal linkage features mild cleavage conditions. Hence, only 5% TFA was necessary to affect product recovery in good yields and exceptional purity.[36] A trifluoroacetic acid content >5% resulted in shorter cleavage times, but in some cases, we observed partial cleavage of the glycosidic bond. To avoid concentration changes in TFA due to solvent evaporation, we split the 24-h incubation time into 3 subjections using freshly prepared cleavage cocktail. Liquid chromatography coupled mass spectrometry (LC−MS) analysis of 6% of the library (1500 members) showed that 75% of the compounds were >85% pure. A gravimetric analysis of the plates containing the final compounds **80** and **81** gave an average yield of ~4 mg compound per well. Some representative members of the library (examples **I-XXXI**) were characterized by $^1$H NMR and MS and can be found in the Experimental Section. High-pressure liquid chromatography

**Table 2.** Alkyne Scope for the 1,3-Dipolar Electrocyclic Addition to Resin-Bound Azides[a]




**29**: B = Py
**31**: B = Pu

**35**: B = Py, X = $R^1$, Y = $R^2$
**36**: B = Py, X = $R^2$, Y = $R^1$
**37**: B = Pu, X = $R^1$, Y = $R^2$
**38**: B = Pu, X = $R^2$, Y = $R^1$

| acetylene | | conditions | | conversion, % | | |
|---|---|---|---|---|---|---|
| $R_1$ | $R_2$ | temp/°C | time/h | Py | Pu | comment |
| H | alkyl | 75 | 24 | <20 | <20 | low reactivity |
| H | aryl | 75 | 24 | >90 | >90 | |
| H | $CH_2X$ | 75 | 24 ×2 | >80 | >80 | |
| H | COOR | 50 | 24 | >90 | >90 | decay at 75 °C |
| H | $SiR_3$ | 75 | 24 ×2 | >90 | >90 | |
| alkyl | alkyl | 75 | 24 | <10 | <10 | low reactivity |
| alkyl | aryl | 75 | 24 | <20 | <20 | low reactivity |
| alkyl | $CH_2X$ | 75 | 24 ×2 | <50 | <50 | low reactivity |
| alkyl | COOR | 75 | 24 ×2 | >90 | >90 | |
| COOR | COOR | 50 | 10 | >90 | >90 | decay at 75 °C |
| $CH_2OR$ | $CH_2OR$ | 75 | 24 ×2 | >90 | >90 | |

[a] B = substituted purine (Pu) and pyrimidine (Py) scaffold. ×2 = Second subjection.

(HPLC) purification of selected representatives of the library resulted in an average yield of ~2 mg of pure compound per well. Considering an average molecular weight of 450 g/mol per compound, this translates to ~45% yield of pure compound per well. Taking into account the weight of extractables in the nonpurified wells as well as typical compound loss during HPLC purification, we were delighted by such a high recovery of pure compound.

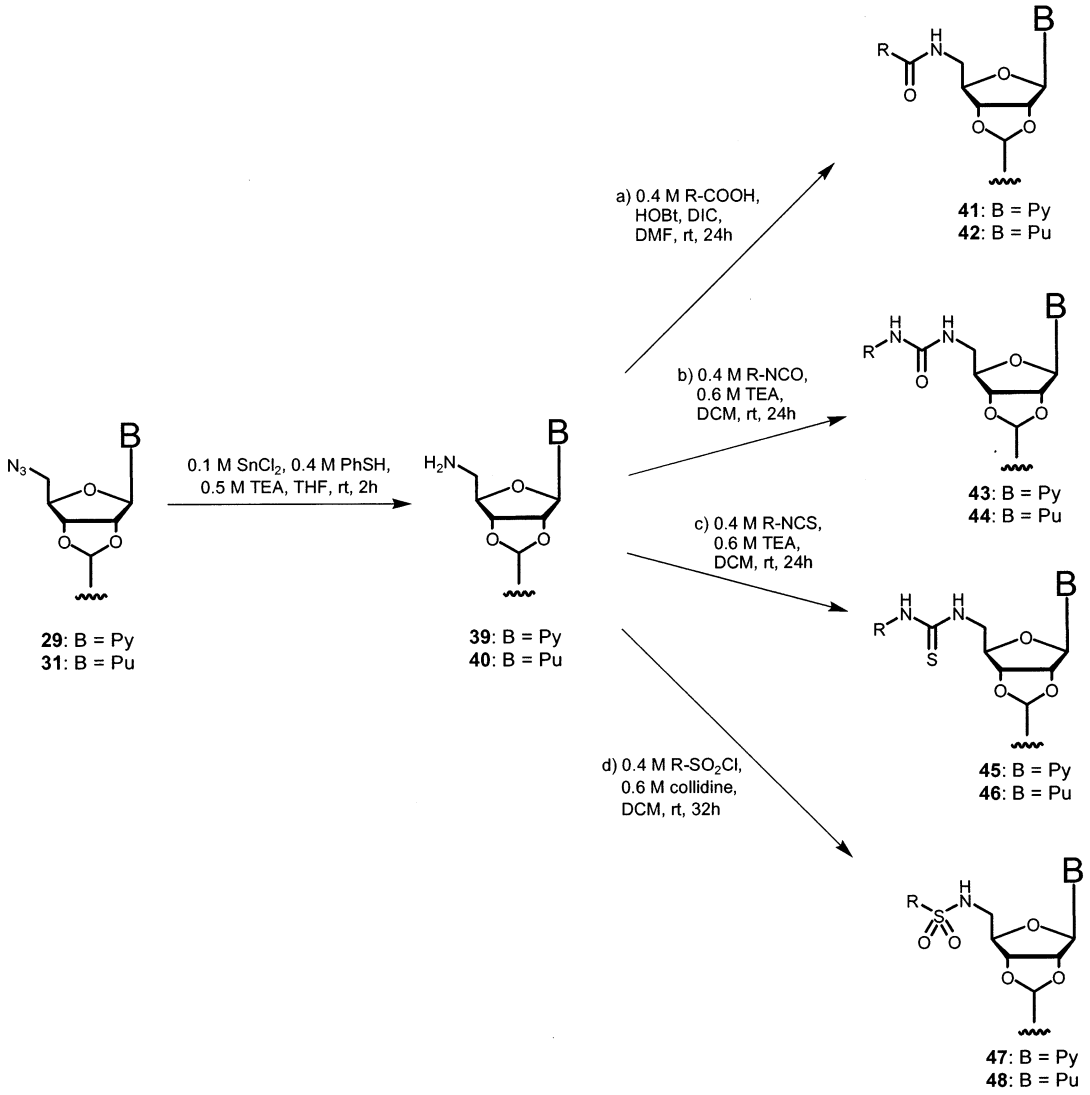
In summary, the goal of providing a high number of potential biologically active compounds in reasonable amount and purity has been accomplished. The array of nucleoside compounds displayed in Scheme 10 provides an immense opportunity for the accelerated discovery and optimization of nucleoside leads displaying similar substitution patterns. In addition, the synthetic strategy involved leaves room for further derivatizations and higher substitution patterns on both scaffolds, to refine and focus further libraries directed at specific targets. The existing 25 000 member library is currently being subjected to high-throughput cell-based assays, the results of which will be reported in due course.

## Experimental Section

**General Experimental Details.** Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 400 MHz with a Bruker DPX-400 instrument. The chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Multiplicity, coupling constants, and integrations are listed in brackets. Infrared (IR) spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P. spectrophotometer. High-resolution mass spectra (HRMS) were performed by The Scripps Center of Mass Spectrometry. On-bead conversions were monitored by on-bead IR, by cleavage followed by reversed-phase LC−MS analysis (Agilent Series 1100), or by standard staining tests,[37] if applicable. The purity of final compounds was determined using LC−MS analysis together with ultraviolet (UV) trace analysis at 220, 255, and 280 nm. Thin-layer chromatography was performed on Merck (EM Science) Silica gel $F_{254}$ sheets. Materials obtained from commercial suppliers were used without purification. 6-Chloroinosine **22** was obtained from General Intermediates of Canada, Inc. The loading and directed sorting of IRORI nanokan microreactors was performed at IRORI. To ensure proper solvent and reagent diffusion, the nanokan microreactors were short-time-evacuated ("burped") for 1 min prior to the reactions and washing steps using a Labconco vacuum desiccator cabinet (model no. 55300-00).

**6-(4-Formyl-phenoxy)-hexanoic Acid Ethyl Ester (5).** A mixture of 4-hydroxybenzaldehyde (**3**, 0.60 kg, 4.91 mol), ethyl-6-bromohexanoate (**4**, 1.10 kg, 4.91 mol), and $K_2CO_3$ (1.36 kg, 9.83 mol) in DMF (2 L) was stirred at 50 °C for 20 h. The mixture was filtered to remove remaining $K_2CO_3$. The resulting solution was concentrated in vacuo, diluted with EtOAc (3 L), and subsequently washed with saturated aqueous NaCl (3 × 1.5 L). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give an off-white solid (**5**, 1.23 kg, 4.66 mol, 95%) with no need for further purification: mp, 33−35 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 9.87 (s, 1H), 7.81 (d, $J$ = 8.7, 2H), 6.97 (d, $J$ = 8.7, 2H), 4.12 (q, $J$ = 7.1, 2H), 4.04 (t, $J$ = 6.4, 2H), 2.33 (t, $J$ = 7.4, 2H), 1.82 (m, 2H), 1.69 (m, 2H), 1.53 (m, 2H), 1.25 (t, $J$ = 7.1, 3H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ = 191.0, 173.7, 164.3, 132.1 (2C), 130.1, 114.9 (2C), 68.3, 60.5, 34.4, 29.0, 25.8, 24.8, 14.4; IR (film) $\nu$ = 2941, 1719, 1688, 1595, 1579, 1509, 1466, 1392, 1307, 1252, 1213, 1155,

**Scheme 5.** Reduction and Subsequent Diversification of the 5′-Azide Functionality

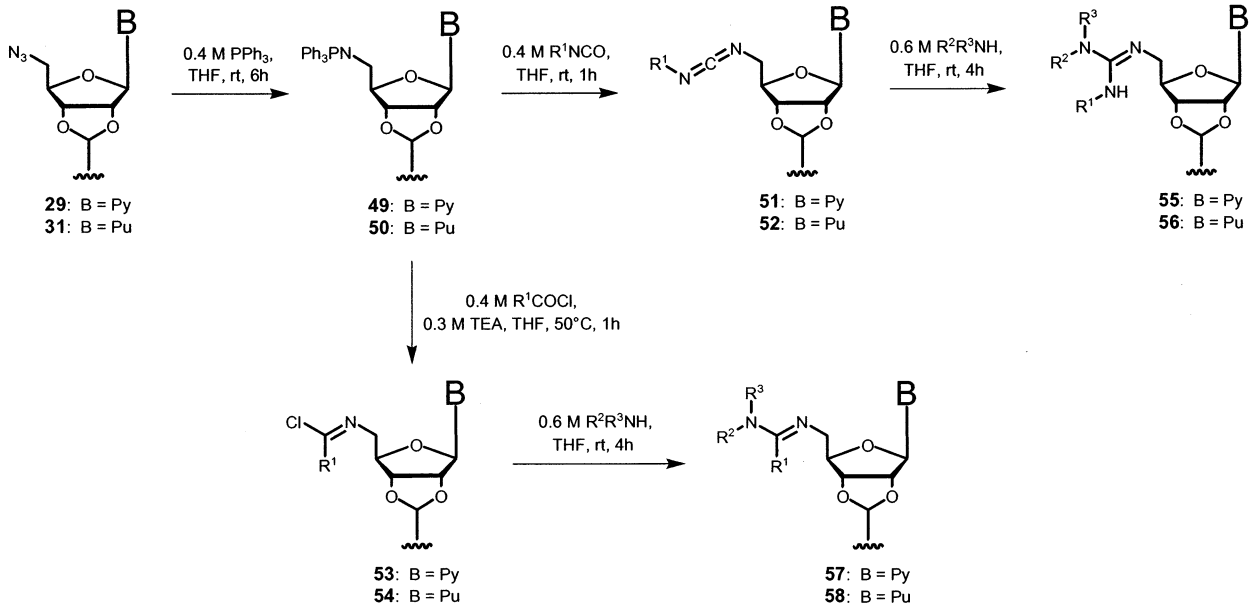



1108, 1030, 999, 832 $cm^{-1}$; HRMS (MALDI-FTMS) *m*/*z* 287.1254 (287.1254 calcd for $C_{15}H_{20}O_4Na$, $[M + Na]^+$).

