Solid-Phase Synthesis of a Thymidinyl Dipeptide Urea Library

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A thymidinyl dipeptide urea library with structural similarity to the nucleoside peptide class of antibiotics was designed and synthesized. To generate the library, a solid-phase synthesis was developed starting from 5′-azidothymidine attached to a polystyrene butyl diethylsilane (PS-DES) resin support. This study describes the prelibrary solid-phase synthesis development including maximum loading capacity optimization, selection of orthogonal functionalized side-chain protection strategies, synthesis of a 64-member test library, and optimization of the final cleavage step. Using the optimized procedures, we synthesized a 1000-member library in a 50 μmol quantity using IRORI-directed sorting technology in MiniKans, producing the target library in good yields and purity.

Introduction

Pervasive and increasing antibacterial drug resistance requires the scientific community to continually develop new therapeutic regimes for bacterial infections. Novel antibacterial agents with new mechanisms of action are urgently needed to treat infections such as *Mycobacterium tuberculosis*, methicillin-resistant *Staphylococci aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*.[1] In recent years, the application of genomic data has led to the discovery of many new antibacterial targets.[2] Many of these targets have been the subject of large high-throughput screening (HTS) regimes in the pharmaceutical industry and to some degree in academia. The net result of these screening programs has been poor with few novel hit compound classes discovered.[3] One of the major reasons cited for the failure of these programs to obtain suitable new preclinical candidates is the lack of diversity in the screening collections.

Nucleoside sugar utilizing enzymes play key roles in the synthesis of bacterial cell walls and are potentially good targets for drug design. However, the hit rate for the HTS program against these targets has been low. Structural analysis of the screening compound collections has shown them to be poor pharmacophoric matches for this enzyme class. In contrast to synthetic screening collections, nucleoside motifs are commonly found in many naturally occurring antibiotics that target the early stages of bacterial cell wall biosynthesis.[4] These nucleoside antibiotics have shown moderate to good antibacterial activity and are thus an important class of compounds worthy of further investigation.[5] Among them is a closely related family of natural products: mureidomycins, pacidamycins, and napsamycins. The compounds in this family possess the same structural core motif, which consists of a 3′-deoxyuridine nucleoside moiety, a 4′,5′-enamide linkage, and a peptide chain (3-aminomethyl-3-deoxythreonine, alanine, or methinine, *meta*-tyrosine residues, etc). Hydrogenation of the 4′,5′-enamide bond of pacidamycins does not cause loss in biological activity, suggesting that the synthetically challenging 4′-exoenamide linkage can be replaced by standard ribosyl-nucleosides.[6] Several synthetic approaches to make analogs of these natural products have been described including a solid-phase synthesis of analogs of mureidomycin.[7] Interest in the development of inhibitors of nucleoside sugar-utilizing enzymes led to the development of a 1338-member uridine-based library that produced inhibitors of mucin-type O-linked glycosylation and UDP-galactopyranose mutase.[8]

We recently reported the solid-phase synthesis of a thymidinyl and 2′-deoxyuridinyl Ugi-derived library in a 96-well filter plate.[9] This paper reports the use of solid-phase synthesis to further our ongoing efforts to identify potent, selective, nucleoside inhibitors that target the unique deoxythymidinediphosphate (dTDP)-utilizing enzymes involved in the biosynthesis and utilization of L-rhamnose in the *M. tuberculosis* cell wall.[10] To target these enzymes, a thymidinyl dipeptide urea library **1** with three-point diversity was designed (Figure 1). Herein, we report the development and synthesis, with good yield and purity, of a 1000-member thymidinyl dipeptide urea library **1** on the PS-DES solid support using IRORI-directed sorting technology in MiniKans.[11]

Results and Discussion

Solid-Phase Synthesis Development. Key to the solid-phase synthesis of the target library was the choice of a suitable linker strategy that would allow orthogonal chemistries to build the target library and mild cleavage conditions, avoiding degradation of the nucleoside bond within the library. A strategy was developed using PS-DES resin[12] for our library synthesis (Scheme 1), in which the 3′-hydroxy of 5′-azidothymidine[13] was attached to the solid support followed by reduction of the azide using $SnCl_2$/HSPh/$N(Et)_3$ in THF,[14] which yielded the target polymer-bound 5′-aminothymidine **5**. This step and the subsequent acylation

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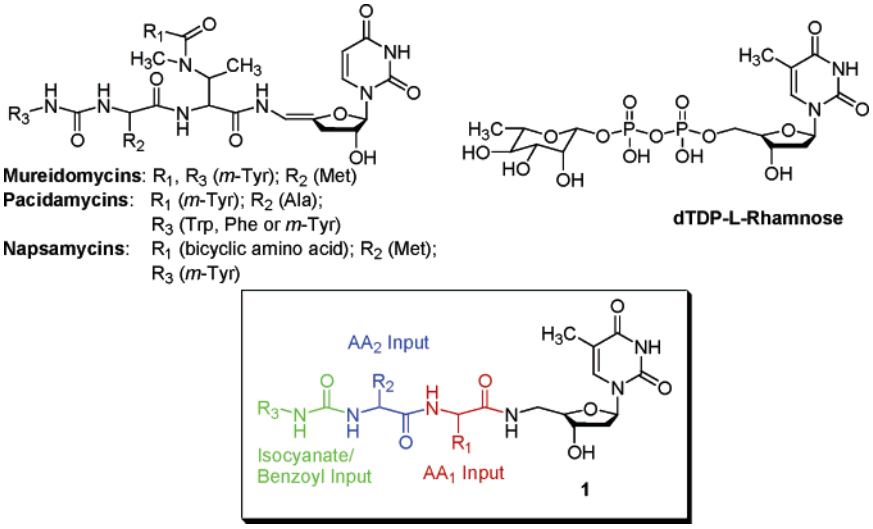
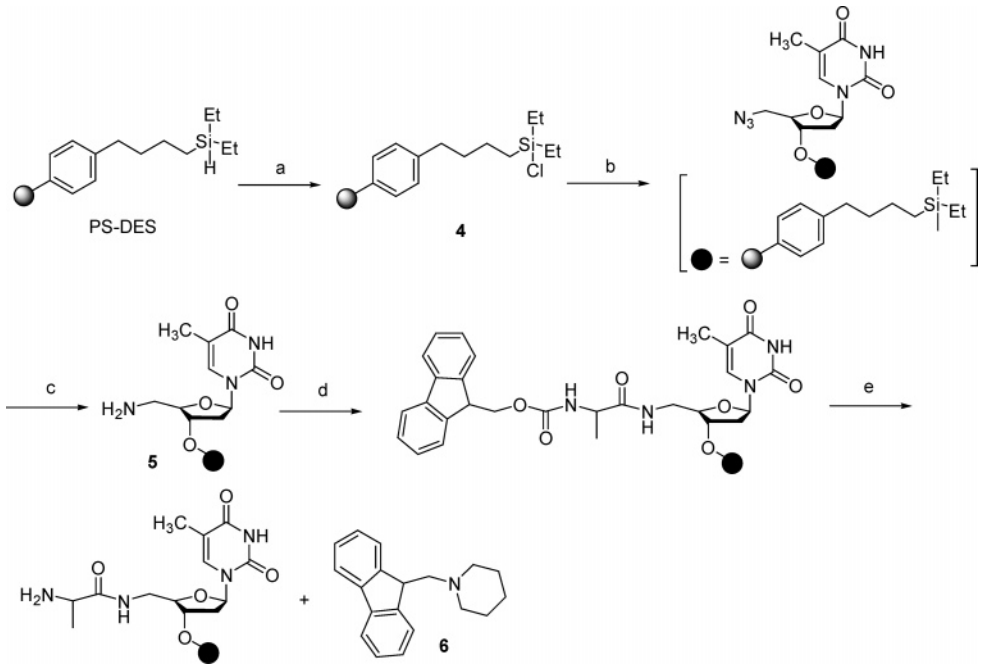


Figure 1. Naturally occurring antibiotics and our targeted library **1**.

Scheme 1. Solid-Phase Synthesis Development and Rationale for Loading Determination[a]



[a] (a) 1,3-Dichloro-5,5-dimethylhydantoin (3 equiv), anhydrous CH_2Cl_2, room temp, 2 h; (b) 5′-azido-5′-deoxythymidine (3 equiv), imidazole (3.5 equiv), anhydrous NMP, 40 °C, 4 h; (c) $SnCl_2$/HSPh/NEt_3 (1/4/5), room temp, overnight; (d) Fmoc-Ala-OH (5 equiv), HOBt (5 equiv), anhydrous CH_2Cl_2/DMF(1/1, v/v), DIC (5 equiv), room temp, 3 h; (e) piperidine/DMF (20%, v/v), room temp, 20 min.

were monitored for completion by colorimetric analysis using the Kaiser test.[15] Following library synthesis, the nucleoside library could then be readily cleaved from the resin using either mild acid conditions or with HF/pyridine, with no evidence of degradation of the products.

Optimization of Loading: Loading Capacity Study. The optimization of the loading of 5′-azidothymidine to the PS-DES resin was performed under a variety of potential loading conditions (Table 1). The loading capacity was determined in a three-step sequence by quantitative Fmoc-removal analysis.[16] Solid-supported azidothymidine was reduced, and the product 5′-aminothymidine **5** was acylated with Fmoc-Ala-OH using standard *N*,*N*′-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) coupling conditions.[17] Subsequent Fmoc deprotection was performed with 20% piperidine in DMF for 20 min. The resulting concentration of piperidine−dibenzofulvene adduct **6** (Scheme 1) and, hence, the resin loading was determined by measurement of the absorbance at 301 nm of the eluent. The effects of temperature and solvent on the loading yield of 5′-azidothymidine were determined using this protocol (Table 1). Results from this study showed that THF was not a good solvent for this loading. In two cases, THF and THF/DMF (entries 3 and 5), the yields are 38.1 and 41.9%, respectively, likely because of the poor solubility of the nucleoside azide in the loading solvent. Optimal loading conditions were determined to be in CH_2Cl_2/NMP at 40 °C (entry 8). Further elevation of the temperature to 80 °C (entries 9 and 10) did not significantly increase the loading and may have led to some decomposition of the activated resin **4**.

Prelibrary Synthesis. Once the loading capacity was maximized and well-loaded solid-supported 5′-aminothymi-

Table 1. Loading Capacity Study Based on Temperature and Solvent Effects

entry	solvent[a]	temp (°C)	abs[b] (301 nm)	loading[c] (mmol/g)	yield[d] (%)
1	CH_2Cl_2/DMF[e]	room temp (25)	0.411	0.397	53.6
2	DMF	room temp (25)	0.490	0.482	65.1
3	THF	40	0.304	0.282	38.1
4	CH_2Cl_2/DMF[e]	40	0.477	0.468	63.2
5	THF/DMF[e]	40	0.330	0.310	41.9
6	DMF	40	0.437	0.425	57.4
7	NMP	40	0.501	0.494	66.8
8	CH_2Cl_2/NMP[e]	40	0.524	0.519	70.1
9	DMF	80	0.462	0.452	61.1
10	NMP	80	0.328	0.307	41.5

[a] Anhydrous solvents were used as received. [b] $abs_{blank} = 0.043$ and $abs_{ref} = 0.729$. [c] Actual loading capacity was calculated according to protocol.[18] [d] Overall yield is calculated based on the theoretical loading of PS-DES resin (0.74 mmol/g). [e] 1/1, v/v.

dine **5** was obtained, a test set of 22 compounds (**2a**−**p** and **3a**−**f**) was synthesized on a Quest 210 synthesizer to validate the proposed synthesis. Fmoc-amino acid coupling was carried out using a DIC and HOBt coupling protocol. The subsequent Fmoc deprotection was performed in 20% piperidine/DMF to afford free amine **7** (Scheme 2). Compound **7** was reacted with another molecule of Fmoc-amino acid or a different isocyanate, followed by final cleavage in HF/pyridine in THF, to generate thymidinyl dipeptide and urea model compound dipeptides **2a**−**p** and peptidyl-ureas **3a**−**f**, respectively (Scheme 2). The excess HF in the final cleavage reaction was quenched by the addition of MeO-$SiMe_3$, and the volatile byproducts were removed in vacuo.[19] All compounds were characterized by ^{1}H NMR and mass spectrometry, and their overall yields, HPLC purities, and MS data are summarized in Table 2. The HPLC purity of all the compounds is over 90% (see Supporting Information 1 for additional data).

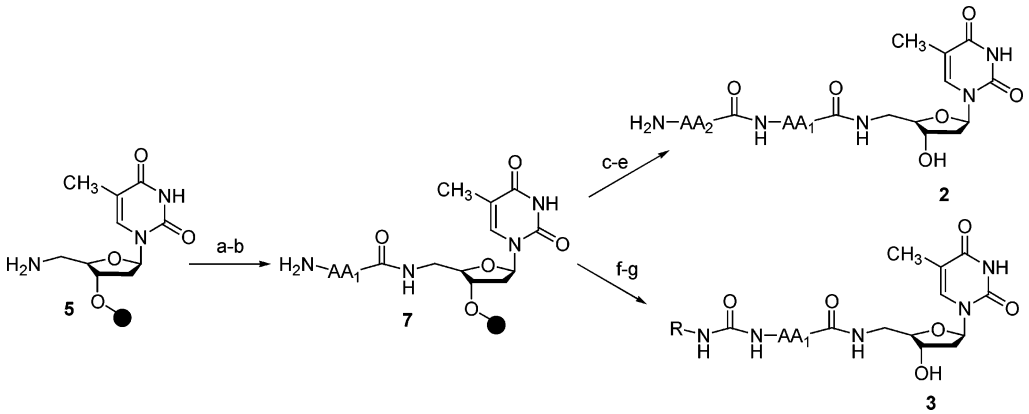
Library Stability, Cleavage, and Side-Chain Deprotection Study. For the synthesis of the large target library, the use of IRORI-directed sorting technology was selected over synthesis in 96-well filter plates because of the increased ease of simultaneous synthesis with the IRORI system. This selection required further modification to the synthesis protocol since the standard cleavage conditions were incompatible with the selected synthesis equipment because of the potential damage to the glass-coated radiofrequency (Rf) tags of the IRORI system by the HF/pyridine cleavage cocktail. Additionally, development of a co-cleavage approach would allow for simultaneous cleavage of resin and side-chain protecting groups to simplify the overall number of steps. Since the target enzyme class usually contains polar sites for phosphate and sugar binding, it was deemed necessary

Table 2. Yield, HPLC Purity, and MS Data of Thymidinyl Dipeptide and Urea Model Compounds **2** and **3**[a]

compd	AA_1	AA_2 or R	overall yield (%)	HPLC purity (%)	MS [MH^+] (m/z)
2a	Ala	Ala	61.2	95	384.1
2b	Ala	Phe	52.5	92	460.3
2c	Phe	Ala	57.1	98	460.3
2d	Phe	Phe	51.4	90	536.3
2e	Ala	β-Ala	59.6	98	384.1
2f	β-Ala	Ala	67.0	96	384.1
2g	β-Ala	Phe	44.1	92	460.3
2h	Ala	Ile	43.8	100	448.3 (M + Na)
2i	Ala	Nle	56.7	100	448.3 (M + Na)
2j	Ala	Pro	29.6	97	432.3 (M + Na)
2k	Ala	Phe(4-NO_2)	43.3	100	527.3 (M + Na)
2l	Ala	Trp	36.3	97	521.3 (M + Na)
2m	Ala	ϵ-Ahx	51.3	99	426.3
2n	Ala	Asn(Trt)	54.6	96	691.5 (M + Na)
2o	Ala	Cit	35.0	96	492.3 (M + Na)
2p	Ala	Cys(Acm)	49.4	90	509.4 (M + Na)
3a	Ala	*n*-Pr	54.7	97	398.3
3b	Ala	*i*-Pr	50.3	100	398.2
3c	Ala	C_6H_5	35.0	91	432.3
3d	Phe	*n*-Pr	54.8	98	474.3
3e	Phe	*i*-Pr	45.7	100	474.3
3f	Phe	C_6H_5	32.5	97	508.4

[a] All compounds were characterized by ^{1}H NMR; see Supporting Information 1 for details.

