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Synthesis of *N*-Boc and *N*-Fmoc dipeptoids with nucleobase residues as peptoid nucleic acid monomers

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Abstract—The synthesis of Boc and Fmoc protected peptoid nucleic acid monomers bearing thymine (**4a**, **4b**), adenine (**6a**, **6b**) or guanine (**7a**, **7b**) on the side chain is described. These nucleobases were attached to the amino group of glycine via an ethylene linkage using the Mitsunobu reaction, except cytosine, which was attached using alkylation. After deprotection, these amino acids have been used for synthesizing *N*-Boc and *N*-Fmoc dipeptoids. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The use of 'antisense' oligodeoxynucleotides (ODNs) to inhibit gene or protein expression has become a potentially valuable treatment for a variety of diseases, particularly viral infection and cancers.[1] These ODNs exhibit high binding affinity and sequence specific recognition of mRNA and DNA to suppress the expression of the encoded protein by either sterically blocking transcription processing of the DNA or translation processing of the mRNA.[2,3] An extensive number of structural modifications have been introduced in an attempt to develop analogs that have improved stability to nucleases, the ability to hybridize to complementary ODNs with high specificity and affinity, increased uptake in cells and the appropriate pharmacokinetic properties.[4] Although there have been serious efforts made to modify the natural phosphodiester internucleotide link, these efforts have so far only gained limited success.

In 1991, Nielsen et al. developed a new class of ODN analogs, known as polyamide (or peptide) nucleic acids (PNAs).[5] PNAs consist of achiral monomer subunits derived from *N*-(2-aminoethyl)glycine bearing nucleoside heterocyclic bases, which are coupled by standard methods of amide bond formation. These compounds are resistant to nucleases, form stable duplexes with complementary single-stranded (ss) RNA and DNA, as well as stable triplexes with double-stranded (ds) DNA targets.[6,7]

PNA oligomers can be synthesized by standard peptide chemistry methods. Compared with ODNs, the greater diversity of chemical structures of PNA should provide the possibility of obtaining oligomers with improved properties, e.g. better permeability through cellular membranes.[8] Recently, we developed a kind of new PNA (Fig. 1), using a peptide chain consisting of unnatural *N*-substituted glycine (peptoid), which was named peptoid nucleic acids. Presumably, the resultant PNAs will be easily hybridized to complementary DNA and RNA in view of the conformational flexibility of peptoid.[9]

Previous reports on peptoid synthesis have focused on Fmoc protection methods. In our experience, a Boc based strategy also offers high coupling efficiency and facilitated purification of the final peptoid product.[9] In this paper, we report the synthesis of Boc and Fmoc protected dipeptoids with nucleobases as monomers. Although either dipeptoid **1** or dipeptoid **2** can be considered as building blocks, dipeptoid **2** appeared to be a better building block since its lower steric hindrance allowed more efficient coupling in solid-phase synthesis (Fig. 2).

2. Results and discussion

2.1. Synthesis of Boc and Fmoc monomers

The syntheses of the required dipeptoid monomers with the structure of the *N*-protected sarcosine **3** and *N*-(2-nucleobase substituted ethyl)glycine **4**, **5**, **6**, **7** are shown in Fig. 3. The nucleobases T, A and G were incorporated into the amino acids by the Mitsunobu reaction. For the synthesis of **5**, the nucleobase C was attached by alkylation.

Initial studies were undertaken with the commercially

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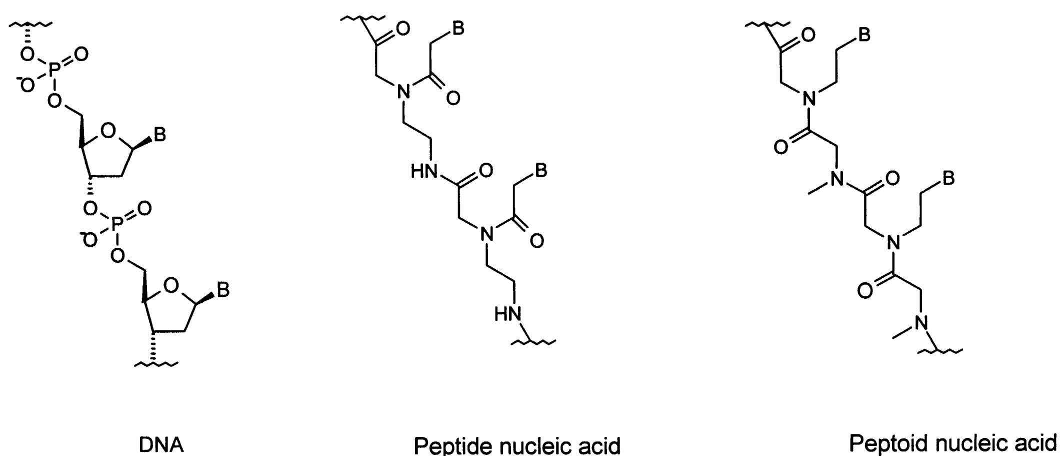


Figure 1. Comparison of DNA, PNA and peptoid nuleic acid structures.

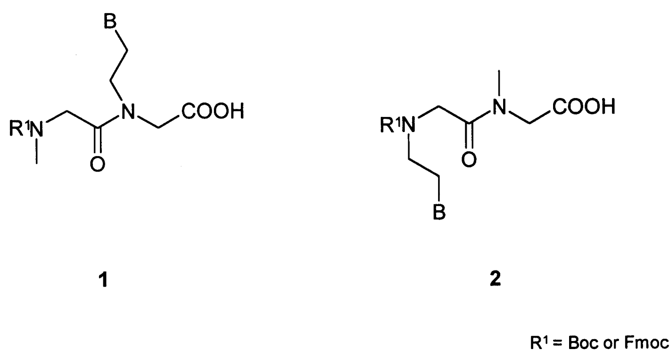


Figure 2.