**6-(4-Dimethoxymethyl-phenoxy)-hexanoic Acid Ethyl Ester (6).** A mixture of **5** (424 g, 1.60 mol), trimethylorthoformate (0.37 L, 3.40 mol), and *p*-toluenesulfonic acid monohydrate (15 g, 79 mmol) in MeOH (1 L) was stirred for 5 h at room temperature. Triethylamine (11 mL, 79 mmol) was added, and the resulting solution was concentrated in vacuo, diluted with EtOAc (2 L), and subsequently washed with $H_2O$ (2 × 1 L) and saturated aqueous NaCl (1 × 1 L). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield an amber liquid (**6**, 481 g, 1.55 mol, 97%) with no need for further purification: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta = 7.33$ (d, $J = 8.7$, 2H), 6.97 (d, $J = 8.7$, 2H), 5.33 (s, 1H), 4.11 (q, $J = 7.1$, 2H), 3.95 (t, $J = 6.4$, 2H), 3.29 (s, 6H), 2.32 (t, $J = 7.4$, 2H), 1.79 (m, 2H), 1.69 (m, 2H), 1.49 (m, 2H), 1.24 (t, $J = 7.1$, 3H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta = 173.7$, 159.3, 130.4, 128.0 (2C), 114.2 (2C), 103.2, 67.8, 60.4, 52.7 (2C), 34.4, 29.1, 25.8, 24.8, 14.4; IR (film) $\nu = 2937$, 1723, 1610, 1513, 1241, 1171, 1104, 1046, 980, 828 $cm^{-1}$; HRMS (MALDI-FTMS) not detectable due to instability; detected: *m*/*z* 287.1254 (287.1252 calcd for parent aldehyde **5** $C_{17}H_{27}O_5Na$, $[M + Na]^+$).

**6-(4-Dimethoxymethyl-phenoxy)-hexanoic Acid Allyl Ester (24).** Sodium hydride (5.0 g, 0.21 mol) was slowly added to allyl alcohol (**23**, 1.2 L). To this solution, the ethyl ester **6** (232 g, 0.78 mmol) was added in allyl alcohol (0.2 L) and was stirred for 6 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with EtOAc (1 L,) and washed with saturated aqueous NaCl (3 × 0.5 L). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a yellow liquid (**24**, 220 g, 0.68 mmol, 88%): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta = 7.33$ (d, $J = 8.2$, 2H), 6.90 (d, $J = 8.2$, 2H), 5.94 (m, 1H), 5.32 (s, 1H), 5.31 (d, $J = 12.3$, 1H), 5.22 (d, $J = 10.4$, 1H), 4.58 (m, 2H), 3.97 (m, 2H), 3.29 (s, 6H), 2.39 (m, 2H), 1.79 (m, 2H), 1.69 (m, 2H), 1.52 (m, 2H); $^{13}C$ NMR (400 MHz, $(CD_3)_2SO$) $\delta = 175.0$, 160.8, 133.9, 131.7, 129.1 (2C), 118.4, 115.2 (2C), 104.7, 68.9, 66.1, 53.2 (2C), 35.0, 30.2, 26.8, 25.9; IR (film) $\nu = 2930$, 1735, 1614, 1513, 1353, 1299, 1241, 1167, 1097, 1050, 980, 933, 828; HRMS (MALDI-

**Scheme 6.** Synthesis of Guanidine and Amidine Nucleoside Analogs through the Use of Phosphinamines as Key Intermediates



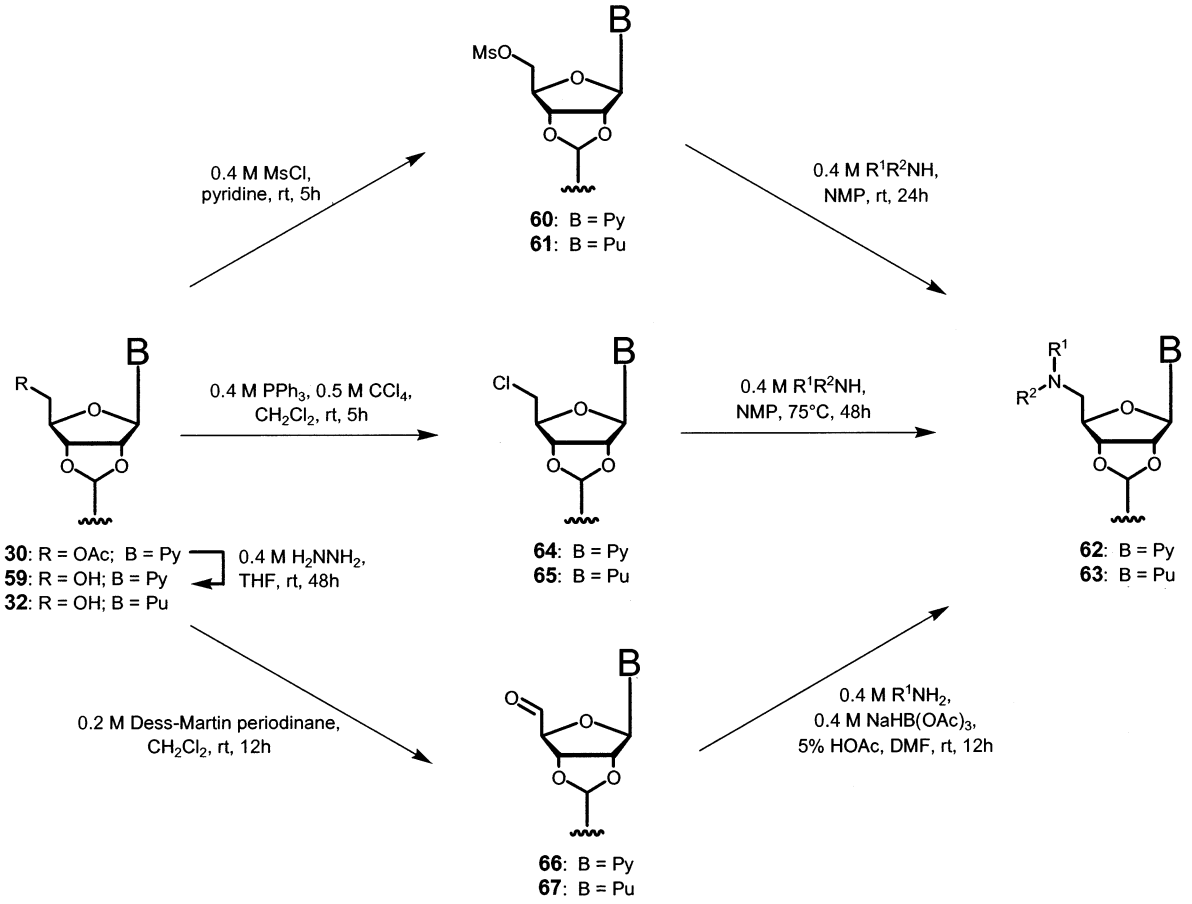

FTMS) not detectable due to instability; detected: *m*/*z* 299.1263 (calcd for parent aldehyde $C_6H_{20}O_4Na$ $[M + Na]^+$ 299.1259).

**6-{4-[4-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-6-hydroxymethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid Ethyl Ester (8).** Uridine (**7**, 50 g, 0.21 mol) together with **6** (70 g, 0.23 mol) was dissolved in DMF (150 mL). *p*-Toluenesulfonic acid monohydrate (3.8 g, 20 mmol) was added, and the mixture was placed on a Buechi R-134 rotavapor and agitated under reduced pressure (70 mbar) at 50 °C for 15 h. The mixture was then neutralized with triethylamine (2.8 mL, 20 mmol) and subsequently concentrated in vacuo. The resulting residue was suspended in EtOAc (400 mL), filtered, and washed with 1:1 EtOAc/$H_2O$ (400 mL), $H_2O$ (2 × 200 mL), 1:1 $H_2O$/$Et_2O$ (200 mL), and $Et_2O$ (2 × 200 mL) to give a colorless solid as a mixture of two diastereomers (**8**, 77 g, 0.16 mol, 76%). Upon recrystallization from EtOH/EtOAc, one of the diastereomers exclusively crystallized: mp, 176−178 °C; $^1$H NMR (400 MHz, $(CD_3)_2SO_3$) $\delta$ = 11.38 (s, 1H), 7.82 (d, $J$ = 8.1, 1H), 7.42 (d, $J$ = 8.6, 2H), 6.95 (d, $J$ = 8.6, 2H), 5.94 (s, 1H), 5.90 (s, 1H), 5.64 (d, $J$ = 8.1, 1H), 5.10 (t, $J$ = 5.2, 1H), 4.99 (m, 1H), 4.82 (m, 1H), 4.23 (m, 1H), 4.04 (q, $J$ = 7.1, 2H), 3.97 (t, $J$ = 6.3, 2H), 3.60 (m, 2H), 2.30 (t, $J$ = 7.4, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.41 (m, 2H), 1.16 (t, $J$ = 7.1, 3H); $^{13}$C NMR (400 MHz, $(CD_3)_2SO$) $\delta$ = 172.8, 163.2, 159.7, 150.3, 142.1, 128.4 (2C), 128.0, 114.2 (2C), 106.5, 101.7, 91.3, 86.4, 84.2, 81.6, 67.4, 61.3, 59.6, 33.4, 28.3, 25.0, 24.2, 14.1; IR (film) $\nu$ = 3467, 2933, 1692, 1677, 1248, 1116, 1077, 828; HRMS (MALDI-FTMS) *m*/*z* 513.1851 (513.1849 calcd for $C_{24}H_{30}N_2O_9Na$ $[M + Na]^+$).