Scheme 2. Solid-Phase Synthesis of Thymidinyl Dipeptide and Urea Model Compounds **2** and **3** on a Quest 210 Synthesizer[a]



[a] (a) Fmoc-AA_1-OH (5 equiv), HOBt (5 equiv), anhydrous CH_2Cl_2/DMF (1/1, v/v), DIC (5 equiv), room temp, 3 h; (b) piperidine/DMF (20%, v/v), room temp, 20 min; (c) Fmoc-AA_2-OH (5 equiv), HOBt (5 equiv), anhydrous CH_2Cl_2/DMF(1/1, v/v), DIC (5 equiv), room temp, 3 h; (d) piperidine/DMF (20%, v/v), room temp, 20 min; (e) (i) HF/pyridine, room temp, 2.5 h, (ii) $MeOSiMe_3$; (f) RNCO (4 equiv), anhydrous CH_2Cl_2, 24 h; (g) (i) HF/pyridine, room temp, 2.5 h, (ii) $MeOSiMe_3$.

Scheme 3. Acidic Deprotection and Cleavage Evaluation on *t*-Butyl, *t*-Boc, and Trityl PGs

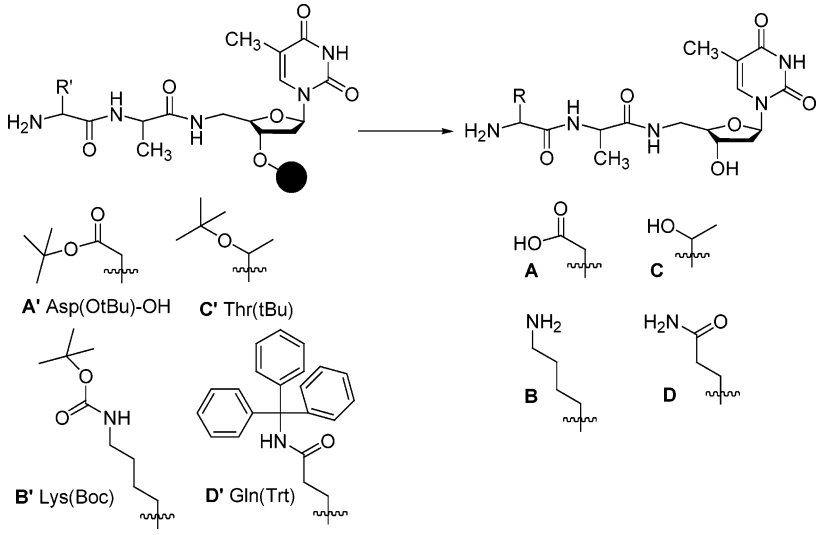


Table 3. Comparison of HPLC Purity of Desired Products under Various Cleavage Conditions

entry	cleavage and side-chain deprotection conditions[a]	HPLC purity of desired product[b] (%)			
		A	**B**	**C**	**D**
1	20% TFA/CH_2Cl_2, 2 h	81(19)	100	92	90
2	10% TFA/CH_2Cl_2, 2 h	51(49)	100	84(13)	85
3	5% TFA/CH_2Cl_2, 2 h	34(66)	94	41(57)	90
4	TFA/THF/H_2O (5/100/10), 2 h	48(52)	98	3(88)	0(97)
5	AcOH/THF/H_2O (6/6/1), 4 h	0(79)	0(88)	0(66)	0(83)
6	10% TFA/CH_2Cl_2, 6 h	75(25)	nd[c]	88(5)	nd
7	10% TFA/CH_2Cl_2, overnight	93(4)	nd	88(7)	nd
8	15% TFA/CH_2Cl_2, 3 h	84(16)	nd	95(5)	nd
9	15% TFA/CH_2Cl_2, 6 h	95(5)	nd	94(6)	nd
10	15% TFA/CH_2Cl_2, overnight	100	nd	89(7)	nd

[a] All cleavage was done at room temperature, except entry 5, which was done at 60 °C; in all cases 2.5% TIS was added, except entry 5. [b] UV detection at 254 nm; figures in parenthesis indicate percentage of side-chain protected product. [c] nd stands for not determined.

to incorporate hydrophilic side-chain constituents with appropriate protection into the library. Therefore, various orthogonally protected side-chain Fmoc-amino acid protection schemes were evaluated. Acidic labile groups were favored because it would allow the use of many commercially available Fmoc-amino acids with orthogonal protecting groups such as trityl, *t*-butyl, and *t*-Boc protecting groups. These could then be co-cleaved with the resin under acidic conditions. Although 95% TFA/CH_2Cl_2 cleavage conditions gave us rapid and complete side-chain deprotection results with good purity, such high TFA concentrations were not desirable because of the relatively difficult removal of large quantities of TFA and potential nucleoside degradation. To reduce the amount of TFA used during the joint cleavage steps, two experiments were designed (Scheme 3, Table 3). The first experiment examined the TFA concentration and different solvent system effects (entries 1−5), while the second experiment was designed to evaluate cleavage time (entries 6−10). Although 20% TFA/CH_2Cl_2 for 2 h provided good cleavage, 10% TFA/CH_2Cl_2 overnight provided optimum results that acceptably minimized TFA concentration while maximizing yield. 10% TFA/CH_2Cl_2 for 2 h conditions led to incomplete deprotection of *t*-butyl protected acids. Under 5% TFA/CH_2Cl_2 or TFA/THF/H_2O (5/100/10) for 2 h conditions, significant incomplete deprotection was observed [Asp(O*t*-Bu) (entries 3 and 4, **A**), Thr(*t*-Bu) (entry 3, **C**)], or almost did not occur at all [Thr(*t*-Bu) and Gln(Trt) (entry 4, **C** and **D**)]. It was noted that the product molecules could be cleaved from the resin with the side-chain protecting groups intact using the mild PS-DES cleavage condition: AcOH/THF/H_2O (6/6/1) (entry 5). After evaluation of these techniques, TFA/TIS/CH_2Cl_2 (10/2.5/90) overnight was selected to jointly remove the side-chain protecting groups and cleave the resin in the synthesis of target library. Triisopropylsilane (TIS) was used to quench the highly stabilized *t*-Bu and Trt cations liberated from side chain deprotection.

Synthesis of Rehearsal Library (4 × 4 × 4) in IRORI MiniKans. A small, 64-member rehearsal library was synthesized in MiniKans to explore the scope and limitation of the designed synthesis. The MiniKans were loaded with solid-supported 5′-aminothymidine **5**. Building blocks used in this library synthesis are illustrated in Figure 2. The Fmoc-amino acid coupling in steps 1 and 2 was performed using the HOBt/DIC coupling method. In this study, three types of capping procedures were evaluated for the final step: benzoylation using benzoyl chloride in the presence of diisopropylethylamine (DIPEA), reductive amination with 3-phenylbutyraldehyde and $NaCNBH_3$ in anhydrous DMF/MeOH containing 1% acetic acid, and urea formation using a pair of isocyanates. Standard cleavage with TFA/TIS/CH_2Cl_2 (95/2.5/2.5) afforded the rehearsal library, which was

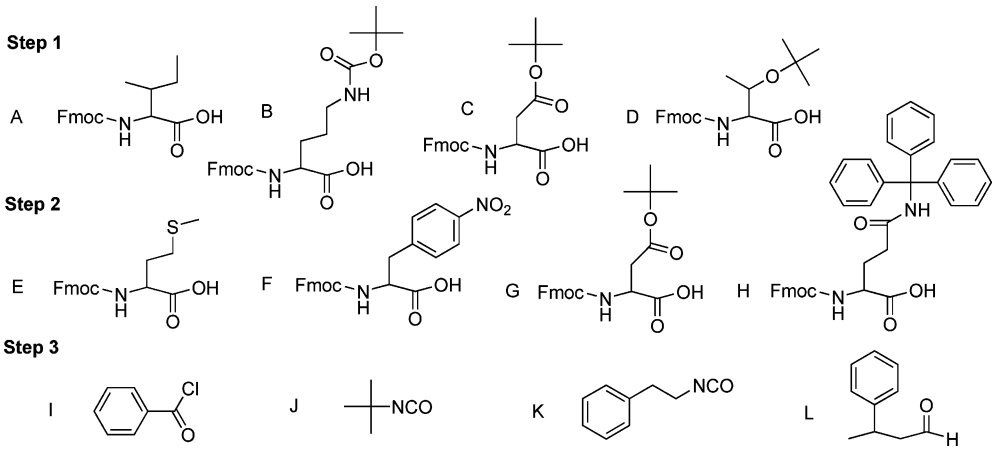
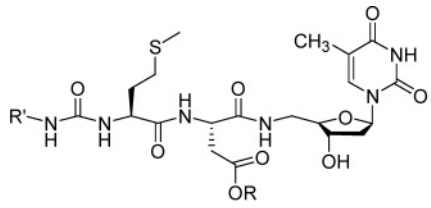


Figure 2. Building blocks used in 4 × 4 × 4 test library synthesis.



A: R' = H, R = H; MS: 553.3(M+Na).
B: R' = H, R = CH_3; MS: 567.4(M+Na).
C: R' = *t*-Bu, R = H; MS: 609.3(M+Na).
D: R' = *t*-Bu, R = CH_3; MS: 623.4(M+Na).

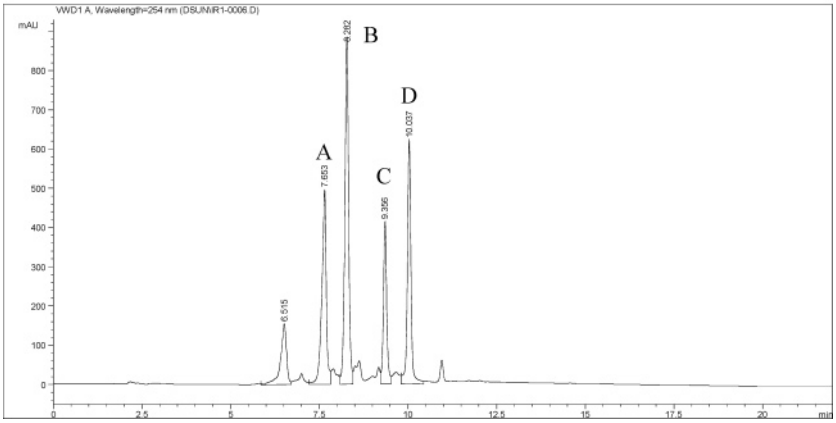
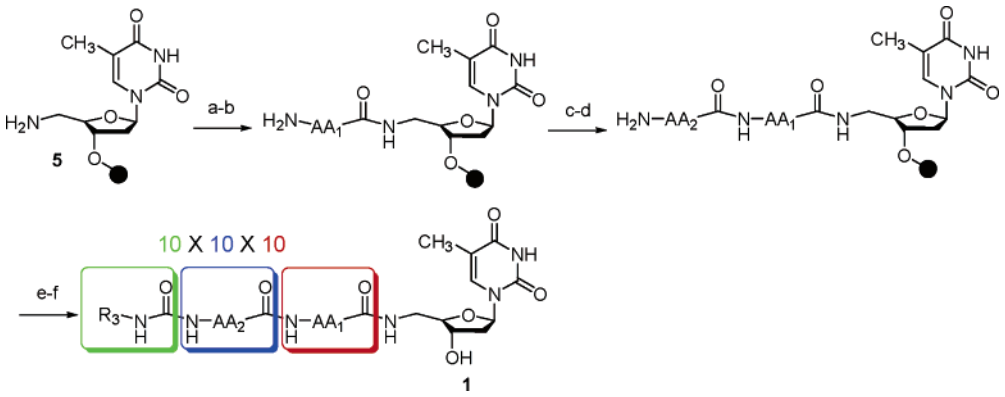


Figure 3. Selected HPLC profile of product {*C,E,J*} in methanol washings after cleavage.

analyzed by LC-MS. Overall products were obtained with good purity except for those that underwent the final reductive amination step and products derived from *t*-butyl isocyanate that were partly de-*t*-butylated under the acidic cleavage conditions afforded a mixture of the desired product and primary urea. An additional potential problem identified in this study was the potential for significant transesterification of carboxylic acid-containing products to their corresponding methyl esters. This transesterification resulted from the methanol washing steps of the final cleavage product. For example, the synthesis of product nucleoside-peptideurea synthesized with *t*-butylurea and aspartic acid functional groups gave four products **A**, **B**, **C**, and **D**; the HPLC trace is shown in Figure 3. On the basis of the results above, *t*-butyl isocyanate and reductive amination were excluded from the final library synthesis. To avoid the formation of methyl esters from carboxylic acid functional groups, 10% H_2O/THF was employed for washes after final cleavage.

Library Synthesis. On the basis of the successful prelibrary optimization studies, a 1000-member library (10 × 10 × 10) (Scheme 4, Figure 4) was generated in IRORI MiniKans. The selection of building blocks was based on the similarity to those found in natural nucleoside antibiotics, chemistry feasibility, and library structural diversity. Resin activation, azidothymidine loading, and azide reduction synthesis were performed in bulk using a standard glass solid-phase peptide synthesizer vessel. This yielded a large quantity of PS-DES-supported 5′-aminothymidine **5**, which was dispersed evenly into 1000 MiniKans containing Rf tags. The MiniKans were subjected to library synthesis using two rounds of Fmoc-amino acid couplings, each with 10 building blocks, and then a final coupling with 9 isocyanates and 1 acid chloride, all using the standardized conditions previously

Scheme 4. Solid-Phase Synthesis of Thymidinyl Dipeptide Urea Library **1** by Using IRORI MiniKan Reactors[a]



[a] (a) Fmoc-AA_1-OH (3.5 equiv), HOBt (3.5 equiv), anhydrous CH_2Cl_2/DMF (1/1, v/v), DIC (3.5 equiv), room temp, overnight; (b) piperidine/DMF (20%, v/v), room temp, 1 h; (c) Fmoc-AA_2-OH (3.5 equiv), HOBt (3.5 equiv), anhydrous CH_2Cl_2/DMF(1/1, v/v), DIC (3.5 equiv), room temp, overnight; (d) piperidine/DMF (20%, v/v), room temp, 1 h; (e) R_3NCO or BzCl (4−8 equiv), anhydrous CH_2Cl_2 or CH_2Cl_2/THF, 24 h; (f) 10% TFA/CH_2Cl_2, room temp, overnight.