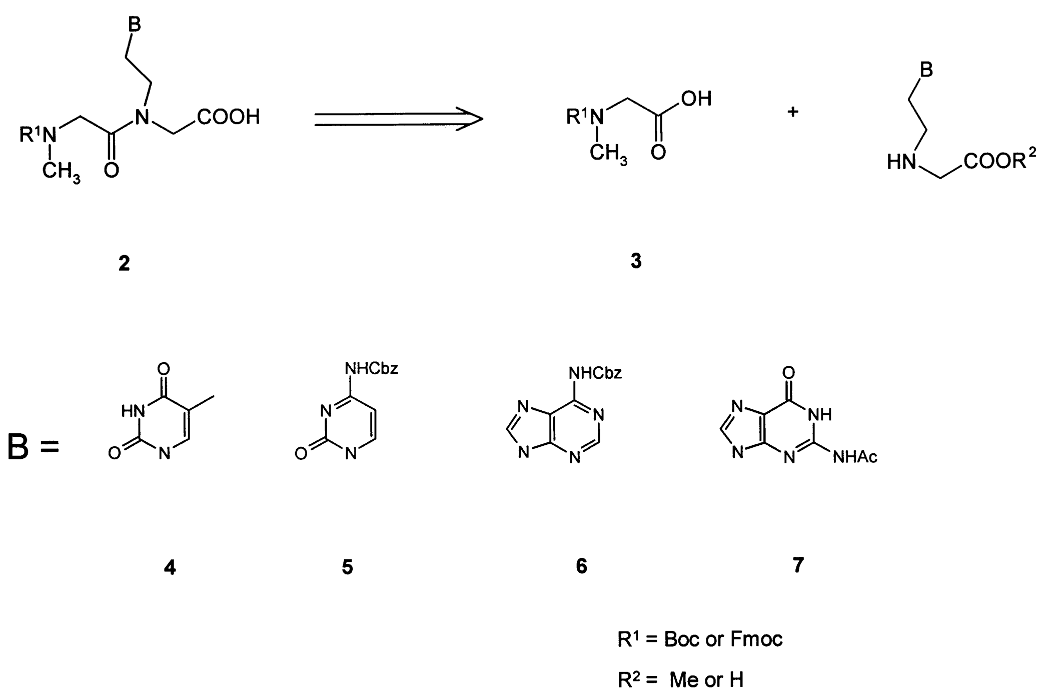
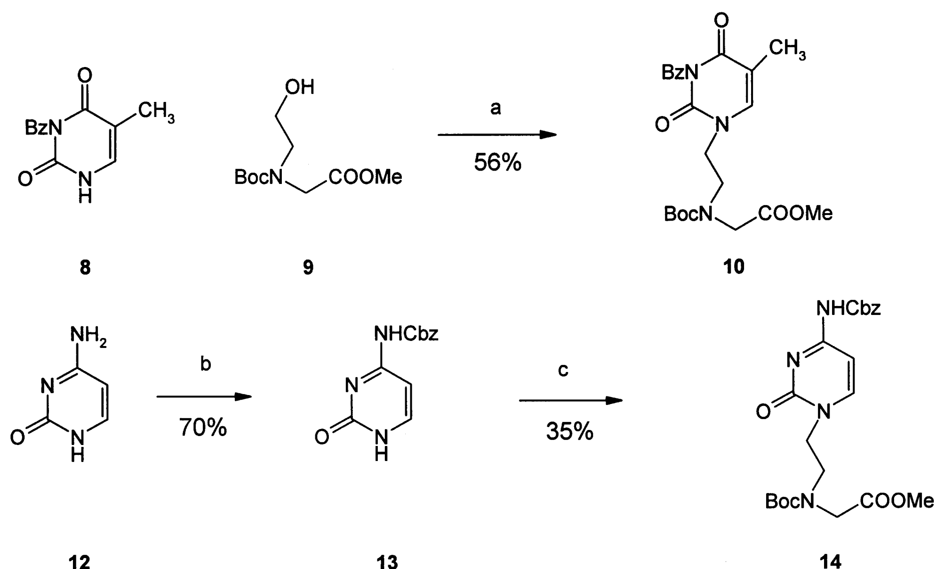


Figure 3. *N*-Boc and *N*-Fmoc protected peptoid nuleic acid monomers.



Scheme 1. Alkylation of pyrimidine. *Reagents*: (a) DEAD, Ph_3P in THF; (b) Cbz–Cl, Py; (c) NaH in DMF; (d) *N*-Boc-(2-bromoethyl)glycine in DMF.

available *N*-(2-hydroxyethyl)glycine, which was protected as its *N*-Boc/Me ester derivative according to the method described by Lowe and Vilaivan.[10] The Mitsunobu reaction of compound **9** with N^3-benzoyl-thymine (BzT)[11] **8** gave the thymine derivative **10** together with a less polar product, possibly the elimination product. Fortunately, the thymine derivative **10** is crystalline. After column chromatography and recrystallization, the pure material was obtained in 59% yield (Scheme 1).

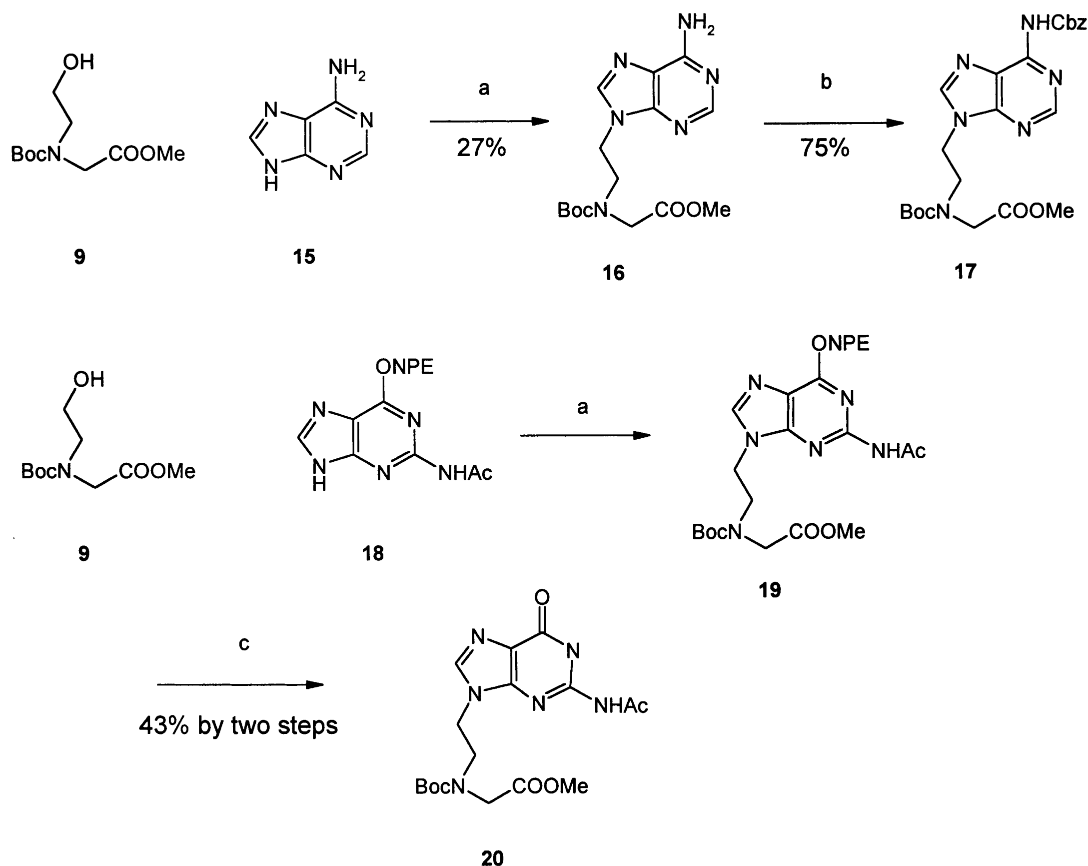
In the synthesis of the cytosine derivative **5**, the exocyclic amino group of cytosine **12** was protected before alkylation by treatment with benzyl chloroformate to give N^4-Cbz-cytosine **13**. The subsequent alkylation of **13** with *N*-Boc-(2-bromoethyl)glycine[12] was accomplished by generating the anion using sodium hydride in anhydrous DMF. After an aqueous workup and purification by flash chromatography, **14** was obtained in 30% yield (Scheme 1).[13]

Reactions of the alcohol **9** and Cbz–A via Mitsunobu conditions or alkylation with the bromo-derivative gave only a mixture of the N^7- and N^9-isomers, which could not be separated easily by column chromatography or crystallization. Unprotected adenine, however, reacted with **9** under Mitsunobu reaction conditions to afford the desired N^9-isomer **16**. The quality of **16** is reflected in the convenient purification. Acylation of the N^6-amino group under usual conditions with benzyl chloroformate or benzoyl chloride did not give the clean product **17**. Nevertheless, when 1-(benzyloxycarbonyl)-3-ethylimidazolium tetrafluoroborate [$PhCH_2OCO–Im^+Et·BF_4^-$, 'Rapoport's reagent'][14] was used instead, acylation was remarkedly improved. Thus, the exocylic amino group in **16** was protected by treatment with a 6 molar excess of freshly prepared Rapoport's reagent in DCM. After purification, **17** was obtained in a 75% yield.