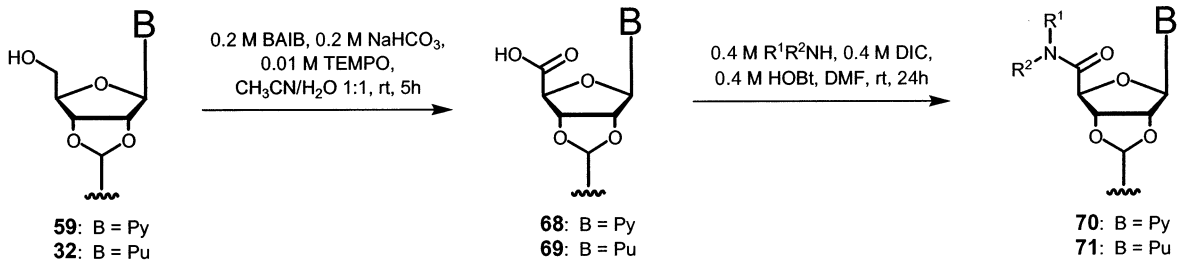
**6-{4-[4-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-6-methanesulfonyloxymethyl-tetrahydro-furo[3,4-*d*][1,3]-dioxol-2-yl]-phenoxy}-hexanoic Acid Ethyl Ester (9).** A 3-L round-bottom flask containing the uridine derivative **8** (99 g, 0.20 mol), DCM (250 mL), and pyridine (250 mL) was placed in a chilled water bath (4 °C). Methanesulfonyl chloride (19.1 mL, 0.25 mol) was added over a period of 15 min, and the solution was allowed to warm to room temperature and left to stir for 18 h. The mixture was then concentrated in vacuo, diluted with EtOAc (1.75 L), washed with $H_2O$ (3 × 1 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a colorless oil (**9**, 107.0 g, 188 mmol, 93%) as a mixture of two diastereomers: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 10.38 (s, 1H, 1H′), 7.39 (d, $J$ = 8.5, 2H), 7.35 (d, $J$ = 8.5, 2H′), 7.27 (d, $J$ = 8.0, 1H, 1H′), 6.88 (d, $J$ = 8.5, 2H), 6.86 (d, $J$ = 8.5, 2H′), 5.97 (s, 1H′), 5.87 (s, 1H), 5.71 (d, $J$ = 8.0, 1H, 1H′), 5.70 (s, 1H), 5.66 (s, 1H′), 5.19−4.93 (m, 2H, 2H′), 4.53 (m, 1H, 1H′), 4.46 (m, 2H, 2H′), 4.10 (q, $J$ = 7.1, 2H, 2H′), 3.92 (q, $J$ = 6.0, 2H, 2H′), 3.00 (s, 3H′), 2.99 (s, 3H), 2.32 (m, 2H, 2H′), 1.75 (m, 2H, 2H′), 1.66 (m, 2H, 2H′), 1.46 (m, 2H, 2H′), 1.22 (t, $J$ = 7.1, 3H, 3H′); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ = 174.5, 174.0, 164.4, 164.3, 160.8, 160.7, 150.9, 150.9, 143.9, 143.7, 128.7 (2C), 128.6 (2C), 127.7, 127.7, 114.8 (2C), 114.8 (2C), 108.1, 104.4, 96.3, 96.0, 86.1, 85.6, 83.8, 83.6, 82.0, 81.4, 69.8, 69.5, 68.1, 68.1, 60.6, 60.6, 37.9, 37.9, 34.6, 34.3, 29.2, 29.2, 26.0, 26.0, 25.1, 25.0, 14.6, 14.6; IR (film) $\nu$ = 3194, 2938, 1684, 1354, 1248, 1178, 1066, 957, 813; HRMS (MALDI-FTMS) *m*/*z* 591.1615 (591.1619 calcd for $C_{25}H_{32}N_2O_{11}SNa$ $[M + Na]^+$).

**6-{4-[4-Azidomethyl-6-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid Ethyl Ester (10).** A mixture of **9** (50 g, 88 mmol) and sodium azide ($NaN_3$, 11.5 g, 177 mmol) in DMF (200 mL) was stirred at 45 °C for 18 h. The resulting mixture was concentrated in vacuo, diluted with EtOAc (500 mL), washed with saturated aqueous NaCl (2 × 500 mL) and $H_2O$ (2 × 500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a colorless foam (**10**, 40.0 g, 77.6 mmol, 88%) as a mixture of two diastereomers: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 9.60 (s, 1H, 1H′), 7.44 (d, $J$ = 8.7, 2H), 7.39 (d, $J$ = 8.7, 2H′), 7.31 (d, $J$ = 8.0, 1H, 1H′), 6.93 (d, $J$ = 8.7, 2H), 6.91 (d, $J$ = 8.7, 2H′), 6.04 (s, 1H′), 5.96 (s, 1H), 5.80 (d, $J$ = 8.0, 1H, 1H′), 5.77 (s, 1H), 5.72 (s, 1H′), 5.17−4.92 (m, 2H, 2H′), 4.44 (m, 1H), 4.34

**Scheme 7.** Transformation of the 5′-Alcohol Functionality into Substituted 5′-Amines



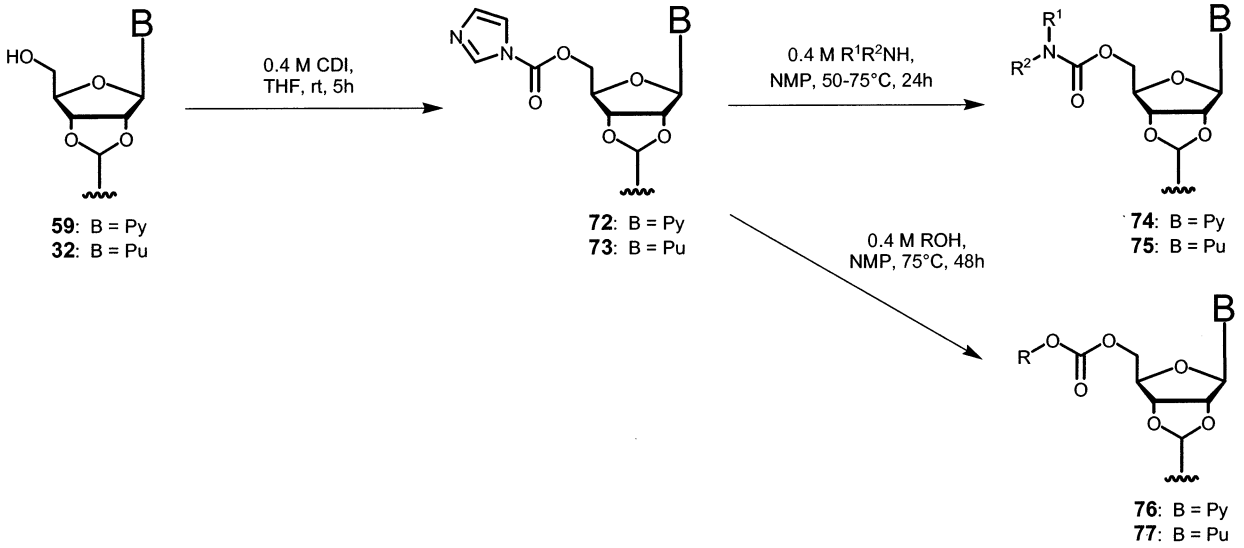

**Scheme 8.** Uronamide Formation through Oxidation of the 5′-Alcohol Functionality to the Corresponding 5′-Carboxylates Followed by Activation and Amide Bond Formation



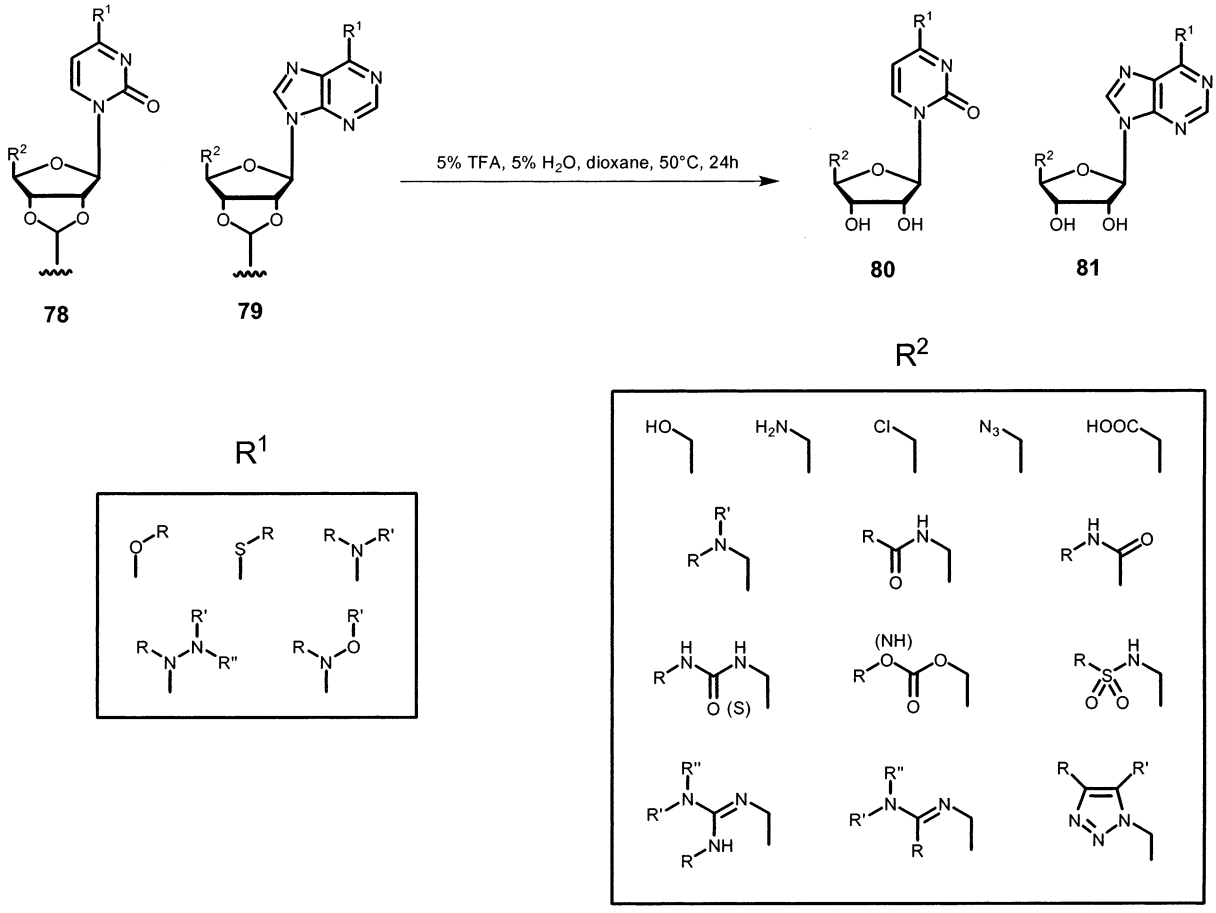

(m, 1H′), 4.15 (m, 2H, 2H′), 3.99 (q, $J$ = 6.3, 2H, 2H′), 3.69 (m, 2H, 2H′), 2.36 (m, 2H, 2H′), 1.82 (m, 2H, 2H′), 1.72 (m, 2H, 2H′), 1.52 (m, 2H, 2H′), 1.27 (m, 3H, 3H′); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ = 174.0, 174.0, 164.5, 163.3, 160.9, 160.8, 150.3, 150.3, 143.0, 142.8, 128.6 (2C), 128.5 (2C), 127.7, 127.6, 115.1 (2C), 114.9 (2C), 108.5, 104.7, 103.5, 103.4, 95.2, 95.1, 86.3, 85.5, 84.0, 83.9, 82.4, 81.8, 68.5, 68.1, 60.7, 60.7, 52.9, 52.7, 34.6, 34.4, 29.3, 29.1, 26.0, 26.0, 25.1, 25.0, 14.7, 14.7; IR (film) $\nu$ = 3198, 2938, 2097, 1684, 1245, 1069, 832, 809; HRMS (MALDI-FTMS) *m*/*z* 538.1916 (538.1908 calcd for $C_{24}H_{29}N_5O_8Na$ [M + Na]$^+$).