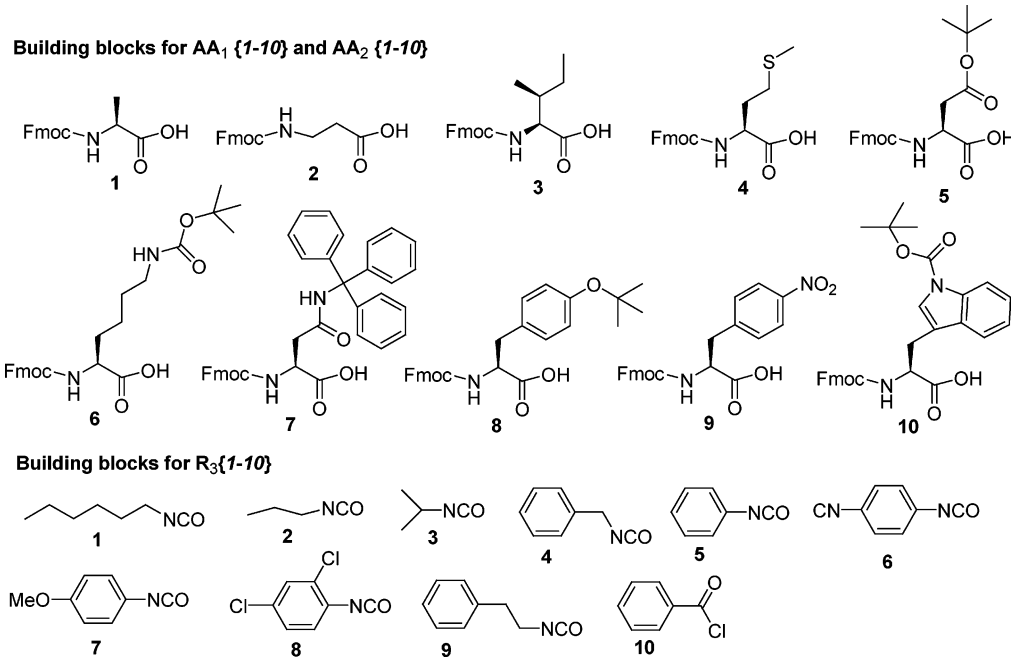


Figure 4. Building blocks used in 1000-member library **1** synthesis.

developed. Cleavage into discrete vials afforded the target library. The Rf tagging and directed sorting ensured that each MiniKan had its unique reaction path and that every member of the library was synthesized.

Analysis of the product library by mass spectroscopy, HPLC, and NMR showed that all samples tested contained the desired products. Sixty-six percent of analyzed samples contained the desired compound with over 80% purity, based on HPLC analysis; twenty-five percent of analyzed samples had a purity of 60−80%. Seven percent of samples had a purity ranging from 40 to 60%, and two percent of samples had a purity of less than 40% (Figure 5). The estimated HPLC purity is in good agreement with the purity indicated in their ^{1}H NMR spectra (see Supporting Information). Analysis of the compounds with the lowest purity showed that there was increased association with the use of Fmoc-Trp(*t*-Boc)-OH in both peptide coupling steps because of incomplete coupling and with the final benzoylation because of over-acylation.

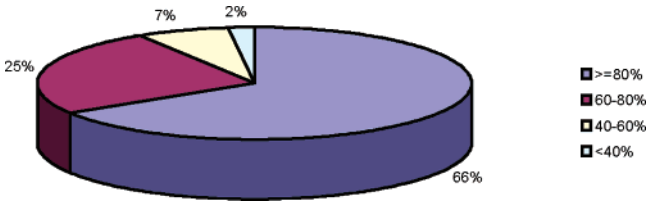


Figure 5. HPLC purity distribution of target library **1**.

Conclusion

A practical solid-phase synthesis was developed to make a thymidinyl dipeptide urea library. Maximum loading capacity determinations, prelibrary optimization, synthesis of 64-member test library using MiniKans, side-chain deprotection, and final cleavage studies are reported. A subsequent 1000-member thymidinyl dipeptide urea library was synthesized using IRORI MiniKans and directed sorting technology. Members of the target library were obtained in quantities of ∼50 μmol each and were characterized by RP-HPLC, MS, and ^{1}H NMR. This library has been screened

for anti-tuberculosis activity and for inhibition of enzymes in the dTDP-L-rhamnose biosynthesis pathway. In both cases, weak inhibitors and probes have been discovered that will be reported subsequently. This library has the potential to inhibit other nucleoside-utilizing enzymes and is available to be screened against other targets. Using the synthetic approach outlined, we are currently developing and synthesizing further, more complex libraries with the goal of increasing the affinity of the library members to nucleoside sugar-utilizing enzymes.

Experimental Section

All solvents were purchased from Sigma-Aldrich and Fisher Scientific and used as received. Fmoc-amino acids and HOBt were purchased from Novabiochem, and the remaining chemicals were from Sigma-Aldrich. PS-DES resin (100−200 mesh, loading = 0.74−1.58 mmol/g) was obtained from Argonaut Technologies, now a Biotage company. Solid-phase synthesis of prelibrary model compounds was performed on a Quest 210 synthesizer (Argonaut Technologies). IRORI AccuTag-100 system, MiniKan reactors, and Rf tags were purchased from Discovery Partners International company (San Diego, CA). Evaporation of solvents was performed using a SpeedVac SPD121P evaporator (Savant). Thin layer chromatography (TLC) analysis was performed on Merck silica gel $60F_{254}$ plates, and the spots were visualized under a UV lamp. The melting point (mp) was determined on a Fisher-Johns melting point apparatus and is uncorrected. UV absorption spectra were recorded on a Varian Cary 1E UV−vis spectrophotometer. ^{1}H NMR spectra were recorded at 500 MHz on a Varian Inova NMR instrument. ^{13}C NMR spectra were recorded at 300 MHz on a Bruker ARX instrument. Mass spectra were recorded on a Bruker Esquire LC-MS using ESI. Analytical RP-HPLC was conducted on an Agilent 1100 HPLC system with an Alltech platinum EPS C18 column (100 Å, 5 μm, 4.6 × 150 mm) with precolumn 4.6 × 10 mm, flow rate of 1.0 mL/min, and a gradient of solvent A (water with 1% acetic acid, method A; water with 0.1% TFA, method B) and solvent B (acetonitrile): 0−2.00 min 100% A, 2.00−17.00 min 0−100% B (linear gradient), 17.00−19.00 min 100% B. UV detection at 254 nm.

5′-Azido-5′-deoxythymidine.[13] Thymidine (3.6 g, 14.7 mmol) was dissolved in anhydrous DMF (50 mL) in a 250 mL reaction flask equipped with a drying tube; triphenylphosphine (3.9 g, 14.7 mmol), sodium azide (4.8 g, 70.5 mmol), and carbon tetrabromide (5.0 g, 14.7 mmol) were added portionwise. The reaction mixture was stirred at room temperature for 2 h; then 5 mL of methanol was added, and the mixture was stirred at room temperature for another 1 h. The reaction mixture was filtered and washed with DMF, and the combined filtrate was evaporated in vacuo to give a crude residue, which was purified by flash column chromatography to give 3.2 g of product as white powder. Yield: 82%. mp: 161−163 °C. TLC: R_f = 0.46 (methanol/chloroform = 1/10) (v/v). ^{1}H NMR (DMSO-d_6): δ 11.33 (br s, 1H, exchangeable with D_2O, ^{3}N*H*), 7.49 (d, J = 1.2 Hz, 1H, 6-*H*), 6.20 (t, J = 7.0 Hz, 1H, *H*-1′), 5.41 (d, J = 2.9 Hz, 1H, exchangeable with D_2O, O*H*-3′), 4.19 (q, J = 3.6 Hz, 1H, *H*-3′), 3.84 (dt, J = 3.7 and 5.1 Hz, 1H, *H*-4′), 3.55 (d, J = 5.4 Hz, 2H, CH_2-5′), 2.25 (m, 1H, CH^b-2′), 2.08 (m, 1H, CH^a-2′), 1.79 (d, J = 1.2 Hz, 3H, 5-CH_3). ^{13}C NMR (DMSO-d_6): δ 163.60, 150.42, 136.02, 109.76, 84.51, 83.85, 70.69, 51.68, 38.06, 12.03. Mass spectrum (ESI): m/z $(MNa)^+$ 290.0. HPLC purity (condition A): 99%, t_R = 8.5 min.

Solid-Phase Synthesis of Prelibrary Model Compounds 2 and 3 Using a Quest 210 Synthesizer. Activation of the PS-DES Resin. PS-DES resin (147 mg/tube, 0.109 mmol, stated capacity = 0.74 mmol/g) was distributed into ten 5 mL reaction tubes on the Quest synthesizer; the resin was preswollen in anhydrous CH_2Cl_2 for 30 min, filtered, and washed with anhydrous CH_2Cl_2 (3 × 4 mL). A solution of 1,3-dichloro-5,5-dimethylhydantoin in anhydrous CH_2Cl_2 (1.2 mL/tube, 0.36 mmol, 3.3 equiv, 0.3 M) was added, and the reaction mixture was agitated for 2 h at room temperature. The resin was filtered and washed with anhydrous CH_2Cl_2 (3 × 4 mL) and anhydrous THF (2 × 4 mL) to give the activated resin.

Resin Loading. A solution of 5′-azidothymidine (0.87 g, 3.27 mmol) and imidazole (0.26 g, 3.82 mmol) in anhydrous NMP (15 mL) was dispensed into each reaction tube (1.5 mL/tube, 0.327 mmol, 3 equiv). The reaction mixture was agitated at 40 °C for 4 h; the resin was filtered, washed with DMF (3 × 4 mL), DMF/H_2O (1/1, v/v, 3 × 4 mL), and THF (3 × 4 mL), and then dried on the internal frits under nitrogen.

Solid-Phase Azide Reduction. A freshly prepared solution of $SnCl_2$/PhSH/N(Et)$_3$ in THF (0.2 M/0.8 M/1.0 M) was added (3 mL/tube). The reaction was agitated overnight at room temperature. The resin was filtered and washed with DMF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), and THF (3 × 4 mL) to yield solid-supported 5′-aminothymidine **5**.

General Procedure for Fmoc-Amino Acid Coupling and Fmoc Deprotection. DIC (0.085 mL, 0.545 mmol, 5 equiv) was added to a solution of Fmoc-amino acid (0.545 mmol, 5 equiv) and HOBt·H_2O (0.083 g, 0.545 mmol, 5 equiv) in anhydrous DMF/CH_2Cl_2 (2 mL) (v/v, 1/1). The solution was activated for 10 min at room temperature; then it was added to each tube. The reaction was agitated at room temperature for 3 h. The resin was filtered, washed with DMF (5 × 4 mL) and THF (1 × 4 mL), and dried on the internal frits under nitrogen; 1.5 mL of piperidine in DMF (20%, v/v) was added to each tube, and the reaction mixture was agitated at room temperature for 20 min. The resin was filtered and washed with DMF (3 × 4 mL) and THF (3 × 4 mL).

General Procedure for Capping. A solution of isocyanate (0.436 mmol, 4 equiv) in anhydrous CH_2Cl_2 (1.5 mL) was added to each tube. The reaction was agitated at room temperature for 24 h. The resin was filtered, washed with MeOH (2 × 4 mL), CH_2Cl_2 (2 × 4 mL), and THF (2 × 4 mL).

Resin Cleavage. A solution of HF/pyridine in THF (1.6 mL, 0.64 mmol, 6 equiv, 0.4 M) was added to each tube, and the reaction mixture was agitated at room temperature for 2.5 h, followed by the addition of methoxytrimethylsilane (0.27 mL, 3 equiv relative to HF) to each tube and agitation

at room temperature for another 3.5 h. The cleavage solution was collected, and the resin was washed with MeOH (3 × 4 mL). The combined filtrate was evaporated to give products **2** and **3**.

Optimization of Loading: Loading Capacity Study. A parallel reaction was performed in 10 reaction vessels using a Quest synthesizer as follows: The same solid-phase protocol described above (activation, loading, reduction, coupling, and deprotection) was applied to the synthesis of solid-supported 5′-*N*-(Ala)-aminothymidine, with the exception that the resin-loading step was carried out in a variety of optimization conditions (entries 1−10 in Table 1). In the final deprotection step, the solid-supported 5′-*N*-(Ala)-aminothymidine resin was washed and diluted with acetonitrile to 10 mL, rather than with DMF and THF. A blank solution was prepared from 1.5 mL of piperidine/DMF (20%, v/v), which was diluted to 10 mL with acetonitrile. A reference solution was prepared as follows: Fmoc-Ala-OH (0.0339 g, 0.109 mmol) was treated with 1.5 mL of piperidine/DMF (20%, v/v) for 20 min, and the reaction solution was diluted to 10 mL with acetonitrile. Then 0.27 mL portions of the above test solutions, 1−10, the blank solution, and the reference solution were taken and further diluted to 25 mL with acetonitrile. The silica UV cuvette filled with the test, blank, or reference solution was placed in a Varian Cary 1E UV−vis spectrophotometer, and the optical density was recorded at 301 nm.

Library Stability, Cleavage, and Side-Chain Deprotection Study. Solid-supported products **A′**, **B′**, **C′**, and **D′** (Scheme 3) with different functionalized side chains were synthesized according to the solid-phase protocols described below for the synthesis of the 64-member library in the same synthetic scale. A variety of side chain deprotection optimization conditions with simultaneous resin cleavage (entries 1−10 in Table 3) were evaluated. The yield of the desired product was determined by LC-MS analysis.

Synthesis of a Rehearsal Library (4 × 4 × 4) in IRORI MiniKans. Resin activation, loading, and solid-phase azide reduction synthesis were performed in bulk using a standard glass solid-phase peptide synthesizer vessel using PS-DES resin. A neutral buoyancy suspension of the solid-supported 5′-aminothymidine resin (∼4.8 g, 5.12 mmol) in CH_2Cl_2/THF (2/1, v/v) was evenly distributed into 64 MiniKans containing Rf tags, resulting in ∼80 μmol of total resin per MiniKan. All MiniKans were scanned and directed sorted at each step.

The solid-phase Fmoc-amino acid coupling and Fmoc deprotection protocols were applied to the synthesis of this 64-member library, with the exception that 16 MiniKans (1.28 mmol) were contained in one reaction vessel and the coupling reaction time was increased from 3 h to overnight. DIC (1 mL, 6.4 mmol, 5 equiv) was added to a solution of Fmoc-amino acid (6.4 mmol, 5 equiv) and HOBt·H_2O (0.98 g, 6.4 mmol, 5 equiv) in anhydrous DMF/CH_2Cl_2 (v/v, 1/1) (60 mL). The solution was shaken for 10 min at room temperature; then it was added to a glass container (100 mL) containing the resin-loaded MiniKans (16 pieces, 1.28 mmol). The reaction mixture was shaken on a platform shaker at room temperature overnight. The reaction mixture was decanted, and the MiniKans were washed with DMF (2 × 70 mL), then pooled together and washed with MeOH (1 × 180 mL), CH_2Cl_2 (1 × 180 mL), and DMF (2 × 180 mL). A solution of piperidine in DMF (20%, 176 mL) was added to the 64 pooled Kans, and the reaction mixture was shaken at room temperature for 1 h. The Kans were decanted and sequentially washed with DMF (2 × 180 mL), MeOH (1 × 180 mL), CH_2Cl_2 (1 × 180 mL), DMF (2 × 180 mL), and CH_2Cl_2 (2 × 180 mL). The Kans were dried in vacuo for 2 h. The 64 Kans were directed and sorted, and a second round of Fmoc amino acid coupling and deprotection was performed. Kans were directed and sorted again for the final capping step: benzoylation was performed in a solution of benzoyl chloride (0.74 mL, 6.4 mmol, 5 equiv) in anhydrous CH_2Cl_2 (60 mL) in the presence of DIPEA (1.11 mL, 6.4 mmol, 5 equiv) for 24 h. The reaction with two isocyanates was carried out in a solution of the corresponding isocyanate (6.4 mmol, 5 equiv) in anhydrous CH_2Cl_2 (60 mL) for 24 h, and reductive amination was performed in a solution of 3-phenylbutyraldehyde (0.95 mL, 6.4 mmol, 5 equiv) in anhydrous DMF/MeOH (60 mL, v/v, 2/1), followed by addition of 0.6 mL acetic acid. The reaction mixture was shaken on a platform shaker for 1 h. $NaCNBH_3$ (1.6 g, 24.3 mmol, 20 equiv) was added in portions over a 2 h period, and the reaction mixture was shaken overnight. After sequential washes with CH_2Cl_2, MeOH, and CH_2Cl_2, the 64 Kans were sorted into individual vessels and treated with 95% TFA/TIS/CH_2Cl_2 (2 mL, 95/2.5/2.5) for 2 h. Each Kan was removed and washed with MeOH (3 mL), and TFA was removed by centrifuge in vacuo for 3 h to give product, which was analyzed by LC-MS.

