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# Synthesis of novel exocyclic amino nucleosides by parallel solid-phase combinatorial strategy

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**Abstract**—A versatile parallel solid-phase combinatorial strategy was developed for the synthesis of large nucleoside libraries. Twelve libraries **L1**-**12** of 1152 novel exocyclic triazinylamino nucleosides and one library **L13** of 82 new substituted clitocine derivatives were synthesized in high quality as natural product mimic nucleosides on the semi-automated synthesizer. The polystyrene MMT-Cl resin was selected and utilized. The key intermediate resins **5** and **9** loaded with the corresponding scaffolds were prepared and validated with various amines before parallel synthesis. After a variety of amino building blocks were validated, 56 primary amines in 12 groups (building block set A) and 24 secondary amines in 3 groups (building block set B) were selected and utilized to combinatorialize the first and the second reactive sites on scaffold **5** for the synthesis of libraries **L1**-**12**. Eighty-two amines (building block set C) were utilized for the synthesis of clitocine library **L13**. Thirteen libraries of 1234 novel exocyclic amino nucleosides were all analyzed and characterized by high throughput LC-MS. 81.3–100% of the library members in 13 libraries show more than 60% purity, and 65.7–92.7% of the library members in these libraries show 80–100% purity. The strategy can be widely used for the synthesis of other diverse nucleoside libraries. © 2003 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

After decades of drug discovery and development effort from hundreds of academic laboratories and pharmaceutical companies, approximately 50 nucleoside- and nucleotide-related drugs have been pushed to the market and over 80 nucleosides/tides are in the (pre) clinical studies for various therapeutic indications including antiviral, anticancer, and others.[1] However, some drugs such as AZT, ddI, 3TC etc rapidly develop drug resistance and show mitochondrial, bone-marrow, and other toxicity. Therefore, it is essential to discover novel nucleoside drugs for critical medical needs. A variety of different modified nucleoside derivatives[2] were synthesized by the classical approaches in solution, which is expensive and time-consuming. Combinatorial synthesis of large diverse libraries and high-throughput screening technologies have recently emerged as powerful drug discovery paradigms. Various solid-phase,[3] solution-phase,[4] liquid-phase,[5] and third-phase[6] combinatorial approaches have been successfully utilized for the generation of different oligomeric and small molecule libraries for a wide range of biological screenings. Unfortunately, these powerful technologies, especially parallel solid-phase combinatorial strategies, have not been applied to the nucleoside chemistry for small molecule drug discovery yet although di/tri-[7] and oligonucleotides[8,9] were synthesized on solid support, and the modified solid supports have been used as acylating agent to acylate nucleoside derivatives.[10] There are tremendous difficulties to synthesize a large number of nucleoside analogues in a short period of time utilizing solid-phase combinatorial strategies to explore wide biological activities: (a) most applicable linkers do not meet the general requirements for the solid-phase synthesis of nucleoside libraries: stable enough under the required reaction conditions during synthesis and labile enough to be cleaved easily from solid support without affecting nucleoside products; (b) limited positions on nucleoside can be attached on solid support; (c) limited types of reactions can be utilized and limited number of sites can be combinatorialized on the nucleoside skeletons, which prevent the generation of large diverse nucleoside libraries; (d) it is more difficult to get high quality and purity nucleoside libraries without purification compared to other small molecule libraries.

Although hundreds of modified purine- and pyrimidine-based nucleoside derivatives have been reported,[1,11,12] very little work related to exocyclic nucleosides was reported. Clitocine, 6-amino-5-nitro-4-(β-D-ribofuranosylamino)-pyrimidine, the compound **L13** when $R_4$=$R_5$=H (Fig. 1), is a natural exocyclic amino nucleoside isolated from the mushroom *Clitocybe inversa*,[13] and it was then synthesized from 4,6-diamino-5-nitropyrimidine.[14] Clitocine exhibits

*Keywords*: exocyclic amino nucleoside; triazinyl; clitocine mimic; parallel solid-phase combinatorial; library; automated synthesis.

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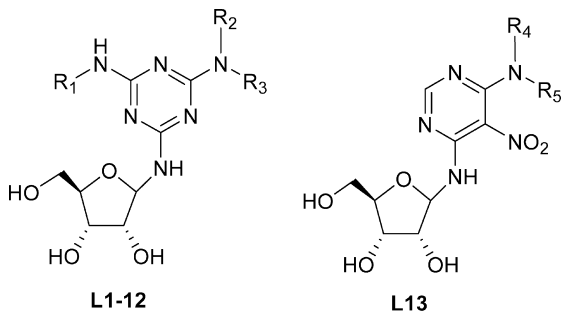