**6-{4-[4-Azidomethyl-6-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid (11).** A solution of sodium hydroxide (NaOH, 20.8 g, 522 mmol) in $H_2O$ (125 mL) was added to a suspension of **10** (89.8 g, 174 mmol) in EtOH (400 mL) and was stirred for 4 h at room temperature. The solvent was removed, and the resulting residue was diluted with $H_2O$ (300 mL). The suspension was then treated dropwise with 1 M aqueous HCl (522 mmol, 522 mL) to afford a white precipitate, which was subsequently partitioned with EtOAc (1.5 L). The organic layer was then washed with $H_2O$ (2 × 1 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a white foam (**11**, 80.2 g, 164 mmol, 95%) as a mixture of two diastereomers: $^1$H NMR (400 MHz, $(CD_3)_2SO$ $_3$) $\delta$ = 12.01 (s, 1H, 1H′), 11.49 (s, 1H, 1H′), 7.78 (d, $J$ = 8.0, 1H), 7.74 (d, $J$ = 8.0, 1H′), 7.43 (d, $J$ = 8.5, 2H), 7.37 (d, $J$ = 8.5, 2H′), 6.96 (d, $J$ = 8.5, 2H), 6.93 (d, $J$ = 8.5, 2H′), 6.07 (s, 1H′), 5.93 (s, 1H), 5.91 (s, 1H, 1H′), 5.67 (d, $J$ = 8.0, 1H), 5.66 (d, $J$ = 8.0, 1H′), 5.20−4.81 (m, 2H, 2H′), 4.31 (m, 1H, 1H′), 3.96 (m, 2H, 2H′), 3.62 (m, 2H, 2H′), 2.22 (m, 2H, 2H′), 1.70 (m, 2H, 2H′), 1.54 (m, 2H, 2H′), 1.41 (m, 2H, 2H′); $^{13}$C NMR (400 MHz, $(CD_3)_2SO$ $_3$) $\delta$ = 175.3, 175.3, 164.1, 164.0, 160.7, 160.6, 151.2, 151.2, 144.3, 143.7, 129.3 (2C), 129.3 (2C), 128.6, 128.6, 115.1 (2C), 115.0 (2C), 107.6, 103.5, 103.1, 102.8, 93.5, 92.5, 85.9, 85.1,

**Scheme 9.** Synthesis of 5′-Carbamates and Carbonates Using CDI Activation of the 5′-Hydroxy Functionality




**Scheme 10.** Cleavage of the Resin-Bound Derivatives to the Final Products




83.2, 82.8, 82.6, 81.5, 68.3, 68.3, 52.7, 52.5, 34.5, 34.5, 29.2, 29.1, 26.0, 25.9, 25.1, 25.1; IR (film) $\nu$ = 3354, 3183, 2941, 2101, 1684, 1245, 1069, 1050, 1023, 995, 824; HRMS (MALDI-FTMS) *m*/*z* 510.1600 (510.1595 calcd for $C_{22}H_{25}N_5O_8Na$ $[M + Na]^+$).

**6-{4-[4-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-6-hydroxymethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid (18).** A solution of NaOH (12.6 g, 315 mmol) in $H_2O$ (100 mL) was added to a suspension of **8** (50 g, 102 mmol) in MeOH (750 mL) and stirred for 8 h at room temperature. Approximately one-half of the solvent was removed in vacuo, and the remainder was treated dropwise with 1 M aqueous HCl (315 mmol, 315 mL). The white precipitate was filtered, washed with $H_2O$ (2 × 200 mL) and $Et_2O$ (3 × 200 mL), and dried in vacuo to afford a white powder (**18**, 46.7 g, 100 mmol, 99%) as a mixture of two diastereomers: mp: 158−160 °C; $^1$H NMR (400 MHz, $(CD_3)_2SO$ $_3$) $\delta$ = 11.95 (s, 1H, 1H′), 11.38 (s, 1H,

1H′), 7.85 (d, $J = 8.0$, 1H), 7.77 (d, $J = 8.0$, 1H′), 7.41 (d, $J = 8.5$, 2H), 7.37 (d, $J = 8.5$, 2H′), 6.96 (d, $J = 8.5$, 2H), 6.93 (d, $J = 8.5$, 2H′), 6.04 (s, 1H′), 5.93 (m, 1H, 1H′), 5.90 (s, 1H), 5.64 (d, $J = 8.0$, 1H), 5.63 (d, $J = 8.0$, 1H′), 5.2 (broad, 1H, 1H′), 4.99−4.83 (m, 2H, 2H′), 4.23 (m, 1H), 4.13 (m, 1H′), 3.97 (m, 2H, 2H′), 3.62 (m, 2H, 2H′), 2.20 (m, 2H, 2H′), 1.70 (m, 2H, 2H′), 1.54 (m, 2H, 2H′), 1.41 (m, 2H, 2H′); $^{13}$C NMR (400 MHz, $(CD_3)_2SO$) $\delta = 176.0$, 176.0, 164.1, 164.1, 160.6, 160.5, 151.2, 151.2, 143.0, 143.0, 129.3 (2C), 129.3 (2C), 128.9, 128.9, 115.1 (2C), 115.0 (2C), 107.4, 103.4, 102.8, 102.6, 92.2, 91.3, 87.3, 85.1, 84.8, 83.7, 82.6, 80.8, 68.3, 68.3, 62.2, 62.2, 35.1, 35.1, 29.3, 29.3, 26.1, 26.1, 25.4, 25.4; IR (film) $\nu = 3467$, 3132, 2938, 1696, 1677, 1245, 1108, 1077, 1046, 1019, 976, 828, 809; HRMS (MALDI-FTMS) *m/z* 485.1534 (485.1536 calcd for $C_{22}H_{26}N_2O_9Na$ $[M + Na]^+$).

**6-{4-[4-(6-Chloro-purin-9-yl)-6-hydroxymethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid Allyl Ester (25).** A mixture of 6-chloroinosine (**22**, 32.5 g, 113 mmol) and the acetal linker **24** (47.5 g, 147 mmol) was dissolved in DMF (230 mL). *p*-Toluenesulfonic acid monohydrate (1.1 g, 5.7 mmol) was added, and the solution was placed on a Buechi R-134 rotavapor and agitated under reduced pressure (70 mbar) at 50 °C for 15 h. The solvent was removed in vacuo, and the resulting residue was dissolved in EtOAc (1 L) and neutralized with triethylamine (0.8 mL, 5.7 mmol). The solution was then washed with saturated aqueous NaCl (3 × 1 L) and $H_2O$ (1 L), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was taken up in EtOAc and triturated with hexanes, upon which the product precipitated as a white powder (**25**, 59.3 g, 109 mmol, 96%, mixture of two diastereomers): mp, 103−105 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta = 8.78$ (s, 1H), 8.77 (s, 1H′), 8.41 (s, 1H), 8.33 (s, 1H′), 7.47 (d, $J = 8.6$, 2H), 7.37 (d, $J = 8.6$, 2H′), 6.95 (d, $J = 8.5$, 2H), 6.89 (d, $J = 8.5$, 2H′), 6.24 (s, 1H), 6.19 (m, 1H, 1H′), 6.02 (s, 1H′), 5.91 (m, 1H, 1H′), 5.37−5.18 (m, 4H, 4H′), 4.77 (m, 1H, 1H′), 4.72 (s, 1H, 1H′), 4.58 (m, 2H, 2H′), 4.04−3.85 (m, 4H, 4H′), 2.37 (m, 2H, 2H′), 1.81 (m, 2H, 2H′), 1.71 (m, 2H, 2H′), 1.52 (m, 2H, 2H′); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta = 173.4$, 173.4, 160.5, 160.4, 152.0, 151.8, 150.8, 150.7, 132.8, 132.6, 132.3, 132.3, 132.1, 132.1, 128.2 (2C), 128.0 (2C), 127.5, 127.5, 118.3, 118.3, 114.8, 114.8, 114.6 (2C), 114.6 (2C), 108.0, 104.9, 93.5, 91.6, 86.4, 86.4, 84.3, 83.8, 83.3, 80.5, 67.9, 67.8, 65.1, 65.1, 63.2, 62.9, 34.2, 34.2, 28.9, 28.9, 25.7, 25.7, 24.7, 24.7; IR (film) $\nu = 3233$, 3109, 3073, 2934, 1727, 1595, 1396, 1245, 1194, 1167, 1101, 1073, 984, 832; HRMS (MALDI-FTMS) *m/z* 567.1627 (567.1617 calcd for $C_{26}H_{29}N_4O_7ClNa$ $[M + Na]^+$).