Solid-Phase Synthesis of a 1000-Member Target Library 1 Using IRORI MiniKans. Resin activation, loading, and solid-phase azide reduction synthesis were performed in bulk using a standard glass solid-phase peptide synthesizer vessel using PS-DES resin (60 g, 100−200 mesh). This yielded ∼75 g of PS-DES-supported 5′-aminothymidine **5**.

Activation of the PS-DES Resin. PS-DES resin (30 g, 43.5 mmol, stated capacity of 1.45 mmol/g) was preswollen in anhydrous CH_2Cl_2 (200 mL) for 30 min in a 500 mL solid-phase peptide synthesizer vessel and filtered. A solution of 1,3-dichloro-5,5-dimethylhydantoin (25.7 g, 130.5 mmol, 3 equiv) in anhydrous CH_2Cl_2 (350 mL) was added, and the reaction mixture was shaken on a platform shaker for 2 h at room temperature. The resin was filtered and washed with anhydrous CH_2Cl_2 (3 × 150 mL) and anhydrous THF (1 × 200 mL) to give the activated resin.

Resin Loading. A solution of 5′-azidothymidine (34.9 g, 130.5 mmol, 3 equiv) and imidazole (10.4 g, 152.3 mmol, 3.5 equiv) in anhydrous DMF (300 mL) was added to the activated resin. The reaction mixture was shaken at room temperature for 4 h, and the resin was filtered. (Note: the filtrate was collected and evaporated in vacuo, and the remaining 5′-azidothymidine was purified by flash column chromatography.) The resin was further washed with DMF (3 × 300 mL), DMF/H_2O (1/1, v/v, 3 × 300 mL), and THF (3 × 300 mL) and dried in vacuo overnight to give solid-supported 5′-azidothymidine.

Solid-Phase Azide Reduction. A freshly prepared solution of $SnCl_2$/PhSH/TEA in THF (400 mL, 0.2 M/0.8 M/1.0 M) was added to the loaded resin. The reaction mixture was shaken at room temperature for 6 h. The resin was filtered, washed with DMF (3 × 300 mL), THF (3 × 300 mL), and CH_2Cl_2 (3 × 300 mL), and dried in a desiccator under vacuum overnight to yield solid-supported 5′-aminothymidine **5**.

The resin generated above was dispersed evenly into 1000 MiniKans containing Rf tags using the neutral buoyancy suspension of the solid-supported 5′-aminothymidine resin in CH_2Cl_2/THF (2/1, v/v), resulting in ∼60−75 mg (87 μmol) of total resin/MiniKan. The 1000 resin-loaded MiniKans with Rf tags were scanned and directed sorted into 10 Erlenmeyer glass reactors (1 L), containing 100 MiniKans per reactor. All MiniKans were scanned and directed sorted at each step.

General Procedure for Fmoc-Amino Acid Coupling and Fmoc Deprotection (AA_1 and AA_2). DIC (4.72 mL, 30.4 mmol, 3.5 equiv) was added to a solution of Fmoc-amino acid (30.4 mmol, 3.5 equiv) and HOBt·H_2O (4.66 g, 30.4 mmol, 3.5 equiv) in anhydrous DMF/CH_2Cl_2 (v/v, 1/1) (250 mL). The resulting solution was shaken for 10 min at room temperature and then added to a glass container (1 L) containing the resin-loaded MiniKans (100 pieces, 8.7 mmol). The reaction mixture was shaken on a platform shaker at room temperature overnight. The reaction mixture was decanted, and the MiniKans were washed with DMF (1 × 250 mL) and THF (1 × 250 mL), then pooled together, and washed with THF (1 × 2 L), MeOH (1 × 2 L), and CH_2Cl_2 (3 × 2 L). The washed MiniKans were allowed to dry in a fume hood. A solution of 20% piperidine in DMF (2.5 L) was added to a plastic container containing 1000 MiniKans, and the reaction mixture was shaken at room temperature for 1 h. The reaction mixture was decanted and washed with DMF (2 × 2 L), MeOH (1 × 2 L), and CH_2Cl_2 (3 × 2 L), and the washed MiniKans were then left to dry in a fume hood.

General Procedure for Capping (R_3). Nine isocyanates and one benzoyl chloride (34.8 mmol, 4 equiv) were dissolved in dried CH_2Cl_2 (250 mL) in 10 separate vessels. DIPEA (6.06 mL, 34.8 mmol, 4 equiv) was added to vessel 10 (benzoylation reaction). Then each solution was transferred to its corresponding Erlenmeyer flask (1 L) containing 100 MiniKans (8.7 mmol). After 2 h, 150 mL of anhydrous THF was added to reaction flasks 5−8 because of the precipitation of some isocyanates, followed by the addition of another portion of isocyanate (34.8 mmol, 4 equiv). All reaction flasks were shaken at room temperature for 24 h. The reaction mixture was decanted, and the MiniKans were washed with DMF (2 × 250 mL), THF (1 × 250 mL), MeOH (1 × 250 mL), and CH_2Cl_2 (3 × 250 mL). The washed MiniKans were allowed to dry in a fume hood.

Product Cleavage. Each 100 MiniKans from the last capping step were scanned and archived in an 8 × 12 array test tube rack. A solution of TFA/TIS/CH_2Cl_2 (3 mL, 10/2.5/90, v/v/v) was distributed into test tubes (13 × 100 mm) containing the MiniKans, and the reaction was shaken on a platform shaker overnight at room temperature. The cleavage solution was decanted to a labeled glass vial in the same 8 × 12 array format, and the MiniKan was washed with 10% H_2O/THF (2 × 3 mL). The combined solution was allowed to evaporate in a fume hood, and then it was concentrated in a SpeedVac SPD121P evaporator to afford product.

Quality Control Assessment of Library 1. Library compounds were archived in glass vials in 8 × 12 arrays. Each array contained library members with the same R_3 building block. The product quantity was determined on the basis the sample weight in the first two arrays. The average product weight is 37 mg, and the calculated overall percentage yield was 70.7% (∼50 μmol per compound), which is consistent with load determination in loading experiment. The library was analyzed and characterized as follows: nineteen samples from two randomly selected rows (1 horizontal and 1 vertical) per array were used for RP-HPLC and MS analysis for a total number of 190 samples (19% of library size). Five samples per array (5% of library size) were selected for ^{1}H NMR based on the samples' purity and structural diversity. (See Supporting Information 1 and 2 for details.)

Sample Analytical Data from the 1000-Member Library. 5′-*N*-(*n*-Hexyl-Ile-Ile)-5′-amino-5′-deoxythymidine 1{*3,3,1*}. Yield: 34.4 mg, 66.5%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.12 (t, *J* = 5.7 Hz, 1H, N*H*), 7.71 (d, *J* = 8.8 Hz, 1H, N*H*), 7.52 (d, *J* = 1.2 Hz, 1H, 6-*H*), 6.15 (dd, *J* = 6.1 and 5.9 Hz, 1H, *H*-1′), 6.04 (br s, 1H, N*H*), 5.96 (d, *J* = 9.0 Hz, 1H, N*H*), 4.17 (dd, *J* = 8.5 and 7.8 Hz, 1H, C*H*(Ile)), 4.12 (m, 1H, *H*-3′), 4.07 (dd, *J* = 7.6 and 7.1 Hz, 1H, C*H*(Ile)), 3.75 (m, 1H, *H*-4′), 3.30 (m, 2H, CH_2-5′), 2.97 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.82 (d, *J* = 1.2 Hz, 3H, 5-CH_3), 1.67 (m, 2H), 1.40 (m, 2H, CH_2), 1.34 (m, 2H, CH_2), 1.25 (m, 6H), 1.03 (m, 2H, CH_2), 0.87 (m, 3H), 0.80 (m, 12H). Mass spectrum (ESI): *m*/*z* (MNa)$^+$ 617.5. HPLC purity (condition B): 97%, t_R = 12.3 min.

5′-*N*-(*n*-Hexyl-Tyr-Asn)-5′-amino-5′-deoxythymidine 1{*7,8,1*}. Yield: 41.4 mg, 73.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 9.18 (s, 1H, O*H*), 8.16 (d, *J* = 8.1 Hz, 1H, N*H*), 7.89 (t, *J* = 6.0 Hz, 1H, N*H*), 7.56 (d, *J* = 1.2 Hz, 1H, 6-*H*), 7.37 (br s, 1H, CON*H*), 6.97 (d, *J* = 8.5 Hz, 2H), 6.91 (br s, 1H, CON*H*), 6.64 (d, *J* = 8.3 Hz, 2H), 6.17 (t, *J* = 5.1 Hz, 1H, N*H*), 6.12 (dd, *J* = 5.9 and 6.1 Hz, 1H, *H*-1′), 5.92 (d, *J* = 6.8 Hz, 1H, N*H*), 4.51 (q, *J* = 6.4 Hz, 1H, C*H*), 4.17 (m, 2H, C*H* and *H*-3′), 3.77 (dt, *J* = 5.6 and 2.9 Hz, 1H, *H*-4′), 3.38 (m, 3H, CH_2-5′ and C*H*), 3.23 (m, 1H), 2.93 (m, 2H, CH_2), 2.84 (m, 1H), 2.60 (m, 1H), 2.05 (m, 2H, CH_2-2′), 1.81 (d, *J* = 1.2 Hz, 3H, 5-CH_3), 1.26 (m, 8H), 0.86 (t, *J* = 7.1 Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* (MNa)$^+$ 668.5. HPLC purity (condition B): 92%, t_R = 10.5 min.

5′-*N*-(*n*-Hexyl-β-Ala-Lys)-5′-amino-5′-deoxythymidine 1{*6,2,1*}. Yield: 35.6 mg, 72.1%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 8.15 (t, *J* = 5.7 Hz, 1H, N*H*), 8.02 (d, *J* = 8.1 Hz, 1H, N*H*), 7.67 (br s, 3H, NH_3^+), 7.49 (s, 1H, 6-*H*), 6.14 (dd, *J* = 6.4 and 7.6 Hz, 1H, *H*-1′), 5.94 (br s, 1H, N*H*), 5.81 (br s, 1H, N*H*), 4.23 (m, 1H, C*H*(Lys)), 4.14 (m, 1H, *H*-3′), 3.77 (m, 1H, *H*-4′), 3.32 (m, 2H, CH_2-5′), 3.19 (m, 2H, CH_2), 2.95 (t, *J* = 6.8 Hz, 2H, CH_2), 2.74 (m, 2H, CH_2), 2.27 (t, *J* = 6.7 Hz, 2H, CH_2),

2.08 (m, 2H, CH_2-2′), 1.82 (s, 3H, 5-CH_3), 1.63 (m, 1H), 1.49 (m, 3H, CH_2 and C*H*), 1.26 (m, 10H), 0.87 (t, $J = 7.0$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(MH)^+$ 568.4. HPLC purity (condition B): 94%, $t_R = 10.0$ min.

5′-*N*-(*n*-Hexyl-Asp-Asp)-5′-amino-5′-deoxythymidine 1{*5,5,1*}. Yield: 32.1 mg, 61.6%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.36 (br s, 2H, COO*H* and COO*H*), 11.30 (s, 1H, N^3*H*), 8.15 (d, $J = 8.1$ Hz, 1H, N*H*), 7.91 (t, $J = 6.0$ Hz, 1H, N*H*), 7.51 (d, $J = 1.0$ Hz, 1H, 6-*H*), 6.22 (m, 2H, N*H* and N*H*), 6.11 (dd, $J = 6.4$ and 7.8 Hz, 1H, *H*-1′), 5.24 (br s, 1H, O*H*-3′), 4.53 (q, $J = 6.8$ Hz, 1H, C*H*(Asp)), 4.33 (ddd, $J = 7.6$, 6.4 and 5.1 Hz, 1H, C*H*(Asp)), 4.15 (m, 1H, *H*-3′), 3.78 (ddd, $J = 6.4$, 6.4 and 2.7 Hz, 1H, *H*-4′), 3.31 (m, 2H, CH_2-5′), 2.98 (m, 2H, CH_2), 2.60 (m, 4H, CH_2(Asp) and CH_2(Asp)), 2.04 (m, 2H, CH_2-2′), 1.81 (d, $J = 1.0$ Hz, 3H, 5-CH_3), 1.35 (m, 2H, CH_2), 1.26 (m, 6H), 0.87 (t, $J = 7.0$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(MNa)^+$ 621.3. HPLC purity (condition B): 96%, $t_R = 9.9$ min.

5′-*N*-(*n*-Hexyl-Tyr-Tyr)-5′-amino-5′-deoxythymidine 1{*8,8,1*}. Yield: 36.1 mg, 59.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 9.14 (br s, 1H, O*H*), 8.14 (t, $J = 5.9$ Hz, 1H, N*H*), 7.95 (d, $J = 8.3$ Hz, 1H, N*H*), 7.50 (d, $J = 1.0$ Hz, 1H, 6-*H*), 7.00 (d, $J = 8.3$ Hz, 2H), 6.90 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 8.1$ Hz, 4H), 6.13 (dd, $J = 7.1$ and 6.7 Hz, 1H, *H*-1′), 6.09 (t, $J = 5.2$ Hz, 1H, N*H*), 5.82 (d, $J = 7.6$ Hz, 1H, N*H*), 4.42 (ddd, $J = 8.5$, 8.3 and 5.4 Hz, 1H, C*H*(Tyr)), 4.21 (m, 1H, C*H*(Tyr)), 4.10 (m, 1H, *H*-3′), 3.75 (dt, $J = 6.1$ and 2.9 Hz, 1H, *H*-4′), 3.33 (m, 2H, CH_2-5′), 2.90 (m, 3H, CH_2 and C*H*), 2.75 (m, 2H), 2.56 (m, 1H), 2.02 (dd, $J = 4.9$ and 4.6 Hz, 2H, CH_2-2′), 1.82 (d, $J = 0.7$ Hz, 3H, 5-CH_3), 1.25 (m, 8H), 0.86 (t, $J = 7.1$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(MNa)^+$ 717.5. HPLC purity (condition B): 91%, $t_R = 11.1$ min.

5′-*N*-(n-Pr-Phe(NO_2)-Lys)-5′-amino-5′-deoxythymidine 1{*6,9,2*}. Yield: 44.3 mg, 78.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.23 (d, $J = 8.3$ Hz, 1H, N*H*), 8.19 (t, $J = 5.5$ Hz, 1H, N*H*), 8.13 (d, $J = 8.8$ Hz, 2H), 7.68 (br s, 3H, NH_3^+), 7.50 (d, $J = 1.0$ Hz, 1H, 6-*H*), 7.45 (d, $J = 8.8$ Hz, 2H), 6.15 (m, 2H, *H*-1′ and N*H*), 6.06 (d, $J = 8.3$ Hz, 1H, N*H*), 5.32 (br s, 1H, O*H*-3′), 4.50 (ddd, $J = 8.3$, 8.1 and 4.6 Hz, 1H, C*H*), 4.26 (ddd, $J = 8.5$, 8.3 and 5.4 Hz, 1H, C*H*), 4.15 (m, 1H, *H*-3′), 3.78 (m, 1H, *H*-4′), 3.35 (m, 3H, CH_2-5′ and C*H*), 3.10 (m, 1H, C*H*), 2.89 (m, 2H, CH_2), 2.74 (m, 2H, CH_2), 2.10 (m, 2H, CH_2-2′), 1.82 (d, $J = 1.0$ Hz, 3H, 5-CH_3), 1.64 (m, 1H), 1.51 (m, 3H, CH_2 and C*H*), 1.31 (m, 4H), 0.79 (t, $J = 7.4$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(MH)^+$ 647.4. HPLC purity (condition B): 87%, $t_R = 10.0$ min.