**Figure 1.** Novel exocyclic amino nucleoside libraries **L1-13**.

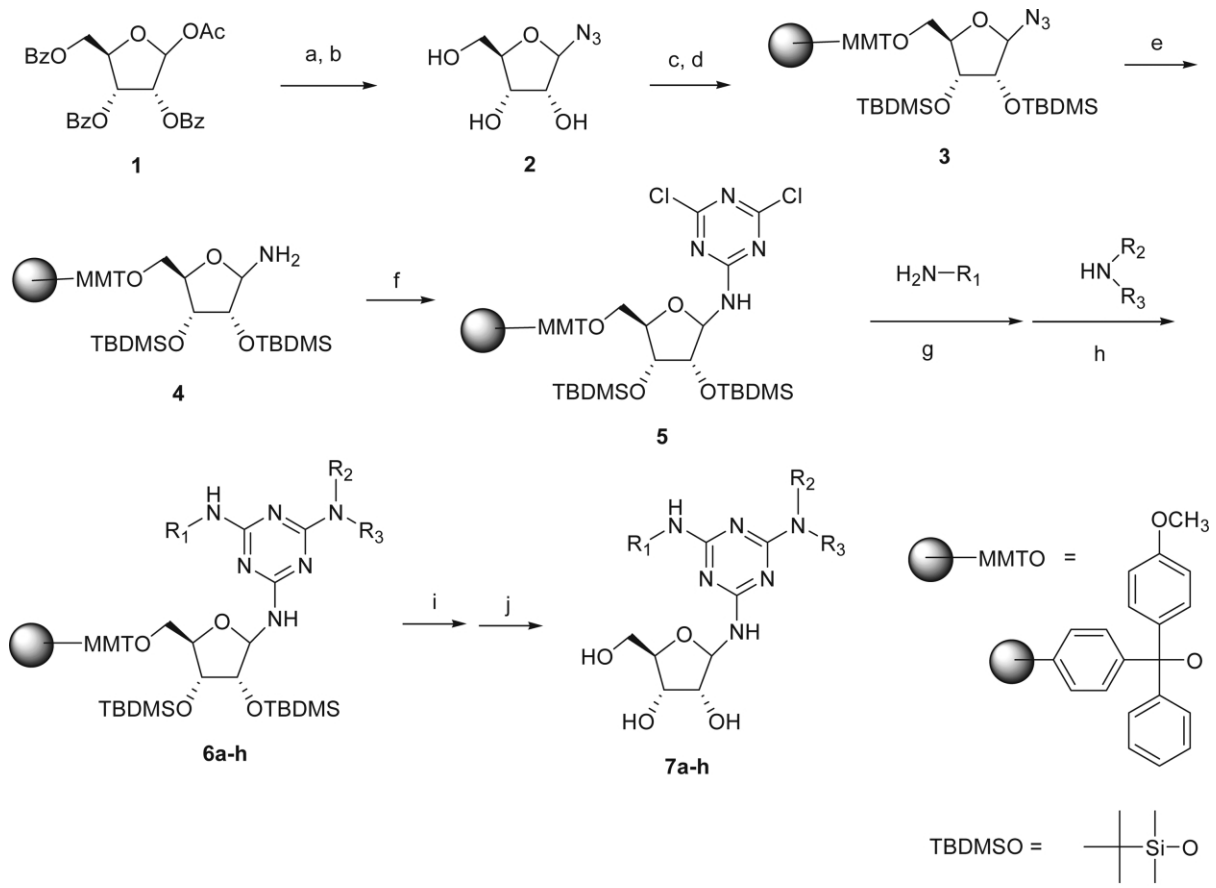
potent cytostatic effects against several leukemia cell lines through the inhibition of adenosine kinase. It also shows strong insecticidal activity against the pink bollworm *Pectinophora gossypiella*.[13,14] Other exocyclic amino pyrimido[5.4-*d*]pyrimidine[15] and pyrimidine nucleosides[16] with different bases were also reported. It will be valuable to explore clitocine mimic libraries with substituted triazine as the heterocyclic base that has one more nitrogen in the heterocyclic ring compared to that of clitocine. Although triazine derivatives without sugar moieties have been synthesized to study their corticotropin-releasing factor$_1$ receptor antagonists and other biological effects,[17] triazine-based exocyclic nucleosides, the clitocine mimic, have not been studied up to today. To efficiently explore the potential antitumor, antiviral, and other biological activities of clitocine mimic exocyclic nucleoside derivatives, we designed and synthesized novel triazine- and pyrimidine-based exocyclic nucleoside libraries.

In this paper, we describe the exploration, development, synthesis, and characterization of novel disubstituted exocyclic triazinylamino nucleoside libraries **L1-12** and substituted clitocine library **L13** of 1234 novel nucleoside analogues by the parallel solid-phase combinatorial approach that, for the first time, was applied to the synthesis of nucleoside libraries. Polystyrene monomethoxytrityl chloride resin was selected from various available solid supports with different linkers. Resin **5**, the key intermediate resin for the synthesis of triazine-based exocyclic amino nucleoside libraries **L1-12**, was developed and validated by different amino building blocks in different solvent systems without prior synthesis in solution. Fifty-six selected primary amines in 12 groups were utilized for the first combinatorialization step, and 24 selected secondary amines in 3 groups were used for the second nucleophilic substitution step after a variety of amino building blocks with different sizes, lipophilicity, diversity and reactivity were validated. Twelve groups of 56 primary amines (building block set A) and twenty-four secondary amines (building block set B) were selected for the combinatorialization of the first and the second reactive sites of the triazinyl nucleoside scaffold. Twelve plates of libraries **L1-12** containing 1152 (12×96) triazine-based exocyclic amino nucleoside derivatives were synthesized in high quality by the parallel array combinatorial strategy on the ACT Vanguard semi-automated synthesizer. Eighty-two substituted clitocine derivatives in library **L13** were synthesized by our newly developed reaction conditions and strategy from 82 selected amines as building blocks (set C). All library members were analyzed and characterized by the high-throughput LC-MS. High quality libraries (plates) were obtained with the successful rates[18] ranging from 75–100%. 65.7–92.7% of the library members in 13 plates show 80–100% purity. Totally, 1234 novel exocyclic amino nucleosides were synthesized for the first time utilizing the parallel solid-phase combinatorial approach. Average 20–30 mg of sample was obtained for each library member and ready for a wide range of biological studies.

## 2. Results and discussion

In order to widely explore the biological activity of the natural product mimic exocyclic amino nucleosides, we decided to generate large diverse novel nucleoside libraries by the parallel solid-phase combinatorial approach on the semi-automated synthesizer. As described above, there are various difficulties to be overcome, and a lot of new area needs to be explored. Choosing solid support with a suitable linker became our first challenge even though over a hundred different types of solid supports with various linkers are available and have been utilized for the synthesis of oligomeric and other small molecule libraries.[19] The carbamate resin has been successfully used for the synthesis of five carbocyclic L-nucleosides[20] and eight unsaturated carbocyclic adenosine analogues[21] based on well-established reaction conditions in solution. The non-glycosidic bond of these carbocyclic nucleosides is much more stable than glycosidic bond of ribofuranosyl nucleosides, which contributed to the synthetic possibility of these carbocyclic nucleosides on solid support although the method has not been used for the generation of large diverse libraries yet. 6-Chloropurine ribose was reacted with diamine-modified trityl resins providing several 6-aminoalkyl adenosine derivatives.[22] However, the isolation of dimers from the reaction mixture indicated the cleavage of diamines from the resins during the reaction even in the presence of triethylamine. Based on the commonly used protecting groups at 5′-position and the reactivity of 5′-hydroxyl group, we have studied the applicability of carboxylic acid, trityl chloride, dimethoxytrityl chloride, monomethoxytrityl chloride (MMT-Cl), THP, Wang, and other resins to attach the ribose onto resins through 5′-hydroxyl group of the ribofuranosyl nucleosides. Most of these resins are either too labile during the synthesis or not labile enough to cleave the product from solid support after synthesis (data not shown). Trityl chloride and monomethoxytrityl chloride (MMT-Cl) resins are applicable for the synthesis of nucleoside libraries. However, the cleavage of products from trityl resin requires stronger acid that caused partial deglycosylation of the base from nucleoside sugar ring. MMT-Cl resin was more applicable than trityl chloride resin, therefore, it was utilized for the synthesis of libraries **L1-13** (Fig. 1). The products were cleaved from the resin by 1.5–2% trifluoroacetic acid (TFA) in dichloromethane.