**6-{4-[4-(6-Chloro-purin-9-yl)-6-hydroxymethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-2-yl]-phenoxy}-hexanoic Acid (26).** A mixture of **25** (59.31 g, 108.8 mmol), tetrakis-(triphenylphosphine)palladium ($Pd(PPh_3)_4$, 12.6 g, 10.9 mmol), and dimedone (45.7 g, 326.4 mmol) in dry DCM (600 mL) was stirred in a nitrogen atmosphere for 3.5 h at room temperature. A 500-mL portion of the solvent was removed in vacuo, and the remaining volume was loaded onto a silica plug. After the dimedone byproducts were removed by washing the plug with MeOH/DCM 1:100, the product was eluted with MeOH/DCM 1:10. The fraction containing the product was concentrated in vacuo to afford **26** as a white powder (46.6 g, 92.3 mmol, 85%) as a mixture of two diastereomers: mp, 127−129 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta = 11.50$ (s, 1H, 1H′), 8.79 (s, 1H), 8.78 (s, 1H′), 8.42 (s, 1H), 8.34 (s, 1H′), 7.47 (d, $J = 8.6$, 2H), 7.37 (d, $J = 8.6$, 2H′), 6.95 (d, $J = 8.5$, 2H), 6.90 (d, $J = 8.5$, 2H′), 6.24 (s, 1H), 6.19 (m, 1H, 1H′), 6.02 (s, 1H′), 5.37−5.19 (m, 2H, 2H′), 4.73 (s, 1H, 1H′), 4.57 (m, 1H, 1H′), 4.04−3.86 (m, 4H, 4H′), 2.40 (m, 2H, 2H′), 1.82 (m, 2H, 2H′), 1.72 (m, 2H, 2H′), 1.55 (m, 2H, 2H′); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta = 178.8$, 178.8, 160.6, 160.5, 152.3, 152.2, 150.6, 150.6, 133.4, 133.3, 132.2, 132.2, 128.3 (2C),128.1, 128.0 (2C), 127.6, 114.9, 114.9, 114.8 (2C), 114.7 (2C), 108.1, 105.1, 94.0, 92.0, 86.4, 86.3, 84.2, 83.5, 83.5, 80.5, 68.0, 67.9, 63.3, 63.0, 34.0, 34.0, 29.0, 29.0, 25.8, 25.8, 24.6, 24.6; IR (film) $\nu = 3292$, 3109, 3074, 2938, 1708, 1595, 1392, 1245, 1225, 1194, 1108, 1069, 828; HRMS (MALDI-FTMS) *m/z* 527.1285 (527.1304 calcd for $C_{23}H_{25}N_4O_7ClNa$ $[M + Na]^+$).

**Resin-Bound 5′-Azido-pyrimidine Scaffold (15).** A solution of **11** (66 g, 136 mmol), HOBt (18.4 g, 136 mmol), and DIC (17.1 g, 136 mmol) in DMF (500 mL) was added to aminomethyl resin (**14**, 70 g, 105 mmol) and agitated for 10 h at room temperature. The complete conversion was confirmed by a negative bromophenol blue test. Resin **15** was then washed with DMF (4 × 500 mL), THF (4 × 500 mL), DCM (4 × 500 mL), and MeOH (4 × 500 mL) and dried in vacuo. IR (on bead) $\nu = 3081$w, 3054w, 3023w, 2920m, 2851w, 2097m, 1693s, 1610m, 1511m, 1491m, 1375m, 1243s, 1169m, 1076s, 1024m, 979m, 703s.

**Resin-Bound 5′-Azido-4-triazolo-pyrimidine Scaffold (17).** Phosphorus oxychloride ($POCl_3$, 16.8 mL, 180 mmol) was added over a period of 10 min to a stirred solution of 1,2,4-triazole (**16**, 62.2 g, 900 mmol) in MeCN (500 mL), upon which a white precipitate formed immediately. Subsequently, TEA(134 mL, 960 mmol) was added over a period of 10 min. The slurry was then added to resin **15** (68.2 g, 60 mmol) and agitated for 5 h at room temperature. The bright yellow resin was washed with MeCN (3 × 500 mL), DMF (4 × 500 mL), THF (4 × 500 mL), DCM (4 × 500 mL), and MeCN (4 × 500 mL) and dried in vacuo. IR (on-bead) $\nu = 3082$w, 3058w, 3023w, 2926m, 2856w, 2101m, 1680s, 1630w, 1548m, 1509m, 1470m, 1449w, 1400w, 1375m, 1283m, 1248s, 1174w, 1097s, 937m, 700s.

**Resin-Bound 5′-Hydroxy-pyrimidine Scaffold (19).** Resin **19** was synthesized according to the procedure for resin-bound 5′-azido pyrimidine scaffold **15**, except that 5′-hydroxy uridine derivative **18** was used instead of 5′-azido uridine derivative **11**. IR (on bead) $\nu = 3082$w, 3054w, 3025w, 2920m, 2852w, 1679s, 1652m, 1597s, 1574w, 1508m, 1488m, 1449m, 1309w, 1258s, 1216m, 1161s, 1024w, 697s.

**Resin-Bound 5′-Acetoxy Pyrimidine Scaffold (20).** A solution of DMAP (3.6 g, 30 mmol) and acetic anhydride ($Ac_2O$, 10 mL, 100 mmol) in THF (200 mL) was added to resin **19** (22.3 g, 20 mmol) and agitated for 10 h at room temperature. The resin was subsequently washed in 10-min intervals with THF (4 × 200 mL), DMF (4 × 200 mL), DCM (4 × 200 mL), and MeOH (4 × 200 mL) and dried in

vacuo. IR (on bead) $\nu$ = 3085w, 3058w, 3021w, 2920m, 2849w, 1687s, 1613w, 1512m, 1488m, 1457s, 1383w, 1302w, 1242s, 1171w, 1079s, 701s.

**Resin-Bound 5′-Acetoxy-4-triazolo-pyrimidine Scaffold (21).** Resin **21** was synthesized according to the procedure for resin bound 5′-azido-4-triazolo-pyrimidine scaffold **17**, except that 5′-acetoxy uridine resin **19** was used instead of 5′-azido uridine resin **15**. IR (on bead) $\nu$ = 3120w, 3082w, 3058w, 3021w, 2920m, 2849w, 1738w, 1668s, 1614w, 1543m, 1508s, 1464m, 1453s, 1419w, 1396w, 1374w, 1285s, 1246s, 1164w, 1118m, 1075s, 697s.

**Resin-Bound 5′-Hydroxy-6-chloro-purine Scaffold (27).** A mixture of **26** (56.8 g, 113 mmol), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (42.8 g, 113 mmol) and diisopropyl ethylamine (19.6 mL, 113 mmol) in DMF (500 mL) was added to aminomethyl resin (14, 50.0 g, 75 mmol) and agitated for 1 h at room temperature. The complete conversion was confirmed by a negative bromophenol blue test. The resin was then washed with DMF (4 × 500 mL), THF (4 × 500 mL), DCM (4 × 500 mL), and MeOH (4 × 500 mL), and subsequently dried in vacuo. IR (on bead) $\nu$ = 3056w, 3025w, 2920m, 2849w, 1652m, 1610w, 1590m, 1562m, 1515m, 1488m, 1453m, 1437m, 1395m, 1336m, 1302w, 1246s, 1200s, 1171m, 1079s, 1020m, 700s.

**Resin-Bound 5′-Azido-6-chloro-purine Scaffold (28).** DEAD (59 mL, 375 mmol) was slowly added to a stirred solution of triphenyl phosphine ($PPh_3$, 98.3 g, 375 mmol) in anhydrous THF (400 mL). The mixture was kept at room temp via a water bath. DPPA (80.75 mL, 375 mmol) was added, and the solution was then transferred to a solid-phase peptide synthesis reactor containing resin **27** (86.5 g, 75 mmol). The mixture was allowed to react for 10 h at room temperature using $N_2$ agitation. The resin was subsequently washed with THF (4 × 400 mL), DMF (4 × 400 mL), DCM (4 × 400 mL), and MeOH (4 × 400 mL) and dried in vacuo. IR (on bead) $\nu$ = 3056w, 3021w, 2970w, 2924m, 2861w, 2104m, 1750w, 1652m, 1610w, 1594m, 1562m, 1515m, 1488m, 1449m, 1437m, 1396w, 1336w, 1246s, 1196m, 1171m, 1063s, 1028m, 700s.

**General Procedure for the Formation of Nucleophilic Aromatic Substituted Scaffolds 29−34.** The sorted nanokan microreactors containing resins **17**, **21**, **27** and **28** were placed into amber Quoparc bottles on J-Kem BTS 3000 benchtop shakers equipped with heated reaction blocks. The nanokans were then subjected to the proper conditions for different nucleophiles, as described in Table 1 and Scheme 4. For example, using primary and secondary amines as nucleophiles, the conditions are 24 h agitation at 50 °C with 0.4 M amine in NMP. After the analysis of control nanokans showed a complete conversion, the microreactors were washed with NMP (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×). The microreactors were subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Triazole Scaffolds 35−38.** The nanokan microreactors containing 5′-azido scaffolds of the general structures **29** and **31** were agitated in a 20% v/v solution of validated acetylene (>80% conversion in Table 2) in toluene using the conditions described in Table 2. The nanokans were then washed with NMP (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Amino Scaffolds 39 and 40.** A solution of stannous chloride ($SnCl_2$, 142 g, 0.75 mol) and thiophenol (PhSH, 308 mL, 3 mol) in THF (5 L) was prepared and cooled to 0 °C. TEA (523 mL, 3.75 mol) was added, and the resulting precipitate was filtered off. The remaining solution was then added to the nanokan microreactors containing 5′-azido scaffolds of the general structures **29** and **31** and agitated for 2.5 h at room temperature. The nanokans were then washed with THF (4×), DMF (4×), DCM (4×), and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Aminoacyl Scaffolds 41 and 42.** The nanokan microreactors containing 5′-amino scaffolds of the general structure **39** and **40** were agitated in a 0.4 M solution of carboxylic acid, HOBt, and DIC in DMF for 24 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Urea Scaffolds 43 and 44.** The nanokan microreactors containing 5′-amino scaffolds of the general structure **39** and **40** were agitated in a solution containing 0.4 M of isocyanate and 0.6 M TEA in DCM for 24 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Thiourea Scaffolds 45 and 46.** The nanokan microreactors containing 5′-amino scaffolds of the general structure **39** and **40** were agitated in a solution containing 0.4 M of thioisocyanate and 0.6 M TEA in DCM for 24 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Aryl Sulfonamido Scaffolds 47 and 48.** The nanokan microreactors containing 5′-amino scaffolds of the general structure **39** and **40** were agitated in a solution containing 0.4 M of aryl sulfonyl chloride and 0.6 M collidine in DCM for 32 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Triphenylphosphinamino Scaffolds 49 and 50.** The nanokan microreactors containing 5′-azido scaffolds of the general structure **29** and **31** were agitated in a 0.4 M solution of $PPh_3$ in dry THF for 6 h at room temperature. The nanokans were evacuated in 2 h intervals to allow evolving $N_2$ to leave the microreactor. The nanokans were then washed with dry THF (3×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Carbodiimide Scaffolds 51 and 52.** The nanokan microreactors containing 5′-triphenylphosphinamino scaffolds of the general structure **49** and **50** were agitated in a 0.4 M solution of

isocyanate in dry THF for 90 min at room temperature. The solution was removed, and the nanokans were subjected to the next reaction step without any washing or drying procedure.

**General Procedure for the Formation of 5′-Iminochloride Scaffolds 53 and 54.** The nanokan microreactors containing 5′-triphenylphosphinamino scaffolds of the general structure **49** and **50** were agitated in a solution containing 0.4 M of carboxylic acid chloride and 0.3 M TEA in dry THF for 90 min at 50 °C. The solution was removed, and the nanokans were subjected to the next reaction step without any washing or drying procedure.

**General Procedure for the Formation of 5′-Guanidino and 5′-Amidino Scaffolds 55−58.** The nanokan microreactors containing 5′-carbodiimide and 5′-iminochloride scaffolds of the general structure **51−54** were agitated in a 0.6 M solution of amine in dry THF for 24 h at room temperature. The solution was removed and the nanokans were subjected to the next reaction step without any washing or drying procedure. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeOH (4×) and subsequently dried in vacuo.