5′-*N*-(n-Pr-Ile-Lys)-5′-amino-5′-deoxythymidine 1{*6,3,2*}. Yield: 37.2 mg, 75.3%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 8.04 (t, $J = 5.9$ Hz, 1H, N*H*), 7.96 (d, $J = 8.1$ Hz, 1H, N*H*), 7.65 (br s, 3H, NH_3^+), 7.50 (d, $J = 1.2$ Hz, 1H, 6-*H*), 6.14 (dd, $J = 7.8$ and 6.4 Hz, 1H, *H*-1′), 6.10 (t, $J = 5.5$ Hz, 1H, N*H*), 5.98 (d, $J = 8.3$ Hz, 1H, N*H*), 4.24 (ddd, $J = 8.5$, 8.3 and 5.1 Hz, 1H, C*H*(Lys)), 4.13 (m, 1H, *H*-3′), 3.99 (dd, $J = 6.4$ and 6.6 Hz, 1H, C*H*(Ile)), 3.74 (m, 1H, *H*-4′), 3.33 (m, 2H, CH_2-5′), 2.94 (m, 2H, CH_2), 2.73 (m, 2H, CH_2), 2.09 (m, 2H, CH_2-2′), 1.82 (s, 3H, 5-CH_3), 1.65 (m, 2H), 1.49 (m, 3H, CH_2 and C*H*), 1.34 (m, 5H), 1.05 (m, 1H), 0.83 (m, 9H). Mass spectrum (ESI): *m*/*z* $(MH)^+$ 460.3. HPLC purity (condition B): 87%, $t_R = 9.3$ min.

5′-*N*-(n-Pr-Ala-Ile)-5′-amino-5′-deoxythymidine 1{*3,1,2*}. Yield: 25.1 mg, 56.5%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 8.16 (t, $J = 5.9$ Hz, 1H, N*H*), 7.76 (d, $J = 9.0$ Hz, 1H, N*H*), 7.52 (d, $J = 1.2$ Hz, 1H, 6-*H*), 6.15 (dd, $J = 8.1$ and 6.1 Hz, 1H, *H*-1′), 6.07 (br s, 2H, N*H* and N*H*), 4.15 (m, 3H, C*H*(Ala), C*H*(Ile) and *H*-3′), 3.76 (m, 1H, *H*-4′), 3.32 (m, 2H, CH_2-5′), 2.94 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.82 (d, $J = 0.7$ Hz, 3H, 5-CH_3), 1.69 (m, 1H, C*H*), 1.37 (m, 3H, CH_2 and C*H*), 1.13 (d, $J = 7.1$ Hz, 3H, CH_3), 1.04 (m, 1H, C*H*), 0.80 (m, 9H). Mass spectrum (ESI): *m*/*z* $(MNa)^+$ 533.2. HPLC purity (condition B): 94%, $t_R = 9.6$ min.

5′-*N*-(n-Pr-β-Ala-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,2,2*}. Yield: 26.2 mg, 64.3%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 8.08 (t, $J = 5.9$ Hz, 1H, N*H*), 7.88 (t, $J = 5.6$ Hz, 1H, N*H*), 7.49 (d, $J = 1.2$ Hz, 1H, 6-*H*), 6.14 (dd, $J = 6.4$ and 6.6 Hz, 1H, *H*-1′), 5.93 (br s, 1H, N*H*), 5.78 (br s, 1H, N*H*), 4.14 (m, 1H, *H*-3′), 3.74 (m, 1H, *H*-4′), 3.36 (m, 1H, C*H*^{a}-5′), 3.25 (m, 3H, CH_2 and C*H*$^{a'}$-5′), 3.17 (t, $J = 6.6$ Hz, 2H, CH_2), 2.92 (t, $J = 7.1$ Hz, 2H, CH_2), 2.27 (t, $J = 7.2$ Hz, 2H, CH_2), 2.18 (t, $J = 6.6$ Hz, 2H, CH_2), 2.09 (m, 2H, CH_2-2′), 1.81 (d, $J = 1.0$ Hz, 3H, 5-CH_3), 1.35 (sextet, $J = 7.3$ Hz, 2H, CH_2), 0.82 (t, $J = 7.3$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(MNa)^+$ 491.3. HPLC purity (condition B): 96%, $t_R = 8.3$ min.

5′-*N*-(n-Pr-Ala-Asp)-5′-amino-5′-deoxythymidine 1{*5,1,2*}. Yield: 26.8 mg, 60.1%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.32 (br s, 1H, COO*H*), 11.31 (s, 1H, N^3*H*), 8.14 (d, $J = 8.1$ Hz, 1H, N*H*), 7.97 (t, $J = 6.0$ Hz, 1H, N*H*), 7.52 (d, $J = 1.0$ Hz, 1H, 6-*H*), 6.11 (m, 3H, *H*-1′, N*H* and N*H*), 4.53 (ddd, $J = 8.1$, 7.8 and 5.9 Hz, 1H, C*H*(Asp)), 4.15 (m, 1H, *H*-3′), 4.02 (quintet, $J = 6.6$ Hz, 1H, C*H*(Ala)), 3.76 (m, 1H, *H*-4′), 3.31 (m, 2H, CH_2-5′), 2.95 (m, 2H, CH_2), 2.69 (dd, $J = 5.6$ and 16.6 Hz, 1H, C*H*^{a}), 2.58 (dd, $J = 7.8$ and 16.6 Hz, 1H, C*H*$^{a'}$), 2.05 (m, 2H, CH_2-2′), 1.81 (d, $J = 0.7$ Hz, 3H, 5-CH_3), 1.35 (sextet, $J = 7.3$ Hz, 2H, CH_2), 1.15 (d, $J = 7.1$ Hz, 3H, CH_3), 0.83 (t, $J = 7.3$ Hz, 3H, CH_3). Mass spectrum (ESI): *m*/*z* $(M - H)^-$ 511.1. HPLC purity (condition B): 94%, $t_R = 8.1$ min.

5′-*N*-(i-Pr-Tyr-Lys)-5′-amino-5′-deoxythymidine 1{*6,8,3*}. Yield: 32.6 mg, 60.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.06 (t, $J = 5.9$ Hz, 1H, N*H*), 8.00 (d, $J = 8.3$ Hz, 1H, N*H*), 7.67 (br s, 3H, NH_3^+), 7.50 (s, 1H, 6-*H*), 6.97 (d, $J = 8.3$ Hz, 2H), 6.63 (d, $J = 8.3$ Hz, 2H), 6.13 (dd, $J = 6.4$ and 7.8 Hz, 1H, *H*-1′), 6.02 (br s, 1H, N*H*), 5.79 (br s, 1H, N*H*), 4.22 (m, 2H, C*H*(Tyr) and C*H*(Lys)), 4.13 (m, 1H, *H*-3′), 3.75 (m, 1H, *H*-4′), 3.58 (m, 1H, C*H*), 3.32 (m, 2H, CH_2-5′), 2.83 (dd, $J = 4.4$ and 13.9 Hz, 1H, C*H*^{a}), 2.73 (m, 2H, CH_2), 2.60 (dd, $J = 8.5$ and 13.9 Hz, 1H, C*H*$^{a'}$), 2.07 (m, 2H, CH_2-2′), 1.81 (s, 3H, 5-CH_3), 1.65 (m, 1H), 1.49 (m, 3H, CH_2 and C*H*), 1.27 (m, 2H), 0.97 (d, $J = 6.5$ Hz, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* $(MNa)^+$ 640.4. HPLC purity (condition B): 84%, $t_R = 8.7$ min.

5′-*N*-(i-Pr-Ile-Asp)-5′-amino-5′-deoxythymidine 1{*5,3,3*}. Yield: 31.6 mg, 65.5%. ^{1}H NMR (500 MHz, DMSO-d_6):

δ 11.30 (s, 1H, N^3*H*), 8.17 (d, J = 8.1 Hz, 1H, N*H*), 7.94 (t, J = 5.9 Hz, 1H, N*H*), 7.51 (d, J = 1.0 Hz, 1H, 6-*H*), 6.10 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 5.98 (br s, 1H, N*H*), 5.93 (d, J = 7.1 Hz, 1H, N*H*), 4.51 (ddd, J = 8.1, 7.8 and 5.4 Hz, 1H, C*H*(Asp)), 4.13 (m, 1H, *H*-3′), 3.89 (t, J = 6.4 Hz, 1H, C*H*(Ile)), 3.74 (m, 1H, *H*-4′), 3.64 (m, 1H, C*H*), 3.34 (m, 1H, C*H*^{a}-5′), 3.25 (m, 1H, C*H*$^{a'}$-5′), 2.71 (dd, J = 5.6 and 16.9 Hz, 1H, C*H*^{b}), 2.61 (dd, J = 8.1 and 16.9 Hz, 1H, C*H*$^{b'}$), 2.03 (m, 2H, CH_2-2′), 1.80 (s, 3H, 5-CH_3), 1.61 (m, 1H), 1.39 (m, 1H, C*H*), 1.00 (d, J = 6.6 Hz, 6H, CH_3 and CH_3), 0.81 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MNa)$^+$ 577.3. HPLC purity (condition B): 93%, t_R = 9.2 min.

5′-*N*-(i-Pr-Lys-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,6,3*}. Yield: 30.8 mg, 54.7%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 8.30 (t, J = 5.9 Hz, 1H, N*H*), 8.09 (m, 3H, C*H*, C*H* and N*H*), 7.64 (br s, 3H, NH_3^+), 7.49 (m, 3H, C*H*, C*H* and 6-*H*), 6.13 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 5.92 (d, J = 7.6 Hz, 1H, N*H*), 5.88 (d, J = 7.6 Hz, 1H, N*H*), 5.31 (br s, 1H, O*H*-3′), 4.58 (ddd, J = 9.8, 9.0 and 4.6 Hz, 1H, C*H*(Phe(NO$_2$)), 4.11 (m, 1H, *H*-3′), 4.00 (q, J = 7.6 Hz, 1H, C*H*(Lys)), 3.72 (dt, J = 6.8 and 3.4 Hz, 1H, *H*-4′), 3.62 (m, 1H, C*H*), 3.33 (m, 2H, CH_2-5′), 3.14 (dd, J = 4.4 and 13.7 Hz, 1H, C*H*^{a}), 2.94 (dd, J = 9.8 and 13.7 Hz, 1H, C*H*$^{a'}$), 2.71 (m, 2H, CH_2), 2.09 (m, 2H, CH_2-2′), 1.80 (s, 3H, 5-CH_3), 1.46 (m, 3H), 1.30 (m, 1H, C*H*), 1.18 (m, 2H, CH_2), 1.00 (d, J = 6.5 Hz, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MH)$^+$ 426.3. HPLC purity (condition B): 87%, t_R = 9.9 min.

5′-*N*-(i-Pr-Lys-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,6,3*}. Yield: 23.5 mg, 51.4%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.07 (t, J = 5.7 Hz, 1H, N*H*), 7.97 (t, J = 5.6 Hz, 1H, N*H*), 7.68 (br s, 3H, NH_3^+), 7.47 (s, 1H, 6-*H*), 6.14 (dd, J = 6.6 and 7.3 Hz, 1H, *H*-1′), 5.92 (br s, 2H, N*H* and N*H*), 4.26 (m, 1H, C*H*), 4.13 (m, 1H, *H*-3′), 4.05 (m, 1H, C*H*), 3.72 (m, 1H, *H*-4′), 3.62 (m, 1H, C*H*), 3.35 (m, 1H, C*H*), 3.24 (m, 2H, CH_2-5′), 2.75 (m, 2H, CH_2), 2.27 (t, J = 7.2 Hz, 2H, CH_2), 2.08 (m, 2H, CH_2-2′), 1.80 (s, 3H, 5-CH_3), 1.51 (m, 3H), 1.38 (m, 1H, C*H*), 1.25 (m, 2H, CH_2), 1.00 (d, J = 6.6 Hz, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MH)$^+$ 526.3. HPLC purity (Condition B): 84%, t_R = 7.9 min.

5′-*N*-(i-Pr-Asn-Asp)-5′-amino-5′-deoxythymidine 1{*5,7,3*}. Yield: 38.6 mg, 79.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H, N^3*H*), 8.22 (d, J = 8.3 Hz, 1H, N*H*), 8.12 (t, J = 6.0 Hz, 1H, N*H*), 7.54 (br s, 1H, CON*H*), 7.51 (d, J = 1.0 Hz, 1H, 6-*H*), 7.02 (br s, 1H, CON*H*), 6.20 (d, J = 7.3 Hz, 1H, N*H*), 6.09 (dd, J = 6.6 and 7.6 Hz, 1H, *H*-1′), 6.03 (d, J = 6.4 Hz, 1H, N*H*), 4.54 (ddd, J = 8.3, 7.8 and 5.1 Hz, 1H, C*H*), 4.28 (m, 1H, C*H*), 4.15 (q, J = 3.7 Hz, 1H, *H*-3′), 3.78 (dt, J = 5.6 and 2.4 Hz, 1H, *H*-4′), 3.64 (m, 1H, C*H*), 3.28 (m, 2H, CH_2-5′), 2.72 (dd, J = 5.1 and 16.6 Hz, 1H, C*H*^{a}), 2.56 (dd, J = 7.8 and 16.6 Hz, 1H, C*H*$^{a'}$), 2.46 (m, 2H, CH_2), 2.02 (m, 2H, CH_2-2′), 1.79 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.00 (d, J = 6.6 Hz, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MNa)$^+$ 578.3. HPLC purity (condition B): 94%, t_R = 7.7 min.

5′-*N*-(Bn-Ile-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,3,4*}. Yield: 21 mg, 43.2%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.05 (t, J = 5.9 Hz, 1H, N*H*), 7.99 (t, J = 5.6 Hz, 1H, N*H*), 7.47 (d, J = 1.2 Hz, 1H, 6-*H*), 7.30 (m, 2H), 7.23 (m, 3H), 6.51 (t, J = 6.0 Hz, 1H, N*H*), 6.13 (dd, J = 6.4 and 7.6 Hz, 1H, *H*-1′), 6.10 (d, J = 9.0 Hz, 1H, N*H*), 4.20 (t, J = 5.9 Hz, 2H, CH_2), 4.13 (m, 1H, *H*-3′), 4.00 (dd, J = 8.8 and 6.8 Hz, 1H, C*H*(Ile)), 3.72 (m, 1H, *H*-4′), 3.27 (m, 4H, CH_2 and CH_2-5′), 2.28 (t, J = 7.3 Hz, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.59 (m, 1H), 1.40 (m, 1H), 1.00 (m, 1H), 0.80 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MNa)$^+$ 581.4. HPLC purity (condition B): 87%, t_R = 10.4 min.