β-D-Ribofuranosyl-1-azide (**2**)[23] was synthesized by the reaction of 1′-acetyl-2′,3′,5′-tribenzoyl ribofuranose (**1**) with sodium azide,[24,25] followed by the deprotection of the resultant triprotected azido intermediate with sodium cyanide (Scheme 1). The polystyrene monomethoxytrityl chloride (MMT-Cl) resin was treated with 2 equiv. of




**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.** Development of exocyclic triazinylamino nucleoside scaffold.

azidoribose **2** in pyridine in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP). Compound **2** was attached onto MMT resin through 5′-position because the 5′-hydroxyl group is more reactive than the hydroxyl groups at 2′- and 3′-positions. The loading efficiency of 85% was estimated based on the consumption of compound **2**. The resultant resin was further treated with *t*-butyldimethylsilyl chloride (TBDMS-Cl) to give the loaded resin **3** protected by TBDMS protecting groups. Resin **3** showed strong peak at 2109 $cm^{-1}$ ($\nu$, $N_3$) as illustrated by its IR spectrum b comparing to that of polystyrene MMT-Cl resin itself (IR spectrum a, Figure 2). A portion of resin **3** was cleaved by 2% of TFA in dichloromethane and the resultant 2′,3′-*O*-bis(*t*-butyldimethylsilyl)-β-D-ribofuranosyl-1-azide was confirmed by its MS and NMR spectrometric analyses. This result further confirmed the structure of resin **3**. Trimethylphosphine was used to reduce the azido group of resin **3** resulting in the amino resin **4**. The structure of resin **4** was also confirmed by the disappearance of the azido peak at 2109 $cm^{-1}$ (see IR spectrum c, Figure 2). The three chloro groups of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) have different electrophilic reactivity. We have efficiently utilized the characteristic property of cyanuric chloride for the synthesis of exocyclic triazine amino nucleoside libraries. Resin **4** was reacted with cyanuric chloride at 0–5°C for 1 h. The hydrochloride generated from the reaction was neutralized by adding *N*,*N*-diisopropylethylamine in the reaction mixture to avoid the acidic cleavage of the resulted scaffold from MMT resin. A portion of resin **5** was treated with TFA, and the resultant *N*-[(4,6-dichloro)triazin-2-yl]-1-amino-2′,3′-*O*-bis(*t*-butyldimethylsilyl)-β-D-ribofuranose was confirmed by NMR spectrometry, which also verified the structure of resin **5**.

The reaction conditions from resin **5** to products **7**, building blocks, and solvent systems have to be validated before the synthesis of final libraries on synthesizer. Eight sets of amino building blocks (two in each set, Table 1) were used for the validation of reaction conditions. Amines $H_2NR_1$ were reacted with resin **5** at 0°C to room temperature for 2 h to ensure the completion of the first nucleophilic substitution but not to react with the second reactive site on the triazine moiety. Amines $HNR_2R_3$ were then reacted with the last electrophilic site of the resulted resin at 80°C for 6 h to ensure the completion of the reaction and the quality of the final libraries. Resins **6a**–**h** were treated with tetrabutylammonium fluoride (TBAF) to remove the TBDMS protecting group and then treated with 2% TFA to provide final products **7**. During the validation, we noticed that the excess tetrabutylammonium salt resulted from the deprotection step was very difficult to be removed completely by the usual washing procedures. Therefore, the resin was treated

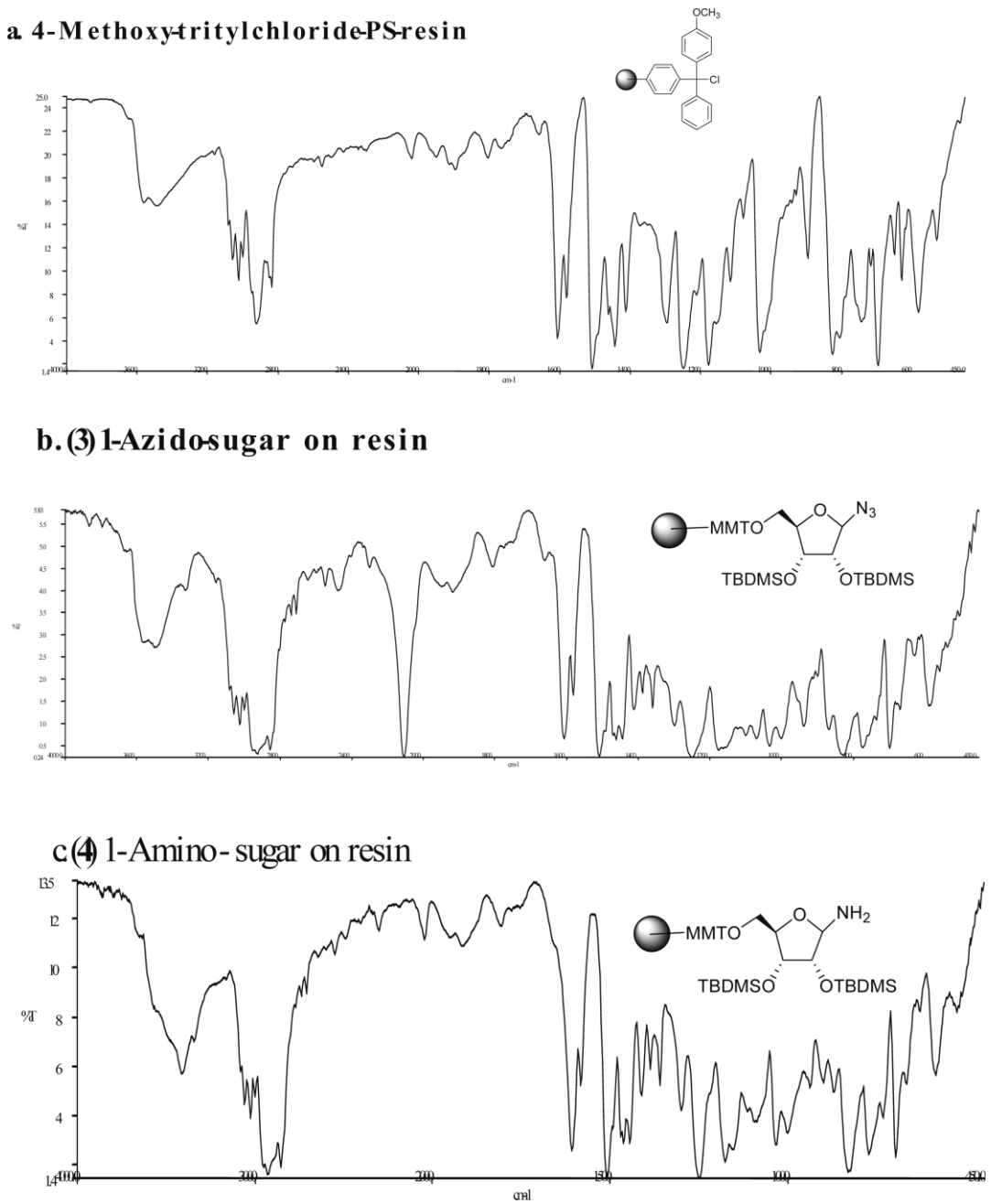
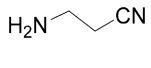
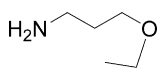
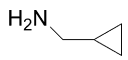
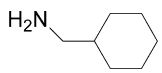
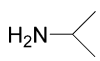
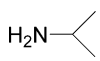
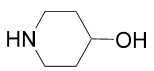
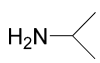
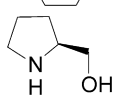
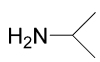
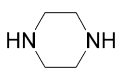