**General Procedure for the Deprotection of 5′-Acetoxy Resins 30 to the 5′-Hydroxy Resins 59.** The nanokan microreactors containing 5′-acetoxy scaffolds **30** were agitated in a 0.4 M solution of hydrazine ($H_2NNH_2$) in THF for 48 h at room temperature. The nanokans were then washed with THF (2×), NMP (4×), and THF (4×) and dried in vacuo.

**General Procedure for the Formation of 5′-Mesyl Scaffolds 60 and 61.** The nanokan microreactors containing 5′-hydroxy scaffolds **59** and **32** were agitated in a 0.4 M solution of mesyl chloride (MsCl) in pyridine for 5 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Chloro Scaffolds 64 and 65.** The nanokan microreactors containing 5′-hydroxy scaffolds **59** and **32** were agitated in a solution containing 0.4 M $PPh_3$ and 0.4 M carbon tetrachloride in DCM for 5 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Aldehyde Scaffolds 66 and 67.** The nanokan microreactors containing 5′-hydroxy scaffolds **59** and **32** were agitated in a 0.2 M solution of Dess−Martin periodinane in DCM for 12 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of Substituted 5′-Amino Pyrimidine Scaffolds 62.** The nanokan microreactors containing 5′-mesyl scaffolds **60** were agitated in a 0.4 M solution of amine in NMP for 24 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of Substituted 5′-Amino Purine Scaffolds 63.** The nanokan microreactors containing 5′-chloro scaffolds **65** were agitated in a 0.4 M solution of amine in NMP for 24 h at 75 °C. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Carboxy Scaffolds 68 and 69.** The nanokan microreactors containing 5′-hydroxy scaffolds **59** and **32** were agitated in a suspension containing 0.2 M BAIB, 0.2 M bicarbonate ($NaHCO_3$) and 0.01 M TEMPO in MeCN/$H_2O$ 1:1 for 5 h at room temperature. The nanokans were then washed with MeCN/$H_2O$ 1:1 (2×), $H_2O$ (2×), DMF (4×), 1,4-dioxane (4×), and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Carboxamido Scaffolds 70 and 71.** A solution of 0.4 M HOBt and 0.4 M DIC in DMF was added to the nanokan microreactors containing 5′-carboxy scaffolds **68** and **69** and agitated for 10 min at room temperature. The appropriate amount of amine (0.4 M) was added, and the nanokans were agitated for 24 h at room temperature. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

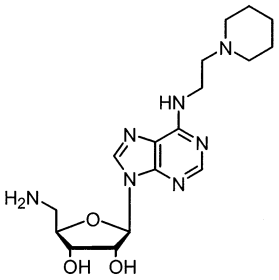
**General Procedure for the Formation of Substituted 5′-Carbonylimidazolo Scaffolds 72 and 73.** The nanokan microreactors containing 5′-hydroxy scaffolds **59** and **32** were agitated in a 0.4 M solution of CDI in dry THF for 5 h at room temperature. The nanokans were then washed with dry THF (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Carbamate Scaffolds 74 and 75.** The nanokan microreactors containing 5′-carbonylimidazolo scaffolds **72** and **73** were agitated in a 0.4 M solution of amine in NMP for 24 h at 50 °C (primary amines) or 48 h at 75 °C (secondary amines). The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

**General Procedure for the Formation of 5′-Carbonate Scaffolds 76 and 77.** The nanokan microreactors containing 5′-carbonylimidazolo scaffolds **72** and **73** were agitated in a 2 M solution of alcohol in NMP for 48 h at 75 °C. The nanokans were then washed with DMF (4×), 1,4-dioxane (4×), and alternating DCM and MeCN (4×) and subsequently dried in vacuo.

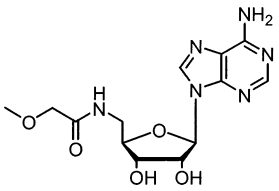
**General Procedure for the Cleavage of the Final Nucleoside Analogues 80 and 81 off the Solid Support.** The nanokan microreactors were sorted into IRORI 96-well cleavage blocks with attached deep-well collection plates. A 250-$\mu$L portion of a solution of 5% TFA and 5% $H_2O$ in 1,4-dioxane (cleavage cocktail) was added to the top plates containing the naokans, and the plates were subsequently evacuated for 1 min. Another 100-$\mu$L aliquot was added to each well, and the cleavage blocks were incubated at 50 °C for 6 h. The cleavage solution containing the products was then spun down from the top cleavage to the bottom collection plates using a Savant Discovery Speed Vac with angled plate holders. The cleavage procedure was repeated twice with incubation times of 6 and 12 h, respectively. Finally, the solvents were removed in vacuo to yield the discrete compounds as dry films in 96-well format.

**Selected Library Members.**



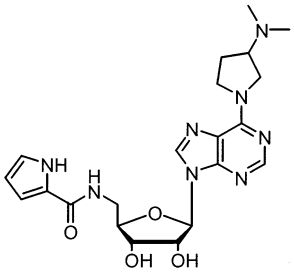
**Example I**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.36 (s, 1H), 8.25 (s, 1H), 6.02 (d, $J$ = 5.3, 1H), 4.77 (t, $J$ = 5.3, 1H), 4.41 (t, $J$ = 4.6, 1H), 4.29 (m, 1H), 4.00 (m, 2H), 3.69 (m, 2H), 3.41 (m, 4H), 3.02 (m, 2H), 1.96 (m, 2H), 1.81 (m, 2H), 1.67 (m, 2H); MS (ESI) $m/z$ 378.2 (378.22 calcd for $C_{17}H_{28}N_7O_3$ $[M + H]^+$).



**Example II**

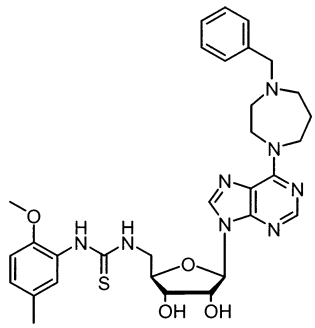
$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.46 (s, 1H), 8.36 (s, 1H), 6.01 (d, $J$ = 5.3, 1H), 4.71 (t, $J$ = 5.3, 1H), 4.24 (t, $J$ = 4.5, 1H), 4.17 (m, 1H), 3.90 (s, 2H), 3.62 (m, 2H), 3.38 (s, 3H); MS (ESI) $m/z$ 339.1 (339.13 calcd for $C_{13}H_{19}N_6O_5$ $[M + H]^+$).



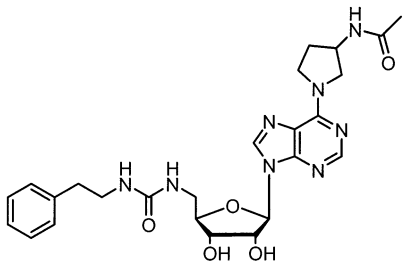
**Example III**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.31 (s, 1H), 8.27 (s, 1H), 6.91 (d, $J$ = 3.4, 1H), 6.74 (d, $J$ = 3.4, 1H), 6.14 (t, $J$ = 3.4, 1H), 5.98 (d, $J$ = 5.5, 1H), 4.80 (t, $J$ = 5.5, 1H), 4.33 (t, $J$ = 4.4, 1H), 4.22 (m, 1H), 4.11 (m, 4H), 3.94 (m, 1H), 3.80 (m, 2H), 3.04 (s, 3H), 3.02 (s, 3H), 2.29 (m, 2H); MS (ESI) $m/z$ 457.2 (457.22 calcd for $C_{21}H_{29}N_8O_4$ $[M + H]^+$).

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.20 (s, 1H), 8.16 (s, 1H), 7.50 (m, 5H), 7.31 (s, 1H), 6.91 (d, $J$ = 9.0, 1H), 6.82 (d, $J$ = 9.0, 1H), 5.96 (d, $J$ = 6.3, 1H), 4.80 (t, $J$ = 5.2, 1H), 4.39 (m, 1H), 4.39 (s, 2H), 4.28 (m, 1H), 4.06 (m, 2H), 3.93−3.52 (m, 6H), 3.65 (s, 3H), 3.42 (m, 2H), 2.28 (m, 2H), 2.14 (s, 3H); MS (ESI) $m/z$ 619.3 (619.27 calcd for $C_{31}H_{39}N_8O_4S$ $[M + H]^+$).

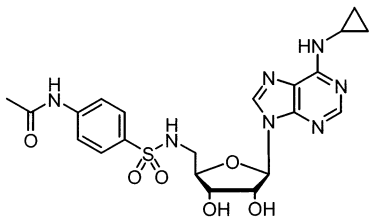


**Example IV**



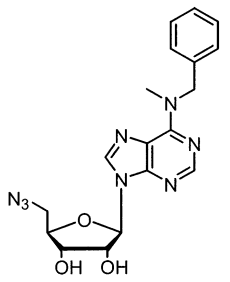
**Example V**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.40 (s, 1H), 8.33 (s, 1H), 7.20 (m, 5H), 6.02 (d, $J$ = 5.8, 1H), 4.65 (t, $J$ = 5.8, 1H), 4.55 (m, 1H), 4.21 (t, $J$ = 4.5, 1H), 4.10 (m, 1H), 3.86 (m, 2H), 3.49 (d, $J$ = 5.1, 2H), 3.34 (t, $J$ = 6.9, 2H), 2.73 (t, $J$ = 7.0, 2H), 2.36 (m, 2H), 2.15 (m, 2H), 1.95 (s, 3H); MS (ESI) $m/z$ 525.3 (525.25 calcd for $C_{25}H_{33}N_8O_5$ $[M + H]^+$).



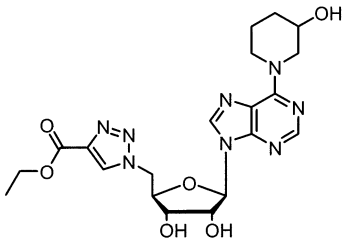
**Example VI**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.41 (s, 1H), 8.39 (s, 1H), 7.76 (d, $J$ = 8.8, 2H), 7.71 (d, $J$ = 8.8, 2H), 5.95 (d, $J$ = 5.9, 1H), 4.73 (t, $J$ = 5.9, 1H), 4.28 (m, 1H), 4.13 (m, 1H), 3.21 (m, 2H), 2.89 (m, 1H), 2.14 (s, 3H), 1.05 (m, 2H), 0.83 (m, 2H); MS (ESI) $m/z$ 504.2 (504.16 calcd for $C_{21}H_{26}N_7O_6S$ $[M + H]^+$).