5′-*N*-(Bn-β-Ala-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,2,4*}. Yield: 23.4 mg, 42.2%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.30 (t, J = 5.9 Hz, 1H, N*H*), 8.21 (d, J = 8.5 Hz, 1H, N*H*), 8.11 (d, J = 8.8 Hz, 2H, C*H* and C*H*), 7.49 (d, J = 8.8 Hz, 2H, C*H* and C*H*), 7.47 (d, J = 1.2 Hz, 1H, 6-*H*), 7.29 (m, 2H), 7.21 (m, 3H), 6.40 (br s, 1H, N*H*), 6.12 (dd, J = 6.4 and 7.6 Hz, 1H, *H*-1′), 5.87 (br s, 1H, N*H*), 4.59 (ddd, J = 9.5, 9.3 and 4.9 Hz, 1H, C*H*(Phe(NO$_2$)), 4.17 (s, 2H, CH_2), 4.10 (m, 1H, *H*-3′), 3.73 (m, 1H, *H*-4′), 3.37 (ddd, J = 5.4, 5.4 and 13.9 Hz, 1H, C*H*^{a}-5′), 3.27 (ddd, J = 6.4, 6.4 and 13.9 Hz, 1H, C*H*$^{a'}$-5′), 3.11 (m, 3H, CH_2 and C*H*^{b}), 2.88 (dd, J = 9.5 and 13.7 Hz, 1H, C*H*$^{b'}$), 2.21 (m, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): *m*/*z* (MH)$^+$ 638.4. HPLC purity (condition B): 90%, t_R = 10.9 min.

5′-*N*-(Bn-Tyr-Ile)-5′-amino-5′-deoxythymidine 1{*3,8,4*}. Yield: 30.5 mg, 53.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 9.14 (br s, 1H, O*H*), 8.18 (t, J = 5.9 Hz, 1H, N*H*), 7.83 (d, J = 9.0 Hz, 1H, N*H*), 7.52 (d, J = 1.2 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.17 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H, C*H* and C*H*), 6.62 (d, J = 8.4 Hz, 2H, C*H* and C*H*), 6.56 (t, J = 6.0 Hz, 1H, N*H*), 6.15 (dd, J = 6.1 and 8.1 Hz, 1H, *H*-1′), 6.09 (d, J = 8.3 Hz, 1H, N*H*), 4.40 (ddd, J = 9.0, 8.3 and 4.9 Hz, 1H, C*H*(Tyr)), 4.17 (m, 3H, C*H*(Ile) and CH_2), 4.13 (m, 1H, *H*-3′), 3.78 (m, 1H, *H*-4′), 3.36 (m, 1H, C*H*^{a}-5′), 3.28 (ddd, J = 5.1, 5.1 and 14.2 Hz, 1H, C*H*$^{a'}$-5′), 2.85 (dd, J = 4.6 and 14.2 Hz, 1H, C*H*^{b}), 2.64 (dd, J = 8.3 and 13.9 Hz, 1H, C*H*$^{b'}$), 2.07 (m, 2H, CH_2-2′), 1.81 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.68 (m, 1H), 1.40 (m, 1H), 1.03 (m, 1H), 0.78 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): *m*/*z* (MH)$^+$ 673.4. HPLC purity (condition B): 92%, t_R = 10.9 min.

5′-*N*-(Bn-Tyr-Tyr)-5′-amino-5′-deoxythymidine 1{*8,8,4*}. Yield: 26.6 mg, 43.6%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 9.15 (br s, 2H, O*H* and O*H*), 8.15 (t, J = 6.0 Hz, 1H, N*H*), 7.99 (d, J = 8.3 Hz, 1H, N*H*), 7.48 (d, J = 1.2 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.16 (m, 3H), 6.99 (d, J = 8.5 Hz, 2H, C*H* and C*H*), 6.91 (d, J = 8.3 Hz, 2H, C*H* and C*H*), 6.62 (d, J = 8.5 Hz, 2H, C*H* and C*H*), 6.60 (d, J = 8.5 Hz, 2H, C*H* and C*H*), 6.56 (t, J = 5.7 Hz, 1H, N*H*), 6.12 (t, J = 7.1 Hz, 1H, *H*-1′), 6.01 (d, J = 7.8 Hz, 1H, N*H*), 4.44 (ddd, J = 8.8, 8.5 and 5.6 Hz, 1H, C*H*(Tyr)), 4.27 (ddd, J = 8.8, 7.8 and 4.6 Hz, 1H, C*H*(Tyr)), 4.19 (dd, J = 6.1 and 15.6 Hz, 1H, C*H*^{a}), 4.10 (m, 2H, C*H*$^{a'}$ and *H*-3′), 3.74 (dt, J = 6.1 and 3.2 Hz, 1H, *H*-4′), 3.31 (t, J = 5.9 Hz, 2H, CH_2-5′), 2.86 (dd, J = 5.1 and 13.9 Hz, 1H, C*H*^{b}), 2.81 (dd, J = 4.6 and 13.9 Hz, 1H, C*H*^{c}), 2.71 (dd, J = 8.8 and

13.7 Hz, 1H, C$H^{b'}$), 2.56 (dd, J = 8.8 and 14.2 Hz, 1H, C$H^{c'}$), 2.01 (dd, J = 4.6 and 6.8 Hz, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 723.4. HPLC purity (condition B): 91%, t_R = 10.3 min.

5′-*N*-(Bn-Asn-Lys)-5′-amino-5′-deoxythymidine 1{*6,10,4*}. Yield: 40.4 mg, 75.3%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3H), 8.16 (t, J = 5.9 Hz, 1H, NH), 8.01 (d, J = 8.3 Hz, 1H, NH), 7.62 (br s, 3H, NH_3^+), 7.51 (br s, 1H, CONH), 7.50 (d, J = 1.0 Hz, 1H, 6-H), 7.23 (m, 2H), 7.12 (m, 3H), 7.00 (br s, 1H, CONH), 6.75 (t, J = 5.9 Hz, 1H, NH), 6.31 (d, J = 7.6 Hz, 1H, NH), 6.11 (dd, J = 6.6 and 7.6 Hz, 1H, H-1′), 4.39 (q, J = 6.5 Hz, 1H, CH), 4.18 (m, 4H, CH_2, CH and H-3′), 3.77 (m, 1H, H-4′), 3.30 (m, 2H, CH_2-5′), 2.71 (m, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.74 (m, 1H), 1.48 (m, 3H), 1.05 (m, 2H). Mass spectrum (ESI): m/z $(MH)^+$ 617.4. HPLC purity (condition B): 91%, t_R = 8.6 min.

5′-*N*-(Ph-Met-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,4,5*}. Yield: 22 mg, 37%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3H), 8.58 (s, 1H, NH), 8.29 (m, 2H, NH and NH), 8.07 (d, J = 8.5 Hz, 2H), 7.50 (m, 3H, CH, CH and 6-H), 7.35 (d, J = 8.1 Hz, 2H), 7.21 (t, J = 7.9 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H, CH), 6.36 (d, J = 7.6 Hz, 1H, NH), 6.14 (t, J = 6.4 and 7.6 Hz, 1H, H-1′), 4.63 (ddd, J = 9.3, 9.0 and 4.6 Hz, 1H, CH(Phe(NO$_2$)), 4.22 (m, 1H, CH(Lys)), 4.11 (m, 1H, H-3′), 3.73 (dt, J = 6.1 and 3.2 Hz, 1H, H-4′), 3.34 (t, J = 5.9 Hz, 2H, CH_2-5′), 3.14 (dd, J = 4.4 and 13.7 Hz, 1H, CH^a), 2.94 (dd, J = 9.8 and 13.4 Hz, 1H, C$H^{a'}$), 2.35 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 2.00 (s, 3H, CH_3), 1.80 (s, 3H, 5-CH_3), 1.75 (m, 2H). Mass spectrum (ESI): m/z $(MNa)^+$ 706.3. HPLC purity (condition B): 82%, t_R = 11.6 min.

5′-*N*-(Ph-β-Ala-Ala)-5′-amino-5′-deoxythymidine 1{*1,2,5*}. Yield: 26.2 mg, 59.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3H), 8.55 (s, 1H, NH), 8.08 (m, 2H, NH and NH), 7.47 (d, J = 1.0 Hz, 1H, 6-H), 7.36 (d, J = 7.6 Hz, 2H), 7.20 (m, 2H), 6.87 (t, J = 7.3 Hz, 1H), 6.16 (t, J = 5.7 Hz, 1H, NH), 6.12 (dd, J = 6.4 and 7.8 Hz, 1H, H-1′), 4.29 (quintet, J = 6.8 Hz, 1H, CH(Ala)), 4.13 (m, 1H, H-3′), 3.75 (m, 1H, H-4′), 3.38 (m, 2H, CH_2-5′), 3.27 (m, 2H, CH_2), 2.32 (t, J = 6.6 Hz, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.18 (d, J = 7.1 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 525.3. HPLC purity (condition B): 97%, t_R = 9.2 min.

5′-*N*-(Ph-Phe(NO$_2$)-Ala)-5′-amino-5′-deoxythymidine 1{*1,9,5*}. Yield: 25.6 mg, 47.2%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3H), 8.67 (s, 1H, NH), 8.44 (t, J = 7.6 Hz, 1H, NH), 8.14 (m, 3H, CH, CH and NH), 7.48 (m, 3H, CH, CH and 6-H), 7.31 (d, J = 7.6 Hz, 2H), 7.19 (t, J = 7.8 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 6.33 (d, J = 8.3 Hz, 1H, NH), 6.14 (dd, J = 6.4 and 7.8 Hz, 1H, H-1′), 4.63 (ddd, J = 7.8, 7.6 and 4.4 Hz, 1H, CH(Phe-(NO$_2$)), 4.32 (quintet, J = 7.1 Hz, 1H, CH(Ala)), 4.14 (m, 1H, H-3′), 3.77 (m, 1H, H-4′), 3.32 (m, 2H, CH_2-5′), 3.17 (dd, J = 4.6 and 13.9 Hz, 1H, CH^a), 2.94 (dd, J = 7.8 and 13.7 Hz, 1H, C$H^{a'}$), 2.09 (m, 2H, CH_2-2′), 1.80 (d, J = 0.5 Hz, 3H, 5-CH_3), 1.23 (d, J = 6.8 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 646.3. HPLC purity (condition B): 91%, t_R = 11.1 min.

5′-*N*-(Ph-Tyr-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,8,5*}. Yield: 29.4 mg, 56.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H, N^3H), 9.17 (s, 1H, OH), 8.64 (s, 1H, NH), 8.08 (m, 2H, NH and NH), 7.46 (d, J = 1.0 Hz, 1H, 6-H), 7.32 (d, J = 7.6 Hz, 2H), 7.19 (t, J = 7.9 Hz, 2H), 6.96 (d, J = 8.3 Hz, 2H), 6.87 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.3 Hz, 2H), 6.23 (d, J = 8.3 Hz, 1H, NH), 6.12 (dd, J = 6.4 and 7.8 Hz, 1H, H-1′), 5.29 (br s, 1H, OH), 4.32 (m, 1H, CH(Tyr)), 4.13 (m, 1H, H-3′), 3.73 (m, 1H, H-4′), 3.35 (m, 2H, CH_2-5′), 3.24 (m, 2H, CH_2), 2.83 (dd, J = 5.1 and 13.7 Hz, 1H, CH^a), 2.94 (dd, J = 7.6 and 13.9 Hz, 1H, C$H^{a'}$), 2.26 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.80 (s, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 617.3. HPLC purity (condition B): 96%, t_R = 9.7 min.

5′-*N*-(Ph-Trp-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,10,5*}. Yield: 30.8 mg, 47.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3H), 10.82 (d, J = 1.7 Hz, 1H, NH(Trp)), 8.64 (s, 1H, NH), 8.34 (d, J = 8.3 Hz, 1H, NH), 8.28 (t, J = 5.7 Hz, 1H, NH), 8.03 (d, J = 8.8 Hz, 2H), 7.47 (m, 4H), 7.31 (m, 2H), 7.20 (m, 3H), 7.08 (d, J = 2.2 Hz, 1H), 7.03 (t, J = 7.1 Hz, 1H), 6.93 (t, J = 7.1 Hz, 1H), 6.88 (t, J = 7.3 Hz, 1H), 6.15 (m, 2H, NH and H-1′), 4.64 (ddd, J = 9.0, 8.8 and 4.9 Hz, 1H, CH), 4.49 (m, 1H, CH), 4.12 (m, 1H, H-3′), 3.76 (m, 1H, H-4′), 3.35 (m, 2H, CH_2-5′), 3.09 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.79 (s, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 761.3. HPLC purity (condition B): 81%, t_R = 12.2 min.

5′-*N*-(4-Cyanophenyl-Phe(NO$_2$)-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,9,6*}. Yield: 31.5 mg, 47.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3H), 9.14 (s, 1H, NH), 8.59 (d, J = 8.5 Hz, 1H, NH), 8.39 (t, J = 5.9 Hz, 1H, NH), 8.11 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.48 (m, 5H), 7.42 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 8.3 Hz, 1H, NH), 6.16 (dd, J = 6.4 and 7.6 Hz, 1H, H-1′), 4.65 (m, 1H, CH(Phe(NO$_2$)), 4.60 (m, 1H, CH(Phe(NO$_2$)), 4.12 (m, 1H, H-3′), 3.76 (m, 1H, H-4′), 3.43 (m, 1H, CH^a-5′), 3.30 (m, 1H, C$H^{a'}$-5′), 3.11 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 2.09 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 792.3. HPLC purity (condition B): 96%, t_R = 12.2 min.

5′-*N*-(4-Cyanophenyl-Ile-Tyr)-5′-amino-5′-deoxythymidine 1{*8,3,6*}. Yield: 34.6 mg, 60.1%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3H), 9.17 (s, 1H, OH), 9.10 (s, 1H, NH), 8.16 (d, J = 8.3 Hz, 1H, NH), 8.11 (t, J = 6.0 Hz, 1H, NH), 7.67 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 1.0 Hz, 1H, 6-H), 7.00 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 8.5 Hz, 2H), 6.44 (d, J = 8.8 Hz, 1H, NH), 6.12 (dd, J = 6.6 and 7.6 Hz, 1H, H-1′), 5.27 (d, J = 4.4 Hz, 1H, OH-2′), 4.47 (ddd, J = 9.0, 8.3 and 5.1 Hz, 1H, CH(Tyr)), 4.12 (dd, J = 8.5 and 5.9 Hz, 1H, CH(Ile)), 4.08 (m, 1H, H-3′), 3.72 (m, 1H, H-4′), 3.32 (m, 2H, CH_2-5′), 2.85 (dd, J = 4.9 and 13.7 Hz, 1H, CH^a), 2.68 (dd, J = 9.5 and 14.2 Hz, 1H, C$H^{a'}$), 2.02 (m, 2H, CH_2-2′), 1.81 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.66 (m, 1H), 1.31 (m, 1H), 0.97 (m, 1H), 0.79 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 684.3. HPLC purity (condition B): 91%, t_R = 11.0 min.

5′-*N*-(4-Cyanophenyl-Trp-Met)-5′-amino-5′-deoxythymidine 1{*4,10,6*}. Yield: 37.9 mg, 62.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 10.83 (d, J = 2.0 Hz, 1H, N*H*(Trp)), 9.24 (s, 1H, N*H*), 8.34 (d, J = 8.1 Hz, 1H, N*H*), 8.13 (t, J = 5.7 Hz, 1H, N*H*), 7.65 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.50 (m, 3H), 7.31 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.04 (m, 1H), 6.93 (m, 1H), 6.43 (d, J = 7.8 Hz, 1H, N*H*), 6.16 (dd, J = 6.1 and 7.8 Hz, 1H, *H*-1′), 4.58 (m, 1H, C*H*), 4.37 (m, 1H, C*H*), 4.13 (m, 1H, *H*-3′), 3.79 (m, 1H, *H*-4′), 3.30 (m, 2H, CH_2-5′), 3.17 (dd, J = 5.1 and 14.9 Hz, 1H, CH^a), 3.00 (dd, J = 7.6 and 14.9 Hz, 1H, C$H^{a'}$), 2.38 (m, 2H, CH_2), 2.08 (m, 2H, CH_2-2′), 1.97 (s, 3H, CH_3), 1.88 (m, 1H), 1.81 (s, 3H, 5-CH_3), 1.78 (m, 1H). Mass spectrum (ESI) m/z (MNa)$^+$ 725.4. HPLC purity (condition B): 87%, t_R = 11.6 min.