**Figure 2.** FT-IR spectral comparison of different resins.

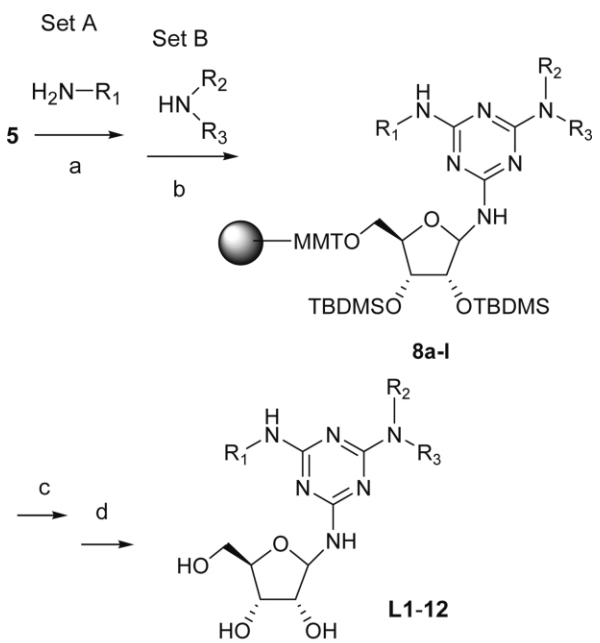
with DMF–AcOH–$H_2O$ (8:1:1) for 10 min, followed by usual washing procedures to completely remove the excess amount of tetrabutylammonium salt. The early stage validation results also indicated that the high quality products were obtained when the primary amines were used for the first reaction site of resin **5**, and the secondary amines were reacted with the last reactive site. Therefore, appropriate combinations of different building blocks were used to validate acetonitrile, *N*,*N*-dimethylformamide (DMF), and 1-methyl-2-pyrrolidinone (NMP) solvent systems for the two substitution steps (Table 1). The high quality of product **7** (Table 1) verified the protocol and the quality of resin **5**. The reaction of resin **5** with isopropylamine and then piperazine did not provide the desired product. The similar results were also observed for other nucleoside scaffolds when piperazine or other diamine-types of compounds were used as nucleophilic building blocks although the reason is still not clear (data not shown). Therefore, the diamine-types of building blocks were excluded for the final library synthesis. The solutions of building blocks needed to be freshly prepared and used within 2 days when DMF was used as the solvent in order to reach the desired quality. *N*,*N*-Dimethylamino substitution was observed during previous validation when DMF solutions of building blocks were kept for more than 2 days. NMP solutions can be used for weeks and still provided more pure products than other two solvents. Therefore, NMP was selected as the solvent for the two substitution steps on the synthesizer.

Based on the size, liphophilicity, diversity, and expected reactivity of amino building blocks, 64 primary amines were

**Table 1**. Validation of solvents on loaded resin **5**

| Entry | $H_2N-R_1$ | $HNR_2R_3$ | LC-MS purity of **7** in MeCN (%) | LC-MS purity of **7** in NMP (%) | LC-MS purity of **7** in DMF (%) |
|---|---|---|---|---|---|
| a |  |  | 0 | 83 | 85 |
| b |  |  | 67 | 70 | 79 |
| c |  |  | 79 | 90 | 85 |
| d |  |  | 99 | 93 | 95 |
| e |  |  | 94 | 82 | 89 |
| f |  |  | 86 | 88 | 90 |
| g |  |  | 87 | 82 | 89 |
| h |  |  | 0 | 0 | 0 |

selected for the first substitution step by fixing one building block for the second step, and 32 secondary amines were selected for the second substitution step by fixing one building block for the first step (Scheme 2). Thus, 96 wells of reactions were validated in one reaction block on the ACT Vanguard semi-automated synthesizer. Based on the