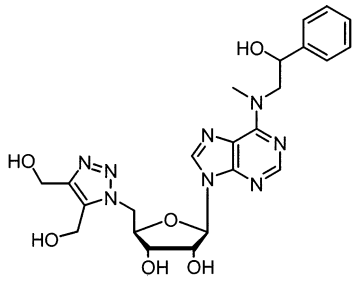
**Example VII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.34 (s, 1H), 8.34 (s, 1H), 7.31 (m, 5H), 6.08 (d, $J$ = 4.6, 1H), 4.72 (t, $J$ = 4.9, 1H), 4.34 (t, $J$ = 5.1, 1H), 4.19 (m, 1H), 3.65 (s, 2H), 3.38 (m, 2H), 3.30 (s, 3H); MS (ESI) *m/z* 397.2 (397.17 calcd for $C_{18}H_{21}N_8O_3$ $[M + H]^+$).



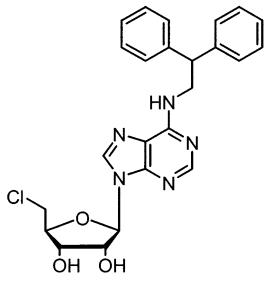
**Example VIII**
major regioisomer

$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ = 8.22 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 5.96 (d, $J$ = 3.4, 1H), 4.86 (m, 2H), 4.64 (t, $J$ = 4.2, 1H), 4.47 (t, $J$ = 5.8, 1H), 4.38 (m, 1H), 4.30 (m, 2H), 3.82 (m, 2H), 3.71 (m, 1H), 2.00 (m, 2H), 1.65 (m, 2H), 1.32 (t, $J$ = 7.1, 3H); MS (ESI) *m/z* 475.2 (475.20 calcd for $C_{20}H_{27}N_8O_6$ $[M + H]^+$).



**Example IX**

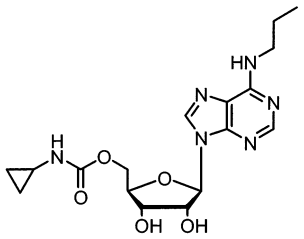
$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ = 8.27 (s, 1H), 8.17 (s, 1H), 7.52 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 6.01 (d, $J$ = 3.5, 1H), 5.14 (m, 1H), 4.83 (m, 2H), 4.64−4.52 (m, 7H), 4.47 (m, 1H), 3.47 (m, 2H), 3.30 (s, 3H); MS (ESI) *m/z* 513.2 (513.21 calcd for $C_{23}H_{29}N_8O_6$ $[M + H]^+$).



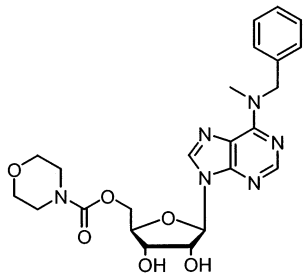
**Example X**

$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ = 8.51 (s, 1H), 8.30 (s, 1H), 7.35−7.16 (m, 10H), 6.04 (m, 1H), 4.72 (t, $J$ = 5.0, 1H), 4.50 (m, 1H), 4.36 (m, 1H), 4.26 (m, 1H), 3.87 (m, 2H), 3.65 (m, 2H); MS (ESI) *m/z* 466.1 (466.16 calcd for $C_{24}H_{25}ClN_5O_3$ $[M + H]^+$).

$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ = 8.31 (s, 2H), 6.06 (m, 1H), 4.64 (m, 1H), 4.40 (m, 1H), 4.31 (m, 1H), 4.24 (m, 2H), 3.64 (m, 2H), 2.50 (m, 1H), 1.76 (m, 2H), 1.04 (t, $J$ = 7.3, 3H), 0.65 (m, 2H), 0.46 (m, 2H); MS (ESI) *m/z* 393.2 (393.18 calcd for $C_{17}H_{25}N_6O_5$ $[M + H]^+$).

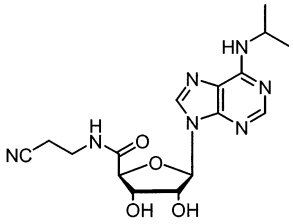


**Example XI**



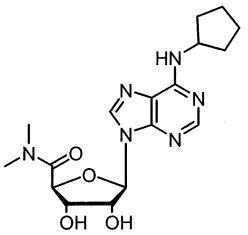
**Example XII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.32 (s, 1H), 8.24 (s, 1H), 7.31 (m, 5H), 6.05 (d, $J$ = 4.1, 1H), 4.70 (t, $J$ = 4.9, 1H), 4.47 (m, 1H), 4.37 (m, 2H), 4.26 (t, $J$ = 4.5, 1H), 3.58 (m, 4H), 3.41 (m, 6H), 3.30 (s, 3H); MS (ESI) *m/z* 485.2 (485.21 calcd for $C_{23}H_{29}N_6O_6$ $[M + H]^+$).



**Example XIII**

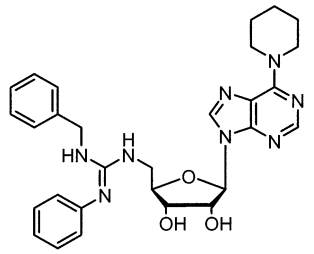
$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.39 (s, 1H), 8.35 (s, 1H), 6.07 (d, $J$ = 7.5, 1H), 4.75 (dd, $J$ = 7.5, $J$ = 4.8, 1H), 4.52 (d, $J$ = 1.7, 1H), 4.38 (dd, $J$ = 4.8, $J$ = 1.7, 1H), 4.38 (m, 1H), 3.57 (m, 2H), 2.75 (m, 2H), 1.35 (d, $J$ = 6.5, 6H); MS (ESI) *m/z* 376.2 (376.17 calcd for $C_{16}H_{22}N_7O_4$ $[M + H]^+$).



**Example XIV**

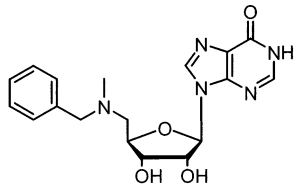
$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.64 (s, 1H), 8.40 (s, 1H), 6.20 (d, $J$ = 6.3, 1H), 5.08 (d, $J$ = 2.7, 1H), 4.55 (m, 1H), 4.46 (m, 1H), 4.40 (m, 1H), 3.16 (s, 3H), 3.04 (s, 3H),

2.13 (m, 2H), 1.85 (m, 2H), 1.72 (m, 4H); MS (ESI) *m/z* 377.2 (377.19 calcd for $C_{17}H_{25}N_6O_4$ $[M + H]^+$).



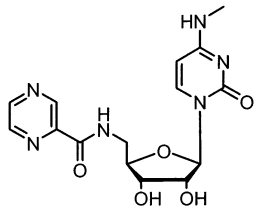
**Example XV**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.12 (s, 1H), 8.07 (s, 1H), 7.32−6.94 (m, 10H), 5.94 (d, $J$ = 5.2, 1H), 4.35 (m, 4H), 4.19 (m, 5H), 3.88 (dd, $J$ = 4.9, $J$ = 8.2, 1H), 3.69 (dd, $J$ = 4.9, $J$ = 2.9, 1H), 1.78 (m, 2H), 1.69 (m, 4H); MS (ESI) *m/z* 543.3 (543.28 calcd for $C_{29}H_{35}N_8O_3$ $[M + H]^+$).



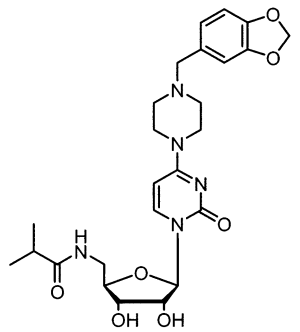
**Example XVI**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 8.59 (s, 1H), 8.06 (s, 1H), 7.46 (m, 5H), 6.21 (d, $J$ = 6.2, 1H), 4.58 (d, $J$ = 2.6, 1H), 4.55 (dd, $J$ = 6.2, $J$ = 4.5, 1H), 4.44 (dd, $J$ = 4.5, $J$ = 2.6, 1H), 4.44 (m, 2H), 3.65 (m, 2H), 2.59 (s, 3H); MS (ESI) *m/z* 372.4 (371.16 calcd for $C_{18}H_{22}N_5O_4$ $[M + H]^+$).



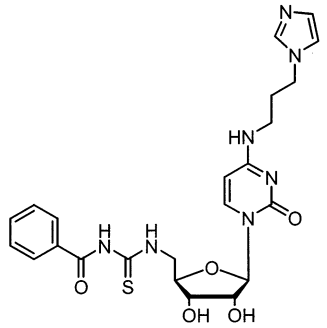
**Example XVII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 9.24 (s, 1H), 8.79 (d, $J$ = 2.0, 1H), 8.69 (d, $J$ = 2.0, 1H), 7.98 (d, $J$ = 7.9, 1H), 6.01 (d, $J$ = 7.9, 1H), 5.78 (d, $J$ = 3.8, 1H), 4.24 (t, $J$ = 4.5, 1H), 4.19 (m, 1H), 4.03 (t, $J$ = 5.5, 1H), 3.79 (m, 2H), 3.03 (s, 3H); MS (ESI) *m/z* 363.1 (363.13 calcd for $C_{15}H_{19}N_6O_5$ $[M + H]^+$).



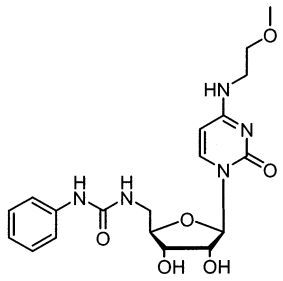
**Example XVIII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 7.91 (d, $J$ = 7.7, 1H), 7.00 (s, 1H), 6.99 (d, $J$ = 7.8, 1H), 6.93 (d, $J$ = 7.8, 1H), 6.30 (d, $J$ = 7.7, 1H), 6.03 (s, 2H), 5.71 (d, $J$ = 3.7, 1H), 4.29 (s, 2H), 4.21 (t, $J$ = 4.5, 1H), 4.04 (m, 1H), 3.93 (t, $J$ = 5.6, 1H), 3.65 (s, 2H), 3.51 (m, 4H), 3.31 (m, 4H), 1.11 (d, $J$ = 6.8, 6H); MS (ESI) *m/z* 516.3 (516.24 calcd for $C_{25}H_{34}N_5O_7$ $[M + H]^+$).



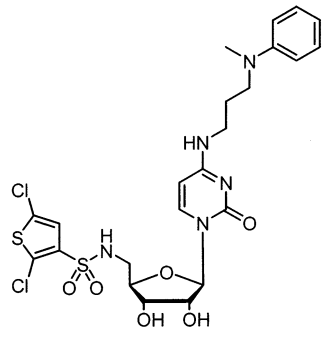
**Example XIX**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 9.09 (s, 1H), 7.97 (s, 1H), 7.84 (d, $J$ = 7.6, 1H), 7.82 (m, 2H), 7.70 (s, 1H), 7.63−7.44 (m, 4H), 5.92 (d, $J$ = 7.6, 1H), 5.77 (d, $J$ = 3.8, 1H), 4.33 (t, $J$ = 6.8, 2H), 4.24 (m, 1H), 4.15 (m, 1H), 4.06 (t, $J$ = 5.6, 1H), 3.73 (m, 2H), 3.44 (t, $J$ = 6.1, 2H), 2.20 (m, 2H); MS (ESI) *m/z* 514.2 (514.18 calcd for $C_{23}H_{28}N_7O_5S$ $[M + H]^+$).