In contrast, guanine cannot be converted to the unique N^9-substituted product under the Mitsunobu conditions or by alkylation with bromo-derivative. It was suggested that protection of guanine at O^6 might be necessary. Consequently, N^2-acetyl-O^6(4-nitrophenylethyl)guanine **18**[15] was synthesized and its reaction with compound **9** was attempted. However, the protecting group used appeared to be labile under the reaction conditions and substantial cleavage was observed as reported by Lowe and Vilaivan.[10] The Mitsunobu reaction between N^2-acetyl-O^6(4-nitrophenylethyl)guanine and the protected compound **9** was carried out in an analogous way to the synthesis of thymine derivative. The product **19**, however, could not be isolated free from diethyl hydrazinedicarboxylate. Treatment with 1.8-diazabicyclo[5,4,0]undec-7-ene (DBU) in pyridine to remove the O^6-nitrophenylethyl protecting group followed by flash column chromatography gave the pure N^9-substituted acetyl-guanine derivative **20** as a solid in 35% overall yield (Scheme 2).

2.2. Solution phase oligomerization

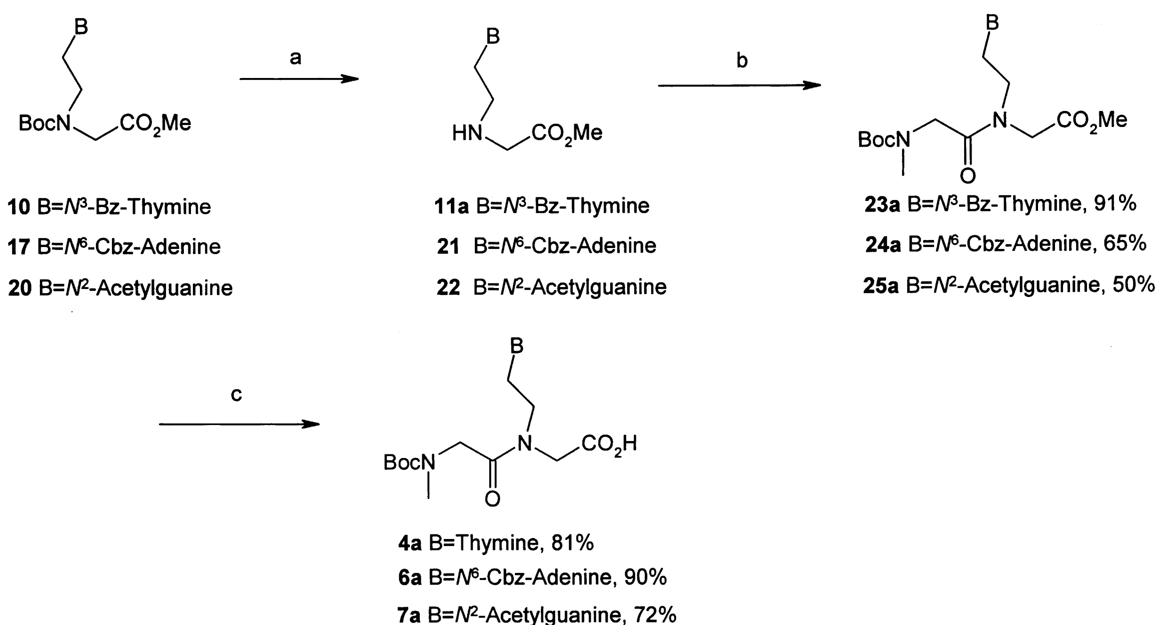
Solution phase techniques were used to prepare the Fmoc and Boc protected dipeptoid building blocks. The synthesis of dipeptiods starting from **10**, **17** and **20** was investigated. The *N*-Boc groups of **10**, **17** or **20** were cleaved using TFA in DCM. The trifluoroacetic acid salts of the amine derivatives, **11**, **21** or **22** were isolated from the reaction mixture by precipitation with ether.[13] They were subsequently condensed with *N*-Boc–sarcosine using BOP and DIPEA in anhydrous DMF. After workup and purification by flash column chromatography, the protected dipeptoids **23a**, **24a** and **25a** were obtained in 91, 55 and 30% yield, respectively. The low yields obtained for the adenine and guanine dipeptoids are probably a result of difficult coupling (the high steric hindrance of purine bases). When the more efficient coupling reagent HBTU was used, the yield reached 65 and 50%. Finally, the methyl esters of **25a** and **26a** were hydrolyzed to give the Boc protected N^6-Cbz adenine monomer **6a** and N^2-acetyl-guanine monomer **7a**. The saponification of the methyl ester **24a** by an equivalent excess of aq. NaOH–acetone overnight led to



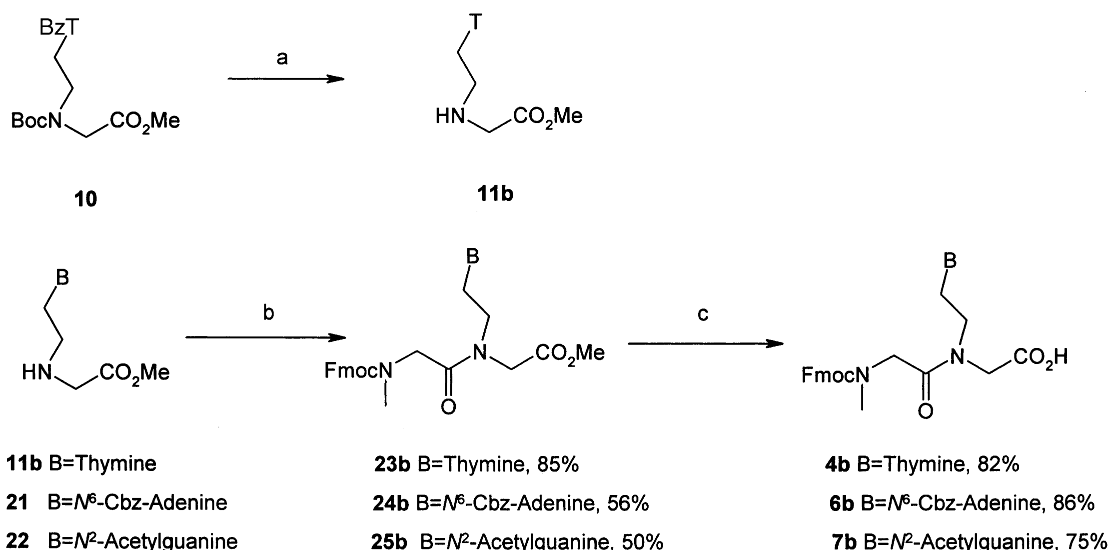
Scheme 2. Alkylation of purine. *Reagents*: (a) DEAD, Ph_3P in THF; (b) $PhCH_2CO_2Im^+Et{\cdot}BF_4^-$ (6 equiv.) in DCM; (c) DBU, Py.

the simultaneous debenzoylation and gave mainly the free thymine acid **4a**.[10] Since the deprotection thymine at N^3 is required, this condition is quite suitable for the synthesis of the *N*-Boc monomer **4a** with good quality after recrystallization (Scheme 3).