**Scheme 2.** Parallel synthesis of exocyclic amino trazinyl nucleoside libraries **L1-12**.

LC-MS results of the validated plate (data not shown), we selected 56 primary amines out of sixty-four as the building block set A ($H_2NR_1$) (Fig. 3) to react with resin **5** first, and 24 secondary amines out of 32 as the building block set B ($HNR_2R_3$) for the last substitution step (Fig. 4). Fifty-six primary amines in building block set A were arranged into 12 groups. Twenty-four secondary amines in building block set B were arranged into three groups, and each group contained eight amines. Figure 5 shows the arrangement of the building blocks and 96-well plates. Therefore, an array combination of building block set A as columns with building blocks B1-24 as rows generated twelve plates representing 12 libraries **L1-12**, which represent 1152 (24×48 or 12×96) novel exocyclic triazinylamino nucleosides. Building blocks B1-8, B9-16, and B17-24 were used as rows for plates **L1-4**, **L5-8**, and **L9-12**, respectively. A1-12, A13-24, A25-36, and A37-48 were used as columns for plates **L1-4**. A49-50, A2-8, A56, and A10-11 were used as columns for plates **L5** and **L9**. A12, A14-21, and A23-25 were used as columns for plates **L6** and **L10**. A27-30, A51-52, A31-33, A53, and A35-36 were used as columns for plates **L7** and **L11**. A37-48 were used as columns for plate **L8**. A37-38, A40-42, A44-48, and A54-55 were used as columns for plate **L12**. The 96 compounds in each plate were enumerated by Afferent TeamWorks software to generate molecular weights, structural, and other related information for the desired library members and the key impurities in each reaction vessel. Afferent TeamWorks transferred the data to Label Automador for automated sample bar code labeling and weighing. Libraries **L1-12** were synthesized in a parallel fashion utilizing the optimized procedures and conditions as well as using NMP as solvent. The first set of building blocks (set A) substituted the first chloro group on the scaffold at room temperature for 2 h, and the second set of building blocks (set B) were reacted with the second reactive site at 80°C for 5 h to ensure the completion of the nucleophilic substitution

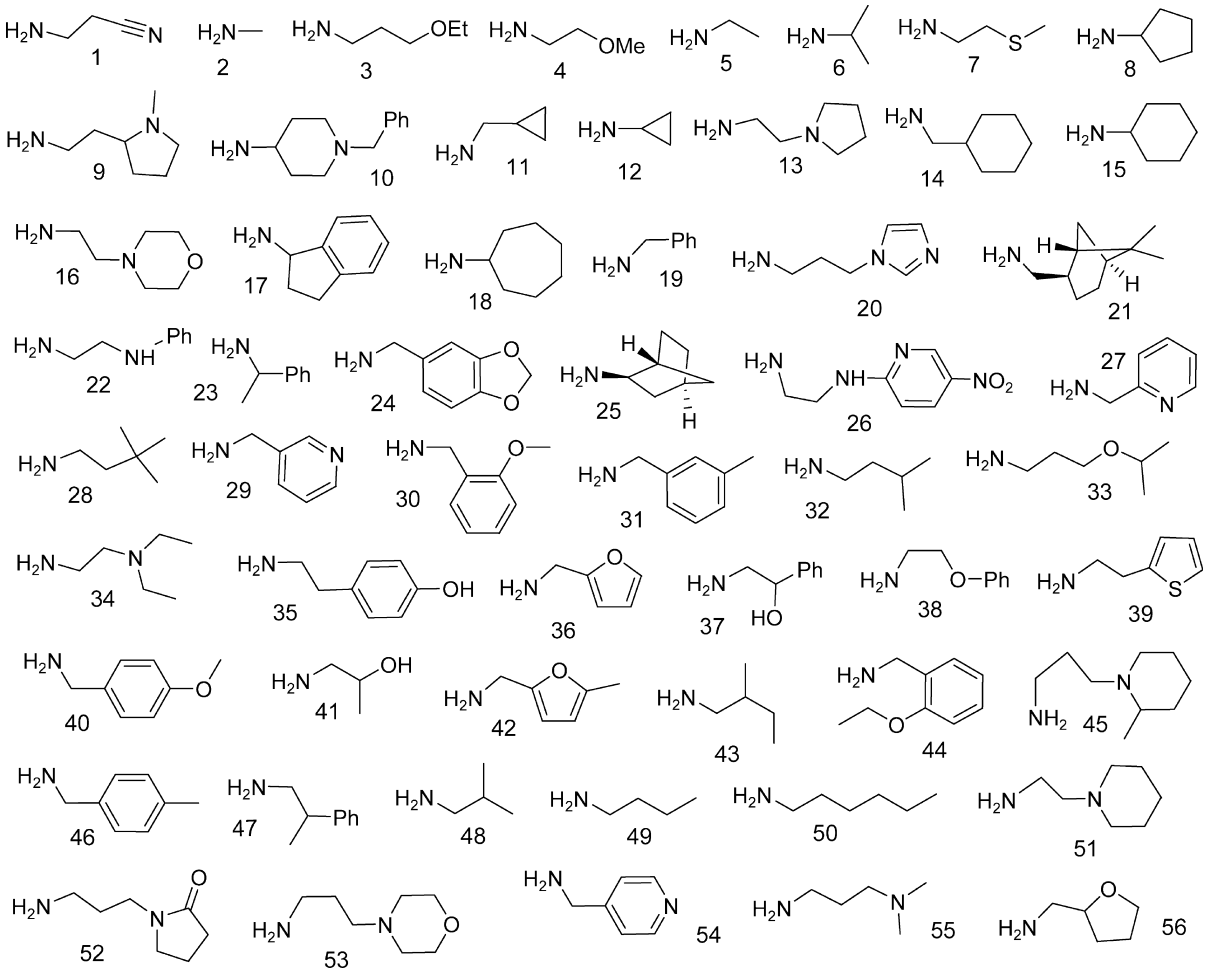


**Figure 3.** Building block set A: 56 primary amines.

because the last reactive site is less reactive than the first one after the substitution of the first reactive site. The washing processes were automatically conducted and controlled by the pre-designed program. After deprotection by TBAF, the final library members were cleaved from resins by 1.5% of TFA in dichloromethane. The synthesized plates were dried using Savant SpeedVac and then analyzed by high-throughput LC-MS. The Afferent TeamWorks software generated compound ID numbers and molecular weights which were input into the sample list for LC-MS data acquisition. The LC-MS data were acquired using MassLynx software, and the LC-MS data were processed using OpenLynx software. The LC-MS data and the compound purity summary were input into Afferent