5′-*N*-(4-Cyanophenyl-Met-Tyr)-5′-amino-5′-deoxythymidine 1{*8,4,6*}. Yield: 31.7 mg, 62.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 9.18 (s, 1H, N*H*), 9.14 (br s, 1H, O*H*), 8.21 (m, 2H, N*H* and N*H*), 7.67 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 1.0 Hz, 1H, 6-*H*), 7.01 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.1 Hz, 1H, N*H*), 6.58 (d, J = 8.5 Hz, 2H), 6.13 (dd, J = 6.6 and 7.3 Hz, 1H, *H*-1′), 4.45 (ddd, J = 9.5, 8.8 and 4.6 Hz, 1H, C*H*(Tyr)), 4.28 (m, 1H, C*H*(Met)), 4.09 (m, 1H, *H*-3′), 3.72 (m, 1H, *H*-4′), 3.32 (t, J = 5.9 Hz, 2H, CH_2-5′), 2.86 (dd, J = 4.9 and 14.2 Hz, 1H, CH^a), 2.68 (dd, J = 9.5 and 13.9 Hz, 1H, C$H^{a'}$), 2.39 (m, 2H, CH_2), 2.03 (m, 2H, CH_2-2′), 2.01 (s, 3H, CH_3), 1.81 (s, 3H, 5-CH_3), 1.80 (m, 2H). Mass spectrum (ESI): m/z (MH)$^+$ 680.4. HPLC purity (condition B): 83%, t_R = 10.7 min.

5′-*N*-(4-Cyanophenyl-Asn-Asp)-5′-amino-5′-deoxythymidine 1{*5,10,6*}. Yield: 43.6 mg, 81.5%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 9.38 (s, 1H, N*H*), 8.41 (d, J = 8.1 Hz, 1H, N*H*), 8.10 (t, J = 6.0 Hz, 1H, N*H*), 7.67 (d, J = 8.8 Hz, 2H), 7.60 (br s, 1H, CON*H*), 7.55 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 1.2 Hz, 1H, 6-*H*), 7.09 (br s, 1H, CON*H*), 6.72 (d, J = 7.8 Hz, 1H, N*H*), 6.10 (dd, J = 6.6 and 7.6 Hz, 1H, *H*-1′), 4.58 (ddd, J = 7.8, 5.6 and 5.4 Hz, 1H, C*H*), 4.45 (m, 1H, C*H*), 4.14 (m, 1H, *H*-3′), 3.79 (dt, J = 5.9 and 2.2 Hz, 1H, *H*-4′), 3.30 (m, 2H, CH_2-5′), 2.76 (dd, J = 5.4 and 16.6 Hz, 1H, CH^a), 2.58 (dd, J = 5.6 and 10.3 Hz, 1H, C$H^{a'}$), 2.56 (m, 2H, CH_2), 2.04 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z (MNa)$^+$ 615.2. HPLC purity (condition B): 95%, t_R = 8.9 min.

5′-*N*-(4-Methoxyphenyl-Tyr-Ala)-5′-amino-5′-deoxythymidine 1{*1,8,7*}. Yield: 28.7 mg, 52.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 9.16 (br s, 1H, O*H*), 8.48 (s, 1H, N*H*), 8.20 (d, J = 7.8 Hz, 1H, N*H*), 8.03 (t, J = 5.9 Hz, 1H, N*H*), 7.49 (d, J = 1.0 Hz, 1H, 6-*H*), 7.22 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 6.13 (dd, J = 6.1 and 7.6 Hz, 1H, *H*-1′), 6.06 (d, J = 8.1 Hz, 1H, N*H*), 4.39 (ddd, J = 8.3, 8.1 and 4.6 Hz, 1H, C*H*(Tyr)), 4.30 (quintet, J = 6.8 Hz, 1H, C*H*(Ala)), 4.13 (m, 1H, *H*-3′), 3.75 (dt, J = 6.1 and 3.2 Hz, 1H, *H*-4′), 3.67 (s, 3H, OCH_3), 3.32 (t, J = 6.0 Hz, 2H, CH_2-5′), 2.90 (dd, J = 4.4 and 13.2 Hz, 1H, CH^a), 2.66 (dd, J = 8.3 and 14.2 Hz, 1H, C$H^{a'}$), 2.07 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.21 (d, J = 7.1 Hz, 3H, CH_3). Mass spectrum (ESI): m/z (MH)$^+$ 625.3. HPLC purity (condition B): 92%, t_R = 9.9 min.

5′-*N*-(4-Methoxyphenyl-Asp-Phe(NO$_2$))-5′-amino-5′-deoxythymidine 1{*9,5,7*}. Yield: 26.2 mg, 43.2%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.54 (s, 1H, N*H*), 8.26 (t, J = 5.9 Hz, 1H, N*H*), 8.06 (d, J = 8.3 Hz, 1H, N*H*), 7.99 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 1.2 Hz, 1H, 6-*H*), 7.45 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 6.38 (d, J = 8.3 Hz, 1H, N*H*), 6.14 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 4.57 (ddd, J = 8.8, 8.5 and 4.4 Hz, 1H, C*H*), 4.45 (m, 1H, C*H*), 4.12 (m, 1H, *H*-3′), 3.75 (m, 1H, *H*-4′), 3.70 (s, 3H, OCH_3), 3.33 (t, J = 6.0 Hz, 2H, CH_2-5′), 3.14 (dd, J = 4.6 and 13.7 Hz, 1H, CH^a), 2.97 (dd, J = 9.0 and 13.7 Hz, 1H, C$H^{a'}$), 2.60 (dd, J = 5.6 and 16.6 Hz, 1H, CH^b), 2.52 (dd, J = 7.3 and 16.6 Hz, 1H, C$H^{b'}$), 2.07 (m, 2H, CH_2-2′), 1.77 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z (MH)$^+$ 720.4. HPLC purity (condition B): 84%, t_R = 10.7 min.

5′-*N*-(4-Methoxyphenyl-Ala-Asp)-5′-amino-5′-deoxythymidine 1{*5,1,7*}. Yield: 29.6 mg, 59.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.32 (br s, 1H, COO*H*), 11.30 (s, 1H, N^3*H*), 8.48 (s, 1H, N*H*), 8.31 (d, J = 8.1 Hz, 1H, N*H*), 7.96 (t, J = 5.8 Hz, 1H, N*H*), 7.49 (d, J = 1.0 Hz, 1H, 6-*H*), 7.26 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 6.31 (d, J = 6.8 Hz, 1H, N*H*), 6.11 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 5.24 (d, J = 4.2 Hz, 1H, O*H*-3′), 4.56 (ddd, J = 8.1, 7.8 and 5.9 Hz, 1H, C*H*(Asp)), 4.17 (quintet, J = 6.8 Hz, 1H, C*H*(Ala), 4.13 (m, 1H, *H*-3′), 3.75 (m, 1H, *H*-4′), 3.68 (s, 3H, OCH_3), 3.36 (m, 1H, CH^a-5′), 3.24 (m, 1H, CH^b-5′), 2.69 (dd, J = 5.6 and 16.6 Hz, 1H, CH^a), 2.54 (dd, J = 7.8 and 16.4 Hz, 1H, C$H^{a'}$), 2.04 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.20 (d, J = 7.1 Hz, 3H, CH_3). Mass spectrum (ESI): m/z (M − H)$^-$ 575.0. HPLC purity (condition B): 96%, t_R = 9.0 min.

5′-*N*-(4-Methoxyphenyl-Ile-Lys)-5′-amino-5′-deoxythymidine 1{*6,3,7*}. Yield: 31.3 mg, 56.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.49 (s, 1H, N*H*), 8.10 (d, J = 8.1 Hz, 1H, N*H*), 8.05 (t, J = 5.9 Hz, 1H, N*H*), 7.62 (br s, 3H, NH_3^+), 7.49 (d, J = 1.2 Hz, 1H, 6-*H*), 7.26 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 6.22 (d, J = 8.5 Hz, 1H, N*H*), 6.14 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 5.30 (br s, 1H, O*H*-3′), 4.25 (ddd, J = 8.5, 8.1 and 5.9 Hz, 1H, C*H*(Lys)), 4.12 (m, 2H, C*H*(Ala) and *H*-3′), 3.73 (dt, J = 6.1 and 3.2 Hz, 1H, *H*-4′), 3.68 (s, 3H, OCH_3), 3.31 (t, J = 6.2 Hz, 2H, CH_2-5′), 2.71 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.81 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.65 (m, 2H), 1.49 (m, 4H), 1.28 (m, 2H), 1.06 (m, 1H), 0.83 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z (MH)$^+$ 632.5. HPLC purity (condition B): 96%, t_R = 10.1 min.

5′-*N*-(4-Methoxyphenyl-Lys-Ile)-5′-amino-5′-deoxythymidine 1{*3,6,7*}. Yield: 34.9 mg, 63.5%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.50 (s, 1H, N*H*), 8.23 (t, J = 5.7 Hz, 1H, N*H*), 7.95 (d, J = 8.8 Hz, 1H, N*H*), 7.65 (br s, 3H, NH_3^+), 7.50 (d, J = 1.2 Hz, 1H, 6-*H*), 7.26 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 6.32 (d, J = 8.3 Hz, 1H, N*H*), 6.15 (dd, J = 6.1 and 7.8 Hz, 1H, *H*-1′), 4.29 (m, 1H, C*H*(Lys)), 4.18 (dd, J = 8.1 and 8.3 Hz, 1H, C*H*(Ile)), 4.11 (m, 1H, *H*-3′), 3.75 (m, 1H, *H*-4′), 3.68 (s, 3H, OCH_3), 3.35 (m, 1H, CH^a-5′), 3.25 (m, 1H, C$H^{a'}$-5′),

2.76 (m, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.81 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.65 (m, 2H), 1.47 (m, 4H), 1.31 (m, 2H), 1.06 (m, 1H), 0.79 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z $(MH)^+$ 632.5. HPLC purity (condition B): 98%, t_R = 10.1 min.

5′-*N*-(2,4-Dichlorophenyl-Trp-Phe(NO_2))-5′-amino-5′-deoxythymidine 1{*9,10,8*}. Yield: 41 mg, 58.4%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, N^3*H*), 10.81 (d, J = 2.0 Hz, 1H, N*H*(Trp)), 8.39 (d, J = 8.5 Hz, 1H, N*H*), 8.27 (s, 1H, N*H*), 8.25 (t, J = 5.7 Hz, 1H, N*H*), 8.13 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 1.2 Hz, 1H, 6-*H*), 7.47 (d, J = 8.8 Hz, 2H), 7.27 (m, 2H), 7.09 (d, J = 2.2 Hz, 1H), 7.04 (m, 1H), 6.95 (m, 1H), 6.15 (dd, J = 6.4 and 7.6 Hz, 1H, *H*-1′), 4.64 (ddd, J = 8.8, 8.5 and 4.9 Hz, 1H, C*H*), 4.52 (ddd, J = 8.3, 7.8 and 5.1 Hz, 1H, C*H*), 4.12 (m, 1H, *H*-3′), 3.76 (dt, J = 6.1 and 3.2 Hz, 1H, *H*-4′), 3.36 (t, J = 6.0 Hz, 2H, CH_2-5′), 3.12 (dd, J = 4.6 and 13.7 Hz, 1H, C*H*^{a}), 3.08 (dd, J = 4.9 and 14.9 Hz, 1H, C*H*^{b}), 2.95 (dd, J = 9.3 and 13.4 Hz, 1H, C*H*$^{a'}$), 2.88 (dd, J = 8.5 and 15.1 Hz, 1H, C*H*$^{b'}$), 2.08 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 829.4. HPLC purity (condition B): 84%, t_R = 13.1 min.

5′-*N*-(2,4-Dichlorophenyl-Phe(NO_2)-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,9,8*}. Yield: 30.5 mg, 50.6% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.27 (s, 1H, N^3*H*), 8.33 (s, 1H, N*H*), 8.26 (t, J = 5.6 Hz, 1H, N*H*), 8.15 (d, J = 8.8 Hz, 2H), 8.09 (t, J = 5.9 Hz, 1H, N*H*), 8.06 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.46 (m, 4H), 7.28 (dd, J = 2.4 and 8.8 Hz, 1H), 6.11 (dd, J = 6.4 and 7.6 Hz, 1H, *H*-1′), 4.52 (ddd, J = 8.3, 8.1 and 5.6 Hz, 1H, C*H*(Phe(NO_2)), 4.13 (m, 1H, *H*-3′), 3.74 (m, 1H, *H*-4′), 3.29 (m, 2H, CH_2-5′), 3.24 (m, 2H, CH_2), 3.10 (dd, J = 5.1 and 13.4 Hz, 1H, C*H*^{a}), 2.90 (dd, J = 8.1 and 13.4 Hz, 1H, C*H*$^{a'}$), 2.27 (t, J = 7.2 Hz, 2H, CH_2), 2.07 (m, 2H, CH_2-2′), 1.79 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 714.3. HPLC purity (condition B): 93%, t_R = 12.1 min.

5′-*N*-(2,4-Dichlorophenyl-Ile-Tyr)-5′-amino-5′-deoxythymidine 1{*8,3,8*}. Yield: 31.3 mg, 51.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 9.11 (br s, 1H, O*H*), 8.38 (s, 1H, N*H*), 8.20 (d, J = 9.0 Hz, 1H, N*H*), 8.08 (m, 2H, C*H* and N*H*), 7.54 (d, J = 2.7 Hz, 1H), 7.48 (d, J = 1.0 Hz, 1H, 6-*H*), 7.31 (dd, J = 2.4 and 9.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, N*H*), 7.01 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 8.5 Hz, 2H), 6.12 (dd, J = 6.8 and 7.3 Hz, 1H, *H*-1′), 4.47 (ddd, J = 9.3, 8.5 and 5.1 Hz, 1H, C*H*(Tyr)), 4.09 (m, 2H, C*H*(Ile) and *H*-3′), 3.72 (m, 1H, *H*-4′), 3.31 (m, 2H, CH_2-5′), 2.86 (dd, J = 5.1 and 13.9 Hz, 1H, C*H*^{a}), 2.90 (dd, J = 9.3 and 13.9 Hz, 1H, C*H*$^{a'}$), 2.02 (m, 2H, CH_2-2′), 1.81 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.68 (m, 1H), 1.31 (m, 1H), 1.00 (m, 1H), 0.79 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 727.3. HPLC purity (condition B): 96%, t_R = 12.1 min.

5′-*N*-(2,4-Dichlorophenyl-β-Ala-Ile)-5′-amino-5′-deoxythymidine 1{*3,2,8*}. Yield: 26.6 mg, 49.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.18 (m, 3H, C*H*, N*H* and N*H*), 7.93 (d, J = 8.8 Hz, 1H, N*H*), 7.53 (d, J = 2.7 Hz, 1H), 7.49 (d, J = 0.7 Hz, 1H, 6-*H*), 7.31 (dd, J = 2.4 and 9.0 Hz, 1H, C*H*), 7.10 (t, J = 5.7 Hz, N*H*), 6.13 (dd, J = 6.1 and 8.1 Hz, 1H, *H*-1′), 4.20 (dd, J = 8.3 and 8.1 Hz, 1H, C*H*(Ile)), 4.12 (m, 1H, *H*-3′), 3.76 (m, 1H, *H*-4′), 3.33 (m, 2H, CH_2-5′), 3.29 (m, 2H, CH_2), 2.37 (m, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (s, 3H, 5-CH_3), 1.67 (m, 1H), 1.40 (m, 1H), 1.05 (m, 1H), 0.78 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 635.3. HPLC purity (condition B): 100%, t_R = 11.7 min.