**Example XX**

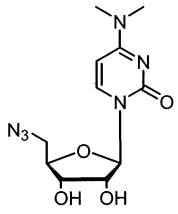
$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 7.92 (d, $J$ = 7.9, 1H), 7.34 (d, $J$ = 7.5, 2H), 7.24 (d, $J$ = 7.5, 2H), 6.98 (t, $J$ = 7.3, 2H), 6.07 (d, $J$ = 7.9, 1H), 5.77 (d, $J$ = 3.8, 1H), 4.23 (t, $J$ = 4.5, 1H), 4.06 (m, 1H), 4.01 (t, $J$ = 5.5, 1H), 3.59 (m, 6H), 3.38 (s, 3H); MS (ESI) *m/z* 420.2 (420.18 calcd for $C_{19}H_{26}N_5O_6$ $[M + H]^+$).



**Example XXI**

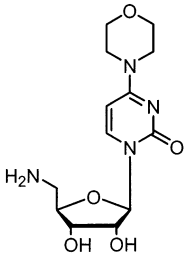
$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ = 7.80 (d, $J$ = 7.6, 1H), 7.52 (m, 3H), 7.37 (m, 2H), 7.19 (s, 1H), 6.98 (t, $J$ = 7.3,

2H), 5.98 (d, $J = 7.6$, 1H), 5.70 (d, $J = 3.9$, 1H), 4.25 (t, $J = 4.2$, 1H), 4.08 (t, $J = 5.8$, 1H), 4.00 (m, 1H), 3.61 (t, $J = 6.6$, 2H), 3.48 (m, 2H), 3.37 (t, $J = 6.3$, 2H), 3.15 (s, 3H), 1.82 (m, 2H); MS (ESI) *m/z* 604.1 (604.08 calcd for $C_{23}H_{28}Cl_2N_5O_6S_2$ $[M + H]^+$).



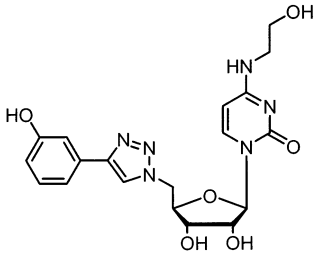
**Example XXII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 8.04$ (d, $J = 8.1$, 1H), 6.36 (d, $J = 8.1$, 1H), 5.82 (d, $J = 3.3$, 1H), 4.21 (dd, $J = 3.3$, $J = 5.0$, 1H), 4.12 (m, 1H), 3.72 (m, 2H), 3.27 (s, 6H); MS (ESI) *m/z* 297.1 (297.12 calcd for $C_{11}H_{17}N_6O_4$ $[M + H]^+$).



**Example XXIII**

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 7.71$ (d, $J = 7.7$, 1H), 6.25 (d, $J = 7.7$, 1H), 5.55 (d, $J = 3.5$, 1H), 4.49 (dd, $J = 3.6$, $J = 5.6$, 1H), 4.20 (t, $J = 5.9$, 1H), 4.12 (m, 2H), 3.88−3.59 (m, 10H); MS (ESI) *m/z* 313.2 (313.14 calcd for $C_{13}H_{21}N_4O_5$ $[M + H]^+$).

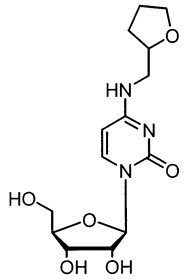


**Example XXIV**

2 regioisomers 1:1

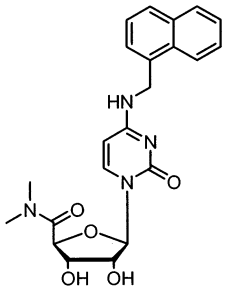
$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 8.27$ (s, 1H), 7.75 (s, 1H), 7.41 (d, $J = 7.8$, 1H), 7.32−7.22 (m, 5H), 6.95−6.89 (m, 3H), 6.77 (d, $J = 7.4$, 1H), 5.94 (d, $J = 7.8$, 1H), 5.92 (d, $J = 7.8$, 1H), 5.74 (d, $J = 3.0$, 1H), 5.64 (d, $J = 2.5$, 1H), 4.86−4.69 (m, 4H), 4.35 (m, 1H), 4.28 (m, 1H), 4.16−4.09 (m, 4H), 3.76 (t, $J = 5.1$, 2H), 3.72 (t, $J = 5.2$, 2H), 3.55 (m, 2H), 3.49 (m, 2H); MS (ESI) *m/z* 431.2 (431.16 calcd for $C_{19}H_{23}N_6O_6$ $[M + H]^+$).

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 8.22$ (d, $J = 7.8$, 1H), 6.02 (d, $J = 7.8$, 1H), 5.86 (d, $J = 3.0$, 1H), 4.14 (m, 2H), 4.08 (m, 1H), 4.04 (m, 1H), 3.87 (m, 2H), 3.76 (m, 2H),



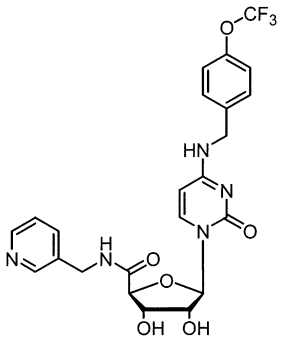
**Example XXV**

3.50 (m, 2H), 2.05 (m, 2H), 1.61 (m, 2H); MS (ESI) *m/z* 328.1 (328.14 calcd for $C_{14}H_{22}N_3O_6$ $[M + H]^+$).



**Example XXVI**

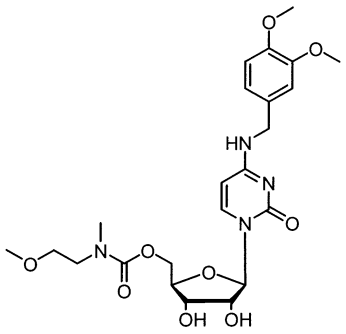
$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 8.52$ (d, $J = 7.6$, 1H), 8.04 (d, $J = 8.2$, 1H), 7.89 (d, $J = 9.2$, 1H), 7.85 (d, $J = 7.8$, 1H), 7.56−7.43 (m, 4H), 5.93 (d, $J = 7.5$, 1H), 6.10 (d, $J = 4.1$, 1H), 5.94 (d, $J = 7.6$, 1H), 5.05 (s, 2H), 4.98 (d, $J = 4.8$, 1H), 4.23 (t, $J = 4.6$, 1H), 4.15 (t, $J = 4.6$, 1H), 3.16 (s, 3H), 2.99 (s, 3H); MS (ESI) *m/z* 425.2 (425.17 calcd for $C_{22}H_{25}N_4O_5$ $[M + H]^+$).



**Example XXVII**

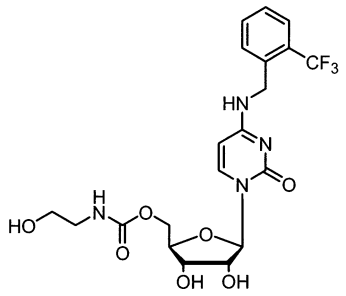
$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 8.68$ (s, 1H), 8.59 (d, $J = 5.0$, 1H), 8.20 (d, $J = 8.0$, 1H), 7.95 (d, $J = 7.6$, 1H), 7.72 (m, 1H), 7.43 (d, $J = 8.3$, 1H), 7.23 (d, $J = 8.3$, 1H), 5.93 (d, $J = 7.5$, 1H), 5.62 (d, $J = 4.5$, 1H), 4.62 (s, 2H), 4.58 (t, $J = 5.5$, 1H), 4.56 (s, 2H), 4.41 (d, $J = 3.5$, 1H), 4.24 (dd, $J = 5.5$, $J = 3.5$, 1H); MS (ESI) *m/z* 522.1 (522.15 calcd for $C_{23}H_{23}F_3N_5O_6$ $[M + H]^+$).

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 7.69$ (d, $J = 7.6$, 1H), 6.98 (s, 1H), 6.91 (s, 2H), 5.93 (d, $J = 7.6$, 1H), 5.81 (d, $J = 3.4$, 1H), 4.51 (s, 2H), 4.37 (m, 2H), 4.16 (m, 2H), 4.08 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.50 (m,



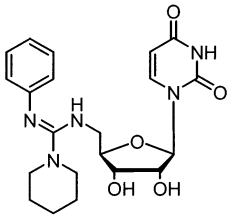
Example XXVIII

2H), 3.47 (m, 2H), 2.95 (m, 3H); MS (ESI) *m*/*z* 509.2 (509.22 calcd for $C_{23}H_{33}N_4O_9$ $[M + H]^+$).



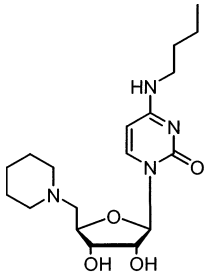
Example XXIX

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 7.71$ (d, $J = 7.6$, 1H), 7.70 (d, $J = 7.5$, 1H), 7.60 (m, 2H), 7.46 (m, 1H), 6.00 (d, $J = 7.6$, 1H), 5.86 (d, $J = 3.7$, 1H), 4.80 (s, 2H), 4.40 (m, 1H), 4.27 (m, 1H), 4.13 (m, 2H), 4.07 (m, 1H), 3.58 (t, $J = 5.9$, 2H), 3.23 (t, $J = 5.9$, 2H); MS (ESI) *m*/*z* 489.1 (489.15 calcd for $C_{20}H_{24}F_3N_4O_7$ $[M + H]^+$).



Example XXX

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 7.47$ (d, $J = 8.0$, 1H), 7.37−7.01 (m, 5H), 5.57 (d, $J = 8.0$, 1H), 5.54 (d, $J = 3.2$, 1H), 4.37 (dd, $J = 6.1$, $J = 3.2$, 1H), 4.13 (t, $J = 6.3$, 1H), 3.98 (m, 1H), 3.62 (m, 2H), 3.36 (m, 4H), 1.64 (m, 2H), 1.59 (m, 4H); MS (ESI) *m*/*z* 430.2 (430.20 calcd for $C_{21}H_{28}N_5O_5$ $[M + H]^+$).



Example XXXI

$^1$H NMR (400 MHz, $CD_3OD$) $\delta = 7.70$ (d, $J = 7.8$, 1H), 6.01 (d, $J = 7.8$, 1H), 5.65 (d, $J = 3.2$, 1H), 4.40 (dd, $J = 5.7$, $J = 3.2$, 1H), 4.30 (m, 1H), 4.08 (dd, $J = 6.6$, $J = 5.7$, 1H), 3.61 (m, 2H), 3.54−3.38 (m, 4H), 3.04 (m, 2H), 1.92 (m, 2H), 1.81 (m, 4H), 1.63 (m, 2H), 1.42 (m, 2H), 0.97 (t, $J = 7.3$, 3H); MS (ESI) *m*/*z* 367.4 (366.23 calcd for $C_{18}H_{31}N_4O_4$ $[M + H]^+$).

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