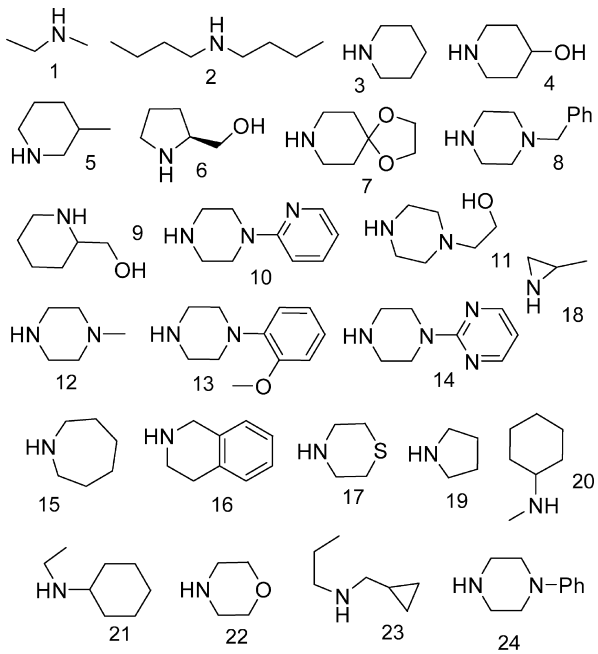


**Figure 4.** Building block set B: 24 secondary amines.

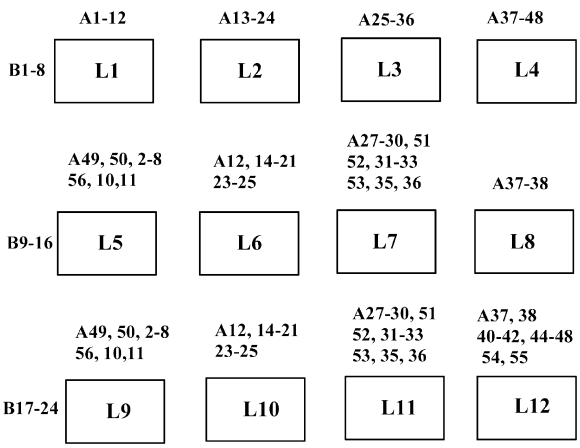


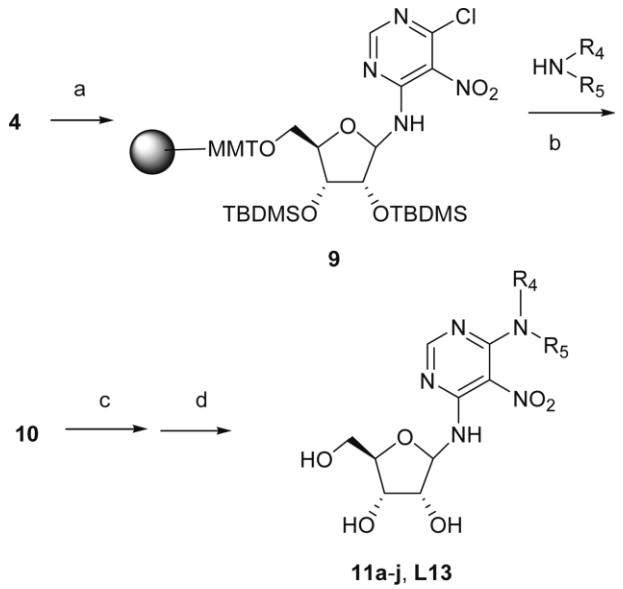

**Figure 5.** Building block and plate arrangement for the synthesis of libraries **L1**-**L12**.

**Table 2**. Quality of libraries **L1-12**

| Library no | Percentage of products 80–100% | Percentage of products >60% |
|---|---|---|
| **L1** | 70.8 | 92.7 |
| **L2** | 65.7 | 88.5 |
| **L3** | 74.0 | 96.9 |
| **L4** | 76.0 | 90.6 |
| **L5** | 84.3 | 95.8 |
| **L6** | 92.7 | 97.9 |
| **L7** | 81.2 | 91.7 |
| **L8** | 81.3 | 100 |
| **L9** | 76.0 | 86.5 |
| **L10** | 76.0 | 81.3 |
| **L11** | 80.3 | 85.4 |
| **L12** | 75.0 | 82.3 |
| Overall | 77.8 | 90.8 |

96 compounds for each library.

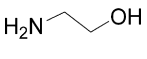
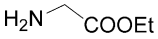
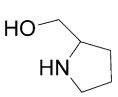
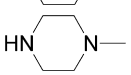
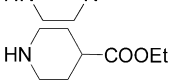
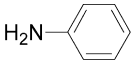
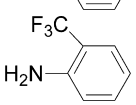
TeamWorks as a record for the database. Table 2 shows the quality of 12 libraries **L1-12**. The LC-MS results indicated that 65.7–92.7% of the library members shown 80–100% purity. 81.3–100% of the library members have more than 60% purity. The percentage of the library members with more than 60% LC-MS purity is defined as the successful rate of a library/plate. Those library members passing 60% purity have been selected by the programmed software and automatically registered to database for biological screening. For example, library **L6** has high successful rate of 97.9%. Therefore, 94 compounds with over 60% purity out of 96 wells of reactions were registered. Eighty-nine compounds out of 96, 92.7% of the library members, shown 80–100% purity, which represented very high quality for eight-step reactions on solid support and the breakthrough in nucleoside chemistry. Some representative LC chromatograms and mass spectra (see Supporting Information) further verified the high quality of these libraries. An average of 20–30 mg of sample for each library member was obtained for a wide range of biological screenings. Therefore, 1152 novel exocyclic triazine amino nucleoside derivatives were successfully synthesized by the array parallel solid-phase combinatorial strategy on the semi-automated synthesizer. All library members were obtained in sufficient quantity, excellent yields, and high purity as indicated by LC-MS analysis.




**Scheme 3.** Synthesis of clitocine mimic exocyclic amino nucleoside library.

This developed strategy for the synthesis of exocyclic triazinyl amino nucleoside libraries **L1-12** was utilized further for the synthesis of substituted clitocine library **L13** (Scheme 3). Resin **4** loaded with 1-amino-2,3-*O*-bis-(*t*-butyldimethylsilyl)ribose was treated with 4,6-dichloro-5-nitropyrimidine in NMP for 4 h using *N*,*N*-diisopropyl-ethylamine as a base providing resin **9**. The clitocine scaffold on resin **9** was validated under the similar reaction