In view of the base sensitivity of the Fmoc group, compound **10** should be debenzoylated before coupling with *N*-Fmoc–sarcosine. Treatment of compound **10** with 10% HBr in HOAc, *N*-Boc and N^3-benzoyl groups were cleaved simultaneously. Then, the product **11b** and the other two free



Scheme 3. Synthesis of *N*-Boc protected monomers. *Reagents*: (a) 50% TFA in DCM; (b) *N*-Boc–sarcosine, DIPEA in DMF, uses BOP for **11a**, HBTU for **21** and **22**; (c) for **24a**: aq. NaOH–acetone, 4°C, overnight; for **25a** and **26a**: aq NaOH–THF, rt, 30min.



Scheme 4. Synthesis of *N*-Fmoc protected monomers. *Reagents*: (a) 10% HBr in HOAc; (b) *N*-Fmoc–sarcosine pentafluorophenyl, DIPEA in DMF; (c) 2.5 M NaOH (6–10 equiv.) in THF/H_2O (1:4, v/v) 0°C, 5–10 min.

amino derivatives **19** and **23** were treated with *N*-Fmoc–sarcosine pentafluorophenyl ester. After workup and purification by flash chromatography, the Fmoc protected dipeptoids **23b**, **24b** or **25b** were obtained in yields of 85, 56 and 50%, respectively. Removal of the methyl ester of **23b**, **24b** or **25b** under standard hydrolysis conditions led to deprotection of the *N*-Fmoc group as shown by TLC, which could not be easily separated by crystallization or column chromatography. After several attempts, we found that methyl group is more sensitive to concentrated NaOH than the Fmoc group. On treatment of the methyl ester of **23b**–**25b** with concentrated NaOH (10 equiv., 5 M) at 0°C in 10 min *N*-Fmoc–dipeptoids **4b**, **6b** and **7b** were obtained and the structures were confirmed by mass spectrometry, NMR, elemental analysis and HPLC (Scheme 4).

Solid-phase synthesis of peptoid nucleic acids from the dipeptoid acids **6a**, **6b**, **7a** and **7b** will be described in due course.

3. Experimental

3.1. General

Melting points were taken on digital melting point apparatus. Infrared spectra were recorded on a Shimadazu IR-440 spectrometer. Mass spectra were recorded on HP5989A and VG QUATTRO mass spectrometers. ^1H NMR spectra were recorded on Bruker AM 300 (300 MHz) and Bruker DRX-400 (400 MHz) using TMS as internal standard. Combustion analysis for elemental composition was carried out on an Italy MOD 1106 analyzer. HPLC analyses were carried out on a Waters or Varian-SY-5000 instrument and using a Kromasil RP-18 (5×250 mm) column. Flash column chromatography was performed with 300–400 mesh silica gel, and analytical thin layer chromatography was performed on precoated silica gel plates (GF-254) with the systems (v/v) indicated. Solvents and reagents were purified by standard methods as necessary.

Nucleic acid bases cytosine and guanine were purchased from Aldrich Chemical of Milwaukee; BOP and HBTU from Calbiochem-Novabiochem; DIPEA from Acros Chemical; TFA and DBU from Fluka Chemika, and used without purification. *N*-Boc-(2-hydroxyethyl)glycine, *N*-Fmoc– and *N*-Boc–sarcosine pentafluorophenyl were prepared according to literature methods.[10]

3.1.1. *N-tert*-Butoxycarbonyl-*N*-[2-(N^3-benzoylthymin-1-yl)ethyl]-glycine methyl ester (10). N^3-Benzoylthymine **8** (3.7 g, 16.0 mmol), alcohol **9** (4.2 g, 18.0 mmol) and triphenylphosphine (5.8 g, 22.0 mmol) were suspended in THF (50 ml) in an ice-bath; DEAD (3.6 ml, 22.0 mmol) was added dropwise under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. The solid was filtered off, the filtrate was evaporated to dryness and the residue was purified by column chromatography eluting with 15:1 DCM/acetone. The white solid was washed with methanol and recrystallized from ethanol to give **10** (3.987 g, 56%), mp 172–176°C (lit.[10] mp 177–179°C); R_f 0.33 (15:1 DCM/acetone); δ_H (300 MHz, $CDCl_3$) 8.05–8.15 and 7.85–7.95 (2H, brm, benzoyl *o*-C*H*), 7.35–7.70 (3H, brm, benzoyl *m*- and *p*-C*H*), 7.28 (1H, s, T–C*H*(6)), 3.85–4.05 (4H, brm, CH_2CH_2N and NCH_2CO), 3.80 (3H, s, $-OCH_3$), 3.62 (2H, brm, CH_2CH_2N), 1.95 (3H, s, T–CH_3), 1.45 (9 H, s, Boc).

3.1.2. *N-tert*-Butoxycarbonyl-*N*-[2-(N^4-benzyloxycarbonylcytosine-1-yl)-ethyl]glycine methyl ester (14). Sodium hydride (60% disp, 0.176 g, 4.4 mmol) was added to a vigorously stirred suspension of N^4-Cbz–cytosine **13** (1.088 g, 4.4 mmol) in anhydrous DMF (12 mL) at room temperature. After hydrogen production had ceased, a solution of **9** (0.9 g, 4 mmol) in anhydrous DMF (10 mL) was added, and the reaction mixture was stirred overnight. Subsequently, water (40 mL) was added to the reaction and the aqueous solution extracted with chloroform

(7×40 mL). The combined organic extracts were dried over Na_2SO_4. Filtration followed by evaporation afforded a crude product, which was purified by flash chromatography using ethyl acetate as the eluting solvent. Compound **14** was obtained as a white foam (0.708 g, 35%); R_f 0.2 (acetate); ν_{max} (KBr): 1691 cm^{-1} (C=O), 785 cm^{-1} (Ph); δ_H (300 MHz, d_6-DMSO) 8.00 (1H, d, *J*=7.2 Hz, C–C*H*(6)), 7.38 (5 H, m, Ph), 6.96 (1H, d, *J*=7.3, C–C*H*(5)), 5.18 (2H, s, CH_2Ph), 4.06 (2H, m, CCH_2), 3.85 (2H, brm, NCH_2CO), 3.66 (3H, s, OCH_3), 3.54 (2H, m, CCH_2CH_2), 1.17 (9H, brm, Boc); ESI-MS *m/z*: 461 (100, MH^+), 921 (55, $2MH^+$), 1404 (12, $3MNa^+$).