5′-*N*-(2,4-Dichlorophenyl-Ile-Asp)-5′-amino-5′-deoxythymidine 1{*5,3,8*}. Yield: 31.1 mg, 54.4%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.42 (s, 1H, N*H*), 8.37 (d, J = 7.8 Hz, 1H, N*H*), 8.19 (d, J = 9.0 Hz, 1H, C*H*), 7.87 (t, J = 6.0 Hz, 1H, N*H*), 7.55 (d, J = 2.7 Hz, 1H, C*H*), 7.49 (d, J = 1.2 Hz, 1H, 6-*H*), 7.37 (d, J = 8.1 Hz, 1H, N*H*), 7.30 (dd, J = 2.4 and 9.0 Hz, 1H, C*H*), 6.12 (dd, J = 6.1 and 7.8 Hz, 1H, *H*-1′), 4.56 (ddd, J = 8.5, 8.1 and 5.6 Hz, 1H, C*H*(Asp)), 4.10 (m, 2H, C*H*(Ile) and *H*-3′), 3.73 (m, 1H, *H*-4′), 3.37 (m, 1H, C*H*^{a}-5′), 3.24 (m, 1H, C*H*$^{a'}$-5′), 2.71 (dd, J = 5.6 and 16.9 Hz, 1H, C*H*^{b}), 2.55 (dd, J = 8.5 and 16.6 Hz, 1H, C*H*$^{b'}$), 2.04 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.70 (m, 1H), 1.45 (m, 1H), 1.07 (m, 1H), 0.85 (m, 6H, CH_3 and CH_3). Mass spectrum (ESI): m/z $(MH)^+$ 657.3. HPLC purity (condition B): 96%, t_R = 11.5 min.

5′-*N*-(Phenethyl-Asp-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,5,9*}. Yield: 29.2 mg, 58.4%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.06 (t, J = 5.9 Hz, 1H, N*H*), 7.82 (t, J = 5.7 Hz, 1H, N*H*), 7.46 (d, J = 1.2 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.19 (m, 3H), 6.23 (d, J = 7.8 Hz, 1H, N*H*), 6.14 (br s, 1H, N*H*), 6.13 (dd, J = 6.1 and 7.6 Hz, 1H, *H*-1′), 4.36 (m, 1H, C*H*(Asp)), 4.13 (m, 1H, *H*-3′), 3.73 (m, 1H, *H*-4′), 3.34 (ddd, J = 5.6, 5.6 and 13.7 Hz, 1H, C*H*^{a}-5′), 3.24 (m, 5H, CH_2, CH_2 and C*H*$^{a'}$-5′), 2.67 (t, J = 7.3 Hz, 2H, CH_2), 2.49 (m, 2H, CH_2), 2.26 (t, J = 7.3 Hz, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 597.3. HPLC purity (condition B): 92%, t_R = 9.3 min.

5′-*N*-(Phenethyl-Ala-Tyr)-5′-amino-5′-deoxythymidine 1{*8,1,9*}. Yield: 26.2 mg, 48.4%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.13 (t, J = 5.9 Hz, 1H, N*H*), 7.89 (d, J = 8.3 Hz, 1H, N*H*), 7.49 (d, J = 1.2 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.19 (m, 3H), 6.98 (d, J = 8.5 Hz, 2H), 6.60 (d, J = 8.5 Hz, 2H), 6.11 (dd, J = 6.8 and 7.3 Hz, 1H, *H*-1′), 6.08 (br s, 2H, N*H* and N*H*), 4.37 (m, 1H, C*H*(Tyr)), 4.26 (m, 1H, C*H*(Ala)), 4.11 (m, 1H, *H*-3′), 3.74 (m, 1H, *H*-4′), 3.31 (m, 2H, CH_2-5′), 3.20 (m, 2H, CH_2), 2.84 (m, 1H, C*H*^{a}), 2.71 (m, 1H, C*H*$^{a'}$), 2.65 (t, J = 7.2 Hz, 2H, CH_2), 2.01 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.06 (d, J = 6.8 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 645.4. HPLC purity (condition B): 83%, t_R = 10.3 min.

5′-*N*-(Phenethyl-Ala-β-Ala)-5′-amino-5′-deoxythymidine 1{*2,1,9*}. Yield: 23.9 mg, 51.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.05 (t, J = 5.9 Hz, 1H, N*H*), 7.89 (d, J = 5.7 Hz, 1H, N*H*), 7.47 (d, J = 1.2 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.19 (m, 3H), 6.13 (dd, J = 6.4 and 7.8 Hz, 1H, *H*-1′), 6.09 (d, J = 7.8 Hz, 1H, N*H*), 6.05 (t, J = 5.5 Hz, 1H, N*H*), 5.31 (br s, 1H, O*H*-3′), 4.13 (m, 1H, *H*-3′), 4.08 (quintet, J = 7.0 Hz, 1H, C*H*(Ala)), 3.72 (m, 1H, *H*-4′), 3.35 (m, 1H, C*H*^{a}-5′), 3.22 (m, 5H, CH_2, CH_2

and C*H*$^{a'}$-5′), 2.65 (t, J = 7.4 Hz, 2H, CH_2), 2.26 (t, J = 7.2 Hz, 2H, CH_2), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.10 (d, J = 7.1 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MH)^+$ 531.3. HPLC purity (condition B): 87%, t_R = 9.7 min.

5′-*N*-(Phenethyl-Asp-Lys)-5′-amino-5′-deoxythymidine 1{*6,5,9*}. Yield: 28.6 mg, 52.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.08 (t, J = 5.9 Hz, 1H, N*H*), 7.86 (d, J = 8.3 Hz, 1H, N*H*), 7.66 (br s, 3H, NH_3^+), 7.48 (d, J = 1.0 Hz, 1H, 6-*H*), 7.28 (m, 2H), 7.20 (m, 3H), 6.35 (d, J = 7.6 Hz, 1H, N*H*), 6.24 (t, J = 5.5 Hz, 1H, N*H*), 6.12 (dd, J = 6.4 and 7.6 Hz, 1H, *H*-1′), 4.38 (q, J = 7.1 Hz, 1H, C*H*), 4.22 (m, 1H, C*H*), 4.13 (m, 1H, *H*-3′), 3.75 (m, 1H, *H*-4′), 3.32 (m, 2H, CH_2-5′), 3.22 (m, 2H, CH_2), 2.70 (m, 4H, CH_2 and CH_2), 2.61 (dd, J = 5.4 and 11.7 Hz, 1H, C*H*^{a}), 2.51 (dd, J = 7.3 and 11.7 Hz, 1H, C*H*$^{a'}$), 2.06 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.67 (m, 1H), 1.49 (m, 3H), 1.28 (m, 2H). Mass spectrum (ESI): m/z $(MH)^+$ 632.4. HPLC purity (condition B): 90%, t_R = 9.3 min.

5′-*N*-(Phenethyl-Phe(NO$_2$)-Lys)-5′-amino-5′-deoxythymidine 1{*6,9,9*}. Yield: 37.5 mg, 60.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H, N^3*H*), 8.23 (d, J = 8.3 Hz, 1H, N*H*), 8.19 (t, J = 5.9 Hz, 1H, N*H*), 8.11 (d, J = 8.5 Hz, 2H), 7.66 (br s, 3H, NH_3^+), 7.49 (d, J = 1.0 Hz, 1H, 6-*H*), 7.42 (d, J = 8.5 Hz, 2H), 7.27 (m, 2H), 7.16 (m, 3H), 6.14 (m, 3H, N*H*, N*H* and *H*-1′), 5.31 (br s, 1H, O*H*-3′), 4.51 (m, 1H, C*H*), 4.25 (m, 1H, C*H*), 4.14 (m, 1H, *H*-3′), 3.77 (m, 1H, *H*-4′), 3.37 (m, 1H, C*H*^{a}-5′), 3.30 (m, 1H, C*H*$^{a'}$-5′), 3.14 (m, 3H), 2.87 (m, 1H), 2.73 (m, 2H, CH_2), 2.61 (t, J = 7.2 Hz, 2H, CH_2), 2.08 (m, 2H, CH_2-2′), 1.81 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.63 (m, 1H), 1.50 (m, 3H), 1.28 (m, 2H). Mass spectrum (ESI): m/z $(MH)^+$ 709.5. HPLC purity (condition B): 88%, t_R = 11.0 min.

5′-*N*-(Bz-Lys-Tyr)-5′-amino-5′-deoxythymidine 1{*8,6,10*}. Yield: 30.5 mg, 55.1%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.46 (d, J = 7.8 Hz, 1H, N*H*), 8.19 (t, J = 5.9 Hz, 1H, N*H*), 7.87 (m, 3H), 7.66 (br s, 3H, NH_3^+), 7.55 (m, 1H), 7.48 (m, 3H), 6.98 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 8.5 Hz, 2H), 6.12 (dd, J = 6.6 and 7.6 Hz, 1H, *H*-1′), 4.44 (m, 1H, C*H*), 4.38 (m, 1H, C*H*), 4.09 (m, 1H, *H*-3′), 3.73 (m, 1H, *H*-4′), 3.31 (m, 2H, CH_2-5′), 2.86 (dd, J = 4.9 and 13.9 Hz, 1H), 2.72 (m, 3H), 2.03 (m, 2H, CH_2-2′), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.65 (m, 2H), 1.51 (m, 2H), 1.31 (m, 2H). Mass spectrum (ESI): m/z $(MH)^+$ 637.5. HPLC purity (condition B): 80%, t_R = 9.3 min.

5′-*N*-(Bz-Phe(NO$_2$)-Tyr)-5′-amino-5′-deoxythymidine 1{*8,9,10*}. Yield: 31 mg, 50.9%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 9.15 (br s, 1H, O*H*), 8.60 (d, J = 8.3 Hz, 1H, N*H*), 8.22 (t, J = 5.9 Hz, 1H, N*H*), 8.17 (d, J = 8.3 Hz, 1H, N*H*), 8.12 (d, J = 8.8 Hz, 2H), 7.75 (m, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 1.2 Hz, 1H, 6-*H*), 7.47 (m, 3H), 7.01 (d, J = 8.3 Hz, 2H), 6.57 (d, J = 8.3 Hz, 2H), 6.13 (dd, J = 6.6 and 7.6 Hz, 1H, *H*-1′), 4.78 (m, 1H, C*H*), 4.47 (m, 1H, C*H*), 4.09 (m, 1H, *H*-3′), 3.74 (m, 1H, *H*-4′), 3.37 (m, 1H, C*H*^{a}-5′), 3.28 (m, 1H, C*H*$^{a'}$-5′), 3.18 (dd, J = 4.4 and 13.7 Hz, 1H, C*H*^{b}), 3.07 (dd, J = 10.7 and 13.7 Hz, 1H, C*H*$^{b'}$), 2.88 (m, 1H, C*H*^{c}), 2.72 (m, 1H, C*H*$^{c'}$), 2.03 (m, 2H, CH_2-2′), 1.80 (d, J = 0.7 Hz, 3H, 5-CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 723.4. HPLC purity (condition B): 84%, t_R = 11.3 min.

5′-*N*-(Bz-Ile-Lys)-5′-amino-5′-deoxythymidine 1{*6,3,10*}. Yield: 30.8 mg, 60.3%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 8.34 (d, J = 8.3 Hz, 1H, N*H*), 8.06 (m, 2H, N*H* and N*H*), 7.85 (m, 2H), 7.64 (br s, 3H, NH_3^+), 7.54 (m, 1H), 7.47 (m, 3H), 6.14 (dd, J = 6.1 and 7.8 Hz, 1H, *H*-1′), 5.30 (br s, 1H, O*H*-3′), 4.28 (m, 2H, C*H*(Ile) and C*H*(Lys)), 4.12 (m, 1H, *H*-3′), 3.73 (m, 1H, *H*-4′), 3.32 (m, 2H, CH_2-5′), 2.70 (m, 2H), 2.07 (m, 2H, CH_2-2′), 1.91 (m, 1H), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.63 (m, 1H), 1.48 (m, 4H), 1.24 (m, 3H), 0.88 (d, J = 6.8 Hz, 3H, CH_3), 0.83 (t, J = 7.4 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MH)^+$ 587.5. HPLC purity (condition B): 86%, t_R = 9.9 min.

5′-*N*-(Bz-Ile-Tyr)-5′-amino-5′-deoxythymidine 1{*8,3,10*}. Yield: 33 mg, 61.0%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.31 (s, 1H, N^3*H*), 9.10 (s, 1H, O*H*), 8.27 (d, J = 8.5 Hz, 1H, N*H*), 8.12 (t, J = 5.7 Hz, 1H, N*H*), 7.96 (d, J = 8.3 Hz, 1H, N*H*), 7.84 (m, 2H), 7.53 (m, 1H), 7.47 (m, 3H), 6.98 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 8.5 Hz, 2H), 6.12 (dd, J = 6.6 and 7.6 Hz, 1H, *H*-1′), 5.26 (d, J = 4.2 Hz, 1H, O*H*-3′), 4.49 (ddd, J = 9.0, 8.5 and 5.4 Hz, 1H, C*H*(Tyr)), 4.27 (dd, J = 8.5 and 8.8 Hz, 1H, C*H*(Ile)), 4.07 (m, 1H, *H*-3′), 3.71 (m, 1H, *H*-4′), 3.32 (m, 2H, CH_2-5′), 2.85 (dd, J = 5.1 and 13.9 Hz, 1H, C*H*^{a}), 2.68 (dd, J = 9.0 and 13.9 Hz, 1H, C*H*$^{a'}$), 2.00 (m, 2H, CH_2-2′), 1.83 (m, 1H), 1.80 (d, J = 1.0 Hz, 3H, 5-CH_3), 1.40 (m, 1H), 1.11 (m, 1H), 0.79 (t, J = 7.3 Hz, 3H, CH_3), 0.74 (d, J = 6.6 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 644.4. HPLC purity (condition B): 92%, t_R = 10.8 min.

5′-*N*-(Bz-Ile-Asp)-5′-amino-5′-deoxythymidine 1{*5,3,10*}. Yield: 29 mg, 58.1%. ^{1}H NMR, 500 MHz (DMSO-d_6): δ 11.30 (s, 1H, N^3*H*), 8.32 (m, N*H* and N*H*), 7.90 (m, 3H), 7.50 (m, 4H), 6.14 (dd, J = 6.1 and 8.1 Hz, 1H, *H*-1′), 4.54 (ddd, J = 8.1, 7.7 and 5.6 Hz, 1H, C*H*(Asp)), 4.27 (dd, J = 7.8 and 8.1 Hz, 1H, C*H*(Ile)), 4.13 (m, 1H, *H*-3′), 3.74 (m, 1H, *H*-4′), 3.36 (m, 1H, C*H*^{a}-5′), 3.27 (m, 1H, C*H*$^{a'}$-5′), 2.72 (dd, J = 5.6 and 16.6 Hz, 1H, C*H*^{b}), 2.55 (dd, J = 8.1 and 16.9 Hz, 1H, C*H*$^{b'}$), 2.04 (m, 2H, CH_2-2′), 1.89 (m, 1H), 1.79 (d, J = 0.7 Hz, 3H, 5-CH_3), 1.50 (m, 1H), 1.18 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H, CH_3), 0.83 (t, J = 7.4 Hz, 3H, CH_3). Mass spectrum (ESI): m/z $(MNa)^+$ 596.4. HPLC purity (condition B): 86%, t_R = 10.0 min.

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Supporting Information Available. ^{1}H NMR spectra, HPLC profiles, and MS data of prelibrary compounds, weight of crude products and overall percentage yield of the first two archived arrays, a complete list of analyzed compounds from 1000-member IRORI library, and the LC/MS and ^{1}H NMR spectra of representative analyzed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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