**Table 3**. Validation of clitocine scaffold on resin **9**

| Entry | HN(R4)(R5) | LC-MS purity of **11** |
|---|---|---|
| a |  | 89% |
| b |  | 98% |
| c |  | 100% |
| d |  | No |
| e |  | 65% |
| f |  | 80% |
| g |  | 98% |
| h |  | 79% |
| i |  | 99% |
| j |  | No |

conditions as described above utilizing eleven representative amino building blocks (Table 3). The results indicated that primary, secondary, and cyclic amines as well as aniline all worked efficiently with LC-MS purity of 80–100%. Hydroxyl group did not effect the reactions and the quality of the products (see entries c and e). The nucleophilicity of the amino groups played an important role for the success. The electron-withdrawing group COOEt (entry d) significantly reduced the nucleophilicity of the amino group adjacent to the ester group, therefore, it did not produce the desired product. Although aniline worked very well and provided desired product with 99% purity (entry i), 2-trifluoromethylaniline (entry j) did not generate products because the steric effect and electron-withdrawing property of trifluoromethyl significantly reduced the nucleophilicity of the amino group. After validating the scaffold and building blocks, we selected 82 amines $HNR_4R_5$ as the building block set C (see Supporting Information) considering diversity, reactivity, spatial, and other properties. Resin **9** was reacted with the eighty-two selected building blocks at room temperature for 16 h in a parallel fashion utilizing the similar procedures described above (Scheme 3). After removing the TBDMS protecting groups by TBAF, the products **L13** were cleaved from resins by 1.5% TFA in dichloromethane. 72% compounds out of eighty-two shown the LC-MS purity of 80–100%.

In conclusion, we have for the first time developed a versatile parallel solid-phase combinatorial strategy for the synthesis of large nucleoside libraries. The polystyrene monomethoxytrityl chloride resin and this solid-phase synthetic process can be widely utilized for the rapid synthesis of other large diverse nucleoside libraries to accelerate drug discovery process. The key intermediate resins **5** and **9** were validated and FT-IR spectrometry was used to monitor the reactions on solid support. Twelve plates of 1152 novel exocyclic trazinylamino nucleoside derivatives **L1**-**12**, the natural product clitocine mimic nucleosides, were successfully synthesized utilizing this developed strategy. Eighty-two of substituted clitocine derivatives **L13** were synthesized by the same strategy. 1234 novel exocyclic amino nucleosides were all analyzed and characterized in a parallel fashion by Waters HT LC-MS. 76–100% successful rates and 65.7–92.7% of library members having 80–100% purity demonstrated the high quality of these new libraries and the advantage of the parallel solid-phase combinatorial strategy. Therefore, more than 1108 high quality, novel exocyclic nucleosides out of 1234 reaction wells synthesized were registered for biological screening with sufficient quantity (20–30 mg). High throughput screening of these novel nucleosides in searching antiviral and anticancer active agents is in progress and will be reported in due course.

## 3. Experimental

### 3.1. General methods

NMR spectra were recorded at 300 MHz and the chemical shifts are expressed relative to the added tetramethylsilane. Fourier-transform Infrared (FT-IR) spectra of the samples on solid support were obtained on a Perkin–Elmer FT-IR spectrometer. The libraries were enumerated by Afferent TeamWorks 3.0, labeled and weighted by Label Automador, and synthesized on the ACT Vanguard semi-automated synthesizer. Libraries were analyzed on a LC-MS system. The LC-MS system consists of Waters 2790 HPLC, Waters 996 photodiode array (PDA) detector, and Micromass/Waters ZQ mass spectrometer. Luna $C_{18}$ column from Phenomenex was used for compound separation. The mass spectra at *m*/*z* 100–1000 were acquired using electrospray ionization with both positive and negative ion detections. UV spectra were recorded at 200–400 nm by the PDA, and the compound purity was monitored based on the UV absorbency at 220 nm. The LC-MS operation was controlled by MassLynx software, and the LC-MS data were processed by OpenLynx software. Polystyrene monomethoxytrityl chloride resin was purchased from Novabiochem. Other starting materials, building blocks, and reagents were purchased from Aldrich and other companies, and used directly. β-D-Ribofuranosyl-1-azide (**2**) was synthesized based on the reported procedures.[23–25]

**3.1.1. 2,3-*O*-Bis(*t*-butyldimethylsily)-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 $CH_2Cl_2$ (3×25 mL), a mixture of $CH_2Cl_2$–MeOH–*N*,*N*-diisopropylethylamine (8.5:1:0.5, 2×20 mL). The resulted resin was then dried under vacuum over KOH for 16 h. 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 solution of TFA in $CH_2Cl_2$ (1.5%) for 60 s, filtered, and washed with $CH_2Cl_2$ (2×2 mL). The combined filtrate was concentrated providing the starting azido compound **2**, which was confirmed by $^1H$ NMR ($CD_3OD$) $\delta$ 5.19 (s, 1H), 4.04 (dt, 1H, *J*=6.6, 4.8 Hz), 3.97 (m, 1H), 3.81 (d, 1H, *J*=5.0 Hz), 3.76 (dd, 1H, *J*=12.0, 3.0 Hz), 3.56 (dd, 1H, *J*=12.0, 5.7 Hz); MS (ESI) *m*/*z* 176 $(M)^+$.

To a suspension of the resulted resin (1.2 g), 5-*O*-(monomethoxytrityl-polystyrene resin)-β-D-ribofuranosyl-1-azide, in 10 mL of anhydrous DMF were added excess amount 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 filtered and washed sequentially with DMF (3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 mL). The resin was then dried under vacuum over KOH for 16 h. FT-IR (KBr) 2109.9 $cm^{-1}$ ($N_3$ group). A small portion (0.10 g) of resin **3** was treated with a solution of TFA in $CH_2Cl_2$ (1.5%) for 60 s, filtered, and washed with $CH_2Cl_2$ (2×2 mL). The combined filtrate was concentrated providing 2′,3′-*O*-bis(*t*-butyldimethylsilyl)-β-D-ribofuranosyl-1-azide (30 mg), which was confirmed by $^1H$ NMR ($CDCl_3$) $\delta$ 5.13 (d, 1H, *J*=1.2 Hz), 4.17 (dd, 1H, *J*=7.2, 4.0 Hz), 4.05 (m, 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).

**3.1.2. 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 ($PMe_3$) 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–$H_2O$ (1:1, 3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 mL). The resin was then dried over KOH under vacuum for 16 h. FT-IR (KBr) 2109.9 $cm^{-1}$ ($N_3$ group) peak disappeared (see spectrum c, Figure 2).