3.1.3. *N-tert*-Butoxycarbonyl-*N*-[2-(adenin-9-yl)-ethyl]-glycine methyl ester (16). Adenine **15** (1.71 g, 12.7 mmol), alcohol **9** (2.33 g, 10.0 mmol) and triphenylphosphine (2.9 g, 12.0 mmol) were suspended in THF (150 mL) in an ice-bath; DEAD (1.8 mL, 12.0 mmol) was then added dropwise under nitrogen atmosphere. The reaction mixture was warmed to room temperature and was stirred overnight. The cloudy suspension was evaporated to dryness and the residue was chromatographed on silica gel with acetone/methanol (10:1) as eluant.The product **16** was obtained as a white solid (0.93 g, 27%), mp 170–173°C (lit. 10 mp 173–175°C); R_f 0.55 (15:1 acetone/methanol); δ_H (300 MHz, $CDCl_3$) 8.30 (1H, s, A–C*H*(2)), 8.00 and 7.82 (1H, 2×s, A–C*H*(8)), 6.40 (2H, 2×s, NH_2), 4.33 (2H, m, ACH_2), 3.90–3.55 (7H, m, O*Me* and CH_2NCH_2), 1.35 and 1.11 (9H, 2×s, Boc).

3.1.4. *N-tert*-Butoxycarbonyl-*N*-[2-(N^6-benzyloxycarbonyladenin-9-yl)-ethyl]glycine methyl ester (17). Triethyloxonium tetrafluoroborate (1.14 g, 6.0 mmol) was added to *N*-(benzyloxycarbonyl)imidazole (1.21 g, 6.0 mmol) in anhydrous DCM (15 mL) at 0°C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature and then stirred for 2 h. Subsequently, **16** (0.367 g, 1.0 mmol) was added and this reaction was stirred overnight. Quenched by a solution of $NaHCO_3$ (10 mL), the organic layer was then separated. The aqueous layer was further extracted with DCM (20 mL), and the combined organic extracts were dried over Na_2SO_4. Filtration followed by evaporation gave a viscous oil which was purified by flash chromatography eluting with 98:2 ethyl acetate/methanol to give **17** (2.185, 75%) as a white solid, mp 64–66°C; [Found: C, 56.87; H, 5.73; N, 17.47. $C_{22}H_{28}N_6O_6$ requires: C, 57.02; H, 5.82; N, 17.35%]; R_f 0.3 (95:5 ethyl acetate/methanol); ν_{max} (KBr): 1753 cm^{-1} (C=O), 768, 746 and 699 cm^{-1} (Ph); δ_H (300 MHz, $CDCl_3$) 8.77 (1H, s, A–C*H*(2)), 8.24 and 8.10 (1H, 2×s, A–C*H*(8)), 7.46–7.36 (5H, m, Ph), 5.31 (2H, s, PhCH_2), 4.43 (2H, d, t, *J*=16.0, 6.16 Hz, ACH_2), 3.96–3.71 (7H, m, O*Me* and CH_2NCH_2), 1.35 and 1.11 (9H, 2×s, Boc); EI-MS *m/z*: 485 (1, MH^+), 376 (5), 276 (12.8), 79 (100%).

3.1.5. N^2-Acetyl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (18). A suspension of N^9,N^2-diacetyl-guanine (4.4 g, 20 mmol), triphenylphosine (7.2 g, 30 mmol) and 2-(*p*-nitrophenyl)-ethanol (5.1 g, 30 mmol) was treated over 30 min with diethyldiazodicarboxylate (DEAD, 95%, 4.5 mL, 30 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature overnight. After evaporation, the residue was taken up in EtOH (1300 mL) and water (1300 mL) and the mixture heated under reflux for 30 min. The clear solution was then cooled gradually to room temperature, to 0°C, and then to −18°C in stages over a period of 16 h. After filtration and drying, the title compound was obtained (64%). This crude compound which was contaminated with tripenylphosphone oxide was directly used without further purification.

3.1.6. *N-tert*-Butoxycarbonyl-[*N*-2(2-amino-acetyl-guanine-9-yl)ethyl]glycine methyl ester (19). To a suspension of the alcohol **9** (0.47 g, 2.0 mmol), **18** (0.684 g, 2.0 mmol) and triphenylphosphine (0.536 g, 2.2 mmol) in dry THF (30 mL) was added DEAD (0.364 mL, 2.2 mmol, 1.1 equiv.) dropwise at 0°C under a nitrogen atmosphere; the reaction was stirred for 1 h and overnight at room temperature. The mixture was evaporated to dryness and the residue was purified by column chromatography eluting with ethyl acetate to give *N-tert*-butoxycarbonyl-[*N*-2(N^2-acetyl-O^6-nitrophenylethylguanine-9-yl)ethyl]glycine methyl ether **19** which was contaminated with triphenylphosphine oxide. The impure material was dissolved in dry pyridine (10 mL), treated with DBU (0.30 mL, 2.0 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with DCM (50 mL), washed with 5% HCl and water successively. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product. After purification by flash chromatography eluting with 15:1 ethyl acetate/methanol gave the product **19** (0.35 g, 43%) as a white foam, mp 154–156°C; [Found: C, 50.17; H, 5.61; N, 20.96. $C_{17}H_{24}N_6O_6$ requires: C, 50.01; H, 5.92; N, 20.58%]; R_f 0.35 (8:1 ethyl acetate/methanol); ν_{max} (KBr): 1751, 1681 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 12.01 (1H, brm, G–N*H*), 11.66 (1H, s, G–N*H*), 7.94 (1H, s, G–C*H*(8)), 4.16 (2H, m, GCH_2), 4.05 and 3.96 (2H, 2×s, NCH_2CO), 3.67 and 3.66 (3H, 2×s, OCH_3), 3.64–3.59 (2H, m, GCH_2CH_2), 2.19 (3H, s, Ac–CH_3), 1.24 and 1.02 (9H, 2×s, Boc); EI-MS *m/z*: 408 (1, M^+), 308 (6), 207 (20), 56 (67), 41 (100).

3.2. General procedure of the deprotection (Boc)

TFA (0.5 mL/100 mg) was added dropwise to a stirred solution of **10**, **17** and **19** in anhydrous DCM (0.5 mL/100 mg) at room temperature. The reaction was left to stir for 0.5–1 h. Then the reaction was saturated with diethyl ether until a precipitate formed. The ethereal solution was decanted off from the precipitate, and the precipitate was triturated twice with ether before being dried over phosphorus pentoxide.

3.2.1. *N*-[2-(N^3-Benzoylthymin-1-yl)ethyl]glycine methyl ester (11a). The product **11a** was obtained as a white solid [Found: C, 48.74; H, 4.29; N, 9.28. $C_{17}H_{19}N_3O_5 \cdot CF_3COOH$ $1/2H_2O$ requires: C, 49.20; H, 4.45; N, 9.05%]; δ_H (300 MHz, d_6-DMSO) 9.50 (1H, s, N*H*), 8.02 (2H, d, *J*=7.7 Hz, benzoyl *o*-C*H*), 7.76–7.81 (2H, m, benzoyl *m*-C*H*), 7.57–7.62 (2H, m, T–C*H*(6)+benzoyl *p*-C*H*), 4.06–4.08 (4H, brm, CH_2CH$_2$N and NCH_2CO), 3.75 (3H, s, –OCH_3), 3.34 (2H, t, *J*=6.2 Hz, CH$_2$CH_2N), 1.84 (3H, s, T–CH_3); EI-MS *m/z*: 346 (42, MH^+), 242 (100), 105 (92).

3.2.2. *N*-[2-(N^6-Benzyloxycarbonyladenin-9-yl)-ethyl]-glycine methyl ester (21). The product **21** was obtained as a white solid [Found: C, 44.76; H, 3.79; N, 15.18.

$C_{18}H_{20}N_6O_4$·1.35 CF_3COOH·3/4H_2O requires: C, 45.06; H, 4.17; N, 15.23%]; ν_{max} (KBr): 1755, 1679 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 10.80 (1H, s, A–N*H*), 9.45 (1H, s, N*H*), 8.66 (1H, s, A–C*H*(8)), 7.49–7.31 (5H, m, Ph), 5.23 (2H, s, CH_2Ph), 4.61 (2H, t, *J*=5.7 Hz, ACH_2), 4.10 (2H, s, NCH_2CO), 3.64 (3H, s, OCH_3), 3.57 (2H, t, *J*=5.7 Hz, ACH_2CH_2); ESI-MS *m*/*z*: 385 (100, MH^+), 91 (37), 770 (8, $2MH^+$).

3.2.3. *N*-[2(2-Amino-acetyl-guanine-9-yl)ethyl]glycine methyl ester (22). The product **22** was obtained as a white solid [Found: C 38.11; H, 3.99; N, 18.14. $C_{12}H_{16}N_6O_4$·1.35 CF_3COOH requires: C 38.21; H 3.78; N 18.19%]; ν_{max} (KBr); 1755,1678 and 1614 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 11.73 (1H, s, G–N*H*), 7.99 (1H, s, G–C*H*(8)), 4.15 (2H, t, *J*=5.7Hz, GCH_2), 3.64 (2H, s, NCH_2CO), 3.46 (3H, s, OCH_3+H_2O), 2.99 (2H, t, *J*=5.7 Hz, GCH_2CH_2), 2.19 (3H, s, Ac–CH_3); ESI-MS *m*/*z*: 309 (100, MH^+), 331 (20, MNa^+), 617 (25, $2MH^+$), 639 (21, $2MNa^+$).

3.2.4. *N*-[2-(Thymin-1-yl)ethyl]glycine methyl ester (11b). The protected peptoid **10** (2.5 mmol) was treated with 10% HBr in acetic acid (20 mL) at room temperature for 1 h. The mixture was evaporated under reduced pressure; the residue was triturated with ether washed with methanol–ether. Recrystallization from ethanol–water gave a white solid [Found: C 48.94; H, 6.24; N, 16.85. $C_{10}H_{15}N_3O_4$·1/4 H_2O requires: C 48.87; H 6.36; N 17.10%]; ν_{max} (KBr); 1689 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 11.37 (1H, s, T–N*H*), 9.21 (1H, m, N*H*), 7.49 (1H, s, T–C*H*(6)), 4.03 (2H, s, NCH_2CO), 3.96 (2H, t, *J*=5 Hz, CH_2CH_2N), 3.75 (3H, s, OCH_3), 3.24 (2H, t, *J*=5 Hz, CH_2CH_2N), 1.76 (3H, s, T–CH_3); EI-MS *m*/*z*: 242 (39, MH^+), 153 (45), 102 (100); HRMS *m*/*z*: Calcd for $C_{10}H_{15}N_3O_4$: 241.24692; Found: 241.106.

3.3. Solution phase synthesis of *N*-Boc protected dipeptoids 4a, 6a and 7a

3.3.1. *N*-[(*N*-*tert*-Butoxycarbonyl-*N*-methyl)glycyl]-*N*-[2-(N^3-benzoylthymin-1-yl)ethyl]glycine methyl ester (23a). To a solution of **11a** (1.73 g, 5 mmol) in anhydrous DMF (25 mL) was added a solution of *N*-Boc–sarcosine (0.945 g, 5 mmol), BOP (2.43 g, 5.5 mmol) and DIPEA (1.7 mL, 10 mmol) in anhydrous DMF (10 mL). After stirring at room temperature overnight, the reaction was concentrated in vacuo and the residue was partitioned between ethyl acetate (60 mL) and brine (60 mL), and the aqueous phase was extracted with ethyl acetate (4×60 mL). The combined organic extracts were washed with 1 M citric acid (2×30 mL), $NaHCO_3$ (2×30 mL) and brine (2×30 mL), respectively, dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was purified by flash column chromatography eluting with 1:4 hexane/ethyl acetate to give **23a** (1.625 g, 63%) as a brittle white foam: R_f 0.2 (1:4 hexane/ethyl acetate); [Found: C, 57.61; H, 6.40; N, 10.45. $C_{25}H_{32}N_4O_8$·1/4H_2O requires: C, 57.63; H, 6.29; N, 10.75%]; ν_{max} (KBr): 1749, 1699 and 1656 cm^{-1} (C=O); δ_H (300 MHz, $CDCl_3$) 7.89–8.02 (2H, d, d, *J*=30.0, 7.3 Hz, benzoyl *o*-C*H*), 7.63 (1H, t, *J*=7.3 Hz, benzoyl *p*-C*H*), 7.48 (t, 2H, benzoyl *m*-C*H*), 7.33–7.35 (m, 1H, T–C*H*(6)), 3.89–4.08 (brm, 4H, CH_2CH_2N and NCH_2CO), 3.66–3.76 (5H, m, CH_2CH_2N and –OCH_3), 2.90 (3H, 3×s, NCH_3), 1.93 (3H, s, T–CH_3), 1.45 (9H, s, Boc); FAB-MS *m*/*z*: 539 (19, MNa^+), 517 (20, MH^+), 417 (32), 339 (35), 176 (42), 105 (100).

3.3.2. *N*-[(*N*-*tert*-Butoxycarbonyl-*N*-methyl)glycyl]-*N*-[2-(thymin-1-yl)ethyl]glycine (4a). To a solution of the methyl ester **23a** (2.27 g, 4.4 mmol) in acetone (8 mL) was added NaOH (0.2 M; 8 mL). The solution was left overnight in a refrigerator, then was evaporated to dryness. The residue was taken up in water (20 mL) and acidified to pH 2 with 10% $KHSO_4$. The acid was extracted with ethyl acetate (8×30 mL) and dried over Na_2SO_4. Evaporation to almost dryness followed by addition of ether gave a solid, which was collected by filtration and washed several times with ether. After purification by flash column chromatography eluting with 10:2.5:1.5 ethyl acetate/methanol/water, **4a** was obtained as a white foam (1.418 g, 81%): [Found: C, 49.81; H, 6.48; N, 13.71. $C_{17}H_{26}N_4O_7$·1/2H_2O requires: C, 50.12; H, 6.68; N, 13.75%]; R_f 0.35 (2:1 ethyl acetate/methanol); ν_{max} (KBr): 1750, 1698 cm^{-1} (C=O); δ_H (400 MHz, d-DMSO) 12.78 (1H, s, COO*H*), 11.32, 11.14 and 11.10 (1H, 3×s, T–N*H*), 7.57 and 7.39 (1H, 2×s, T–C*H*(6)), 4.15, 4.14 and 3.98 (2H, 3×s, CH_2COOH), 4.04, 3.89 and 3.87 (2H, 3×s, NCH_2CO), 3.80 and 3.73 (2H, 2×m, TCH_2CH$_2$), 3.51 (2H, m, TCH_2CH_2), 2.73, 2.71, 2.65 and 2.61 (3H, 4×s, NCH_3), 1.74 and 1.71 (3H, 2×s, T–CH_3), 1.38, 1.32 and 1.30 (9H, 3×s, Boc); FAB-MS *m*/*z*: 421 (7, MNa^+), 399 (28, MH^+).

3.3.3. *N*-[(*N*-*tert*-Butoxycarbonyl-*N*-methyl)glycyl]-*N*-[2-(N^6-benzyloxycarbonyladenin-9-yl)ethyl]glycine methyl ester (24a). To a solution of **21** (1.63 g, 4.25 mmol), *N*-Boc–sarcosine (0.803 g, 4.25 mmol) and HBTU (2.15 g, 4.67 mmol) in anhydrous DMF (10 mL) and anhydrous DCM (10 mL) at 0°C was added DIPEA (2.2 mL, 12.75 mmol) dropwise. The solution was allowed to warm slowly to room temperature and was stirred overnight. Subsequently, water (40 mL) was added to the reaction mixture and the resulting aqueous solution extracted with ethyl acetate (6×50 mL). The combined organic extracts were washed with 1 M citric acid (2×60 mL), $NaHCO_3$ (2×60 mL) and brine (60 mL), respectively, dried over Na_2SO_4 and concentrated in vacuo. Filtration followed by evaporation afforded a crude product. After purification using flash chromatography with 96:4 ethyl acetate/methanol as the eluting solvent, a white solid was obtained (1.535 g 65%); [Found: C, 55.30, H, 6.01; N, 17.81. $C_{25}H_{33}N_7O_7$ requires: C, 55.24; H, 6.12; N, 18.00%]; R_f 0.25 (25:1 ethyl acetate/methanol); ν_{max} (KBr): 1749, 1693 cm^{-1} (C=O); δ_H (300 MHz, $CDCl_3$) 8.78 and 8.76 (1H, 2×s, A–C*H*(2)), 8.12 (1H, brm, A–C*H*(8)), 7.43–7.36 (5H, m, Ph), 5.31 (2H, s, CH_2Ph), 4.48 (2H, m, ACH_2), 3.92–3.74 (6H, m, NCH_2CO, NCH_2CO and ACH_2CH_2), 3.74 and 3.72 (3H, 2×s, OCH_3), 2.87 and 2.83 (3H, 2×s, NCH_3), 1.45 and 1.43 (9H, 2×s, Boc); ESI-MS *m*/*z*: 556.7 (100, MH^+), 578.5 (14, MNa^+), 1111.7 (16, $2MH^+$), 1133.7 (10, $2MNa^+$).

3.3.4. *N*-[(*N*-*tert*-Butoxycarbonyl-*N*-methyl)glycyl]-*N*-[2-(N^6-benzyloxycarbonyladenin-9-yl)ethyl]glycine (6a). A 1.0 M solution of sodium hydroxide (5 mmol) was added to a stirred solution of **24a** (1.11 g, 2 mmol) in THF

(5 mL) at room temperature. The reaction was left for 0.5 h before being diluted with water (10 mL). The aqueous solution was washed with DCM (3×10 mL) and the pH adjusted to 3.0 with 2 M solution of 1 M HCl in 0°C. The aqueous layer was extracted with ethyl acetate (8×20 mL), and the combined organic extracts were dried over Na_2SO_4. Filtration followed by evaporation gave the white solid **6a**, which was recrystallized from methanol/ethyl acetate and then dried further over phosphorus pentoxide (0.976 g, 90%) [Found: C, 54.31; H, 5.82; N, 17.35. $C_{25}H_{31}N_7O_7{\cdot}CH_3OH$ requires: C, 54.44; H, 6.16; N, 17.09%]; R_f 0.35 (3:2 ethyl acetate/methanol); ν_{max} (KBr): 1740, 1670 cm^{-1} (C=O); δ_H (300 MHz, d$_6$-DMSO) 10.72 and 10.63 (1H, 2×s, COO*H*), 8.67 and 8.61 (1H, 2×s, A–C*H*(2)), 8.49 and 8.41 (1H, 2×s, A–C*H*(8)), 7.48–7.32 (5H, m, Ph), 5.22 and 5.21 (2H, 2×s, C*H*$_2$Ph), 4.45–4.38 (2H, m, AC*H*$_2$), 4.10 and 4.01 (2H, 2×s, NC*H*$_2$CO), 3.81–3.73 (4H, m, NC*H*$_2$CO and ACH$_2$C*H*$_2$), 2.55 and 2.48 (3H, 2×s, NC*H*$_3$), 1.27, 1.20 and 1.18 (9H, 3×s, Boc); ESI-MS *m/z:* 542 (100, M$^+$), 565 (8, MNa$^+$), 1085 (35, 2MH$^+$).

3.3.5. *N*-[(*N-tert*-Butoxycarbonyl-*N*-methyl)glycyl]-[*N*-2(2-amino-acetyl-guanine-9-yl)ethyl]glycine methyl ester (25a). To a solution of **22** (1.24 g, 4 mmol), *N*-Boc–sarcosine (0.812 g, 4 mmol) and HBTU in anhydrous DMF (25 mL) at 0°C was added DIPEA (2.00 mL, 12 mmol) dropwise. The solution was allowed to warm slowly to room temperature and was stirred overnight. Subsequently, water (40 mL) was added to the reaction mixture and the resulting aqueous solution was extracted with DCM (10×40 mL). The combined organic extracts were washed with 1 M citric acid (2×60 mL), $NaHCO_3$ (2×60 mL) and brine (60 mL), respectively, dried over Na_2SO_4 and concentrated in vacuo. Filtration followed by evaporation afforded a crude product. After purification using flash chromatography with 10:1:0.1 ethyl acetate/methanol/water as the eluting solvent, the white solid **25a** was obtained (0.958 g, 50%) [Found: C 49.76; H 6.76; N 20.47. $C_{20}H_{29}N_7O_7$ requires: C 50.10; H 6.10; N, 20.45%]; R_f 0.33 (5:1 ethyl acetate/methanol); ν_{max} (KBr): 1702, 1667 cm^{-1} (C=O); δ_H (300 MHz, d$_6$-DMSO) 12.05 and 11.65 (2H, brm G–N*H*(1),(2)), 8.03, 7.93 and 7.92 (1H, 3×s, G–C*H*(8)), 4.25 (2H, m, GC*H*$_2$), 4.19 and 4.08 (2H, 2×s, NC*H*$_2$CO), 3.86 and 3.68 (2H, 2×s, NC*H*$_2$CO), 3.68 and 3.64 (3H, 2×s, OC*H*$_3$), 3.64–3.58 (2H, m, GCH$_2$C*H*$_2$), 2.62, 2.57 and 2.58 (3H, 3×s, NC*H*$_3$), 2.19 (3H, s, Ac–C*H*$_3$), 1.37, 1.35 and 1.29 (9H, 3×s, Boc); FAB-MS *m/z*: 502 (10, MNa$^+$), 480 (36, MH$^+$), 154 (40), 77 (100).

3.3.6. *N*-[(*N-tert*-Butoxycarbonyl-*N*-methyl)glycyl]-[*N*-2(2-amino-acetyl-guanine-9-yl)ethyl]glycine (7a). A 1.0 M solution of sodium hydroxide (5 mmol) was added to a stirred solution of **25a** (0.958 g, 2 mmol) in THF (5 mL) in an ice-bath. The saponification reaction was complete within 1 h before being diluted with water (10 mL). The aqueous solution was washed with DCM (3×10 mL) and the pH adjusted to 3.0 with 2 M solution of 1 M HCl in 0°C. The aqueous layer was extracted with ethyl acetate (8×30 mL), and the combined organic extracts were dried over Na_2SO_4. Filtration followed by evaporation, dried further over phosphorus pentoxide, gave the product **7a** (1.668 g, 72%) as a white foam [Found: C 47.34; H 6.02; N 20.46. $C_{19}H_{27}N_7O_7{\cdot}H_2O$ requires: C 47.20; H 6.04; N, 20.28%]; R_f 0.25 (1:1 ethyl acetate/methanol); ν_{max} (KBr); 3449 cm^{-1} (COOH), 1683 cm^{-1} (C=O); δ_H (300 MHz, d$_6$-DMSO) 8.04, 7.95 (1H, 2×s, G–C*H*(8)), 4.17–3.42 (8H, m, C*H*$_2$NC*H*$_2$CO and GC*H*$_2$C*H*$_2$), 2.61–2.53 (3H, 4×s, NC*H*$_3$), 2.18 (3H, s, Ac–C*H*$_3$), 1.36, 1.35, 1.28 and 1.23 (9H, 4×s, Boc); ESI-MS *m/z*: 488 (100, MNa$^+$), 369 (33).

3.4. General procedure for the synthesis of *N*-Fmoc dipeptide methyl esters 4b, 6b and 7b

The *N*-free **11b**, **21** or **22** (1.0 mmol, 1.0 equiv.) was taken up in dry DMF (5 mL) and dry DCM (5 mL) in an ice-bath, and DIPEA (2.2 mmol, 2.2 equiv.) was added. Then *N*-[*N*-(fluoren-9-ylmethoxycarbonyl)-*N*-methyl-glycyl]pentafluorophenyl ester (1.5 mmol, 1.5 equiv.) was added and the solution was stirred at room temperature overnight. The reaction mixture was evaporated to dryness to afford the crude product.

3.4.1. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methyl-glycyl]-*N*-[2-(thymin-1-yl)ethyl]glycine methyl ester (23b). The above procedure was followed using **11b** (0.774 g, 3.2 mmol). After workup, the crude product obtained was purified using flash chromatography with ethyl acetate as the eluting solvent. The dipeptoid **23b** was obtained as a white solid (1.454 g, 85%) [Found: C, 62.15; H, 5.66; N, 10.15. $C_{28}H_{30}N_4O_7{\cdot}1/2\ H_2O$ requires: C, 61.87; H, 5.75; N, 10.31%]; R_f 0.2 (ethyl acetate); ν_{max} (KBr): 1748, 1704 and 1653 cm^{-1} (C=O); δ_H (300 MHz, d$_6$-DMSO) 11.39, 11.34, 11.19 and 11.17 (1H, 4×s, T–N*H*), 7.92–7.28 (9H, m, Fmoc aromatic-C*H* and T–C*H*(6)), 4.32–3.96 (5H, m, Fmoc aliphatic C*H* and C*H*$_2$ and TC*H*$_2$), 3.81–3.52 (7H, m, C*H*$_2$NC*H*$_2$CO and OC*H*$_3$), 2.78, 2.71 and 2.70 (3H, 3×s, NC*H*$_3$), 1.74, 1.71, 1.69 and 1.64 (3 H, 4×s, T–C*H*$_3$); ESI-MS *m/z*: 535 (100, MH$^+$), 1070 (8, 2MH$^+$), 1091 (27, 2MNa$^+$).

3.4.2. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methyl-glycyl]-*N*-[2-(N^6-Benzyloxycarbonyladenin-9-yl)ethyl]-glycine methyl ester (24b). The above procedure was followed using **21** (2.299 g, 6.5 mmol). After workup, the crude product obtained was purified using flash chromatography with 25:1:0.1 ethyl acetate/methanol/water as the eluting solvent. The dipeptoid **24b** was obtained as a white solid (2.472 g, 56%) [Found: C, 62.84; H, 5.15; N, 14.27. $C_{36}H_{35}N_7O_7{\cdot}1/2\ H_2O$ requires: C, 62.96; H, 5.28; N, 14.27%]; R_f 0.2 (25:1 ethyl acetate/methanol); ν_{max} (KBr): 1751,1706 and 1674 cm^{-1} (C=O); 761 and 742 cm^{-1} (Ph); δ_H (300 MHz, $CDCl_3$) 8.77 (1H, s, A–C*H*(2)), 8.27, 8.16 and 8.00 (1H, 3×s, A–C*H*(8)), 7.77–7.27 (13H, m, phenyl and Fmoc aromatic-C*H*), 5.30 and 5.27 (2 H, 2×s, C*H*$_2$Ph), 4.48–4.23 (5H, m, Fmoc aliphatic C*H* and C*H*$_2$ and AC*H*$_2$), 4.00–3.54 (9H, m, NC*H*$_2$CO, C*H*$_2$NC*H*$_2$CO and OC*H*$_3$), 3.01, 2.95, 2.87 and 2.81 (3 H, 4×s, NC*H*$_3$); ESI-MS *m/z*: 678.6 (100, MH$^+$), 700.3 (13, MH$^+$), 1356.4 (8, 2MH$^+$).

3.4.3. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methyl-glycyl]-*N*-[2-(2-amino-acetyl-guanine-9-yl)ethyl]glycine methyl ester (25b). The above procedure was followed using **22** (2.34 g, 7.6 mmol). After workup, the crude product obtained was purified using flash chromatography with 10:1:0.1 ethyl acetate/methanol/water as the eluting solvent. The dipeptoid **25b** was obtained as a white solid

(2.572 g, 50%) [Found: C, 58.59; H, 5.35; N, 15.65. $C_{30}H_{31}N_7O_7 \cdot H_2O$ requires: C, 58.57; H, 5.32; N, 15.94%]; R_f 0.25 (5:1 ethyl acetate/methanol); ν_{max} (KBr): 1748, 1678 and 1611 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 12.00 and 11.63 (2H, 2×brm, G–N*H*(1), (2)), 8.06–7.26 (9H, m, Fmoc aromatic-C*H* and CH_2 and G–C*H*(8)), 4.27–3.94 (7H, m, Fmoc aliphatic-C*H* and CH_2 GCH_2 CH_2 NCH_2CO), 3.74–3.70 (2H, m, NCH_2CO), 3.67–3.64 (5H, m, OCH_3 and GCH_2CH_2), 2.69, 2.68, 2.63 and 2.61 (3H, 4×s, NCH_3), 2.18, 2.17 and 2.15 (3H, 3×s, Ac–CH_3); ESI-MS *m/z*: 603 (36, MH^+), 625 (100, MNa^+).

3.5. Saponification of the ethyl esters 4b, 6b and 7b

A 2.5 M solution of sodium hydroxide (10 equiv.) was added to a stirred solution of **23b**, **24b** or **25b** (1 equiv.) in THF (2 mL/mmol) at 0°C. The completion of the reactions was monitored by TLC.