**3.1.3. $N^{1'}$-[(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 $CH_2Cl_2$ (5 mL, 20% v/v) and cooled to 0–5°C. A solution of cyanuric chloride in $CH_2Cl_2$ (5 mL, 1.0 M) was added. The resultant suspension was shaken well at room temperature for 1 h and filtered using a sintered funnel. The resin was washed with $CH_2Cl_2$ (3×25 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 $CH_2Cl_2$ (1.5%) for 60 s, filtered, and washed with $CH_2Cl_2$ (2×2 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 $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (d, 0.6H, $J$=8.7 Hz, ex. $D_2O$), 6.87 (d, 0.4H, $J$=6.6 Hz, ex. $D_2O$), 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 (4 s, 18H), 0.10–0.06 (ms, 12H).

**3.1.4. $N^{1'}$-[(4-*N*-Alkylamino-6-*N*,*N*-dialkylamino)triazin-2-yl]-1′-(*R*,*S*)-amino-2′,3′-*O*-bis-(*t*-butyl-dimethylsilyl)-5′-*O*-(monomethoxytrityl-polystyrene resin)-β-D-ribofuranose (6).** To a suspension of resin **5** (50 mg) in a solution of *N*,*N*-diisopropylethylemine 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 (3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 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 (3×10 mL) and $CH_2Cl_2$ (3×10 mL). The fully protected and substituted resin was obtained after dried over KOH under vacuum for 16 h.

**3.1.5. $N^{1'}$-[(4-*N*-Alkyl-amino-6-*N*,*N*-dialkylamino)triazin-2-yl]-1′-(*R*,*S*)-amino-β-D-ribofuranose (7).** Resin **6** (50 mg) 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–$H_2O$ mixture (8:1:1, 1.5 mL) for 10 min to remove excess amount of tetrabutylammonium salt. The resin was filtered and washed sequentially with DMF–$H_2O$ mixture (9:1, 3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×20 mL). After dried over KOH under vacuum for 16 h, the resultant resin (50 mg) was suspended in 1.5 mL of TFA solution in $CH_2Cl_2$ (1.5%) and shaken well at room temperature for 60 s. The resin was filtered and further washed with MeOH (2×1 mL). The combined filtrate was concentrated under high vacuum to provide compound **7**.

**3.1.6. $N^{1'}$-[(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) 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 (3×25 mL) and $CH_2Cl_2$ (3×25 mL). After dried under vacuum over $P_2O_5$ for 16 h, resin **9** was obtained.

**3.1.7. $N^{1'}$-[(5-Nitro-*N*-isopropyl)pyrimidin-4-yl]-1′-(*R*,*S*)-amino-β-D-ribofuranose (11b).** To a suspension of resin **9** (50 mg) 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 (3×10 mL), $CH_2Cl_2$ (3×10 mL), an NMP–$H_2O$ mixture (3:1, 3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 mL). The resulted 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 (3×10 mL), MeOH (3×10 mL), an NMP–$H_2O$ mixture (3:1, 3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 mL). The resin was treated with a mixture of DMF–$H_2O$–AcOH (8:1:1, 2 mL) and shaken well for 15 min to remove the excess amount of tetrabutylammonium salt. The resin was filtered and washed with MeOH (3×10 mL), an NMP–$H_2O$ mixture (3:1, 3×10 mL), MeOH (3×10 mL), and $CH_2Cl_2$ (3×10 mL). The resulted clean resin was treated with a solution of TFA in $CH_2Cl_2$ (1.5 mL, 1.5%) for 60 s. The resin was filtered and washed with MeOH (2×2.5 mL). The combined filtrate was concentrated to provide product **11b** (15–20 mg). $^1$H NMR ($CD_3OD$) $\delta$ 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, 6.6 Hz).

### 3.2. General procedures for the synthesis of exocyclic nucleoside libraries L1-12

**3.2.1. 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 mixtures were filtered, and the resins were washed with DMF (×3), alternatively with MeOH and $CH_2Cl_2$ (×3), and finally with $CH_2Cl_2$ (×2), and then dried under nitrogen.

**3.2.2. Second amine substitution.** To the resulting monochloro triazine resins were added a solution of *N*,*N*-diisipropylethylamine in NMP (20%, 0.75 mL), followed by the addition of eight 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 with DMF (×3), alternatively with MeOH and $CH_2Cl_2$ (×3), and finally with $CH_2Cl_2$ (×2), and then dried under nitrogen.

**3.2.3. Deprotection.** A solution of tetrabutylammonium fluoride (TBAF) in THF (1.5 mL, 1.0 M) was added to the resin in each well. The reaction block was shaken at room temperature overnight. After 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 (×3), alternatively with MeOH and $CH_2Cl_2$ (×3), and finally with $CH_2Cl_2$ (×2), and then dried under nitrogen.

**3.2.4. Cleavage from the resin.** A solution of trifluoroacetic acid in $CH_2Cl_2$ (1.5%) was added 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 using Savant SpeedVac vacuum evaporator to dryness.

**3.2.5. Synthesis of clitocine library L13. 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 with DMF (×3), alternatively with MeOH and $CH_2Cl_2$ (×3), and finally with $CH_2Cl_2$ (×2), and then dried under nitrogen.

**3.2.6. Deprotection.** A solution of tetrabutylammonium fluoride in THF (1.5 mL, 1.0 M) was added to the resin in each well, and the reaction block was shaken at room temperature overnight. The resins were filtered and washed with DMF. A mixture of DMF–AcOH–$H_2O$ (7:2:1, 1.5 mL) was added to the resins, which were shaken at room temperature for 1 h to remove excess amount of tetrabutylammonium salt. The resins were filtered and washed with DMF (×3), alternatively with MeOH and $CH_2Cl_2$ (×3), and finally with $CH_2Cl_2$ (×2), and then dried under nitrogen.

**3.2.7. Cleavage from the resin.** A solution of trifluoroacetic acid in $CH_2Cl_2$ (1.5%) was added to the resin in each well, and 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 using Savant SpeedVac vacuum evaporator to dryness.

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18. 'Successful rate' for a plate of 96 compounds was defined as the percentage of the library members with more than 60% LC-MS purity comparing with all 96 compounds in the plate. Therefore, it represents the quality of a plate synthesized. Library members with more than 60% LC-MS purity are registered to database for the biological screening to reduce false-positive and false-negative results. The higher of the successful rate is, the higher quality of the plate has.
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## Further Reading

Building block set C, LC-MS profiles of 10 representative library members, structural and quality data of the representative plate **L8** (Table 2) as well as NMR and MS spectral data of 12 representative library members (Table 3) (18 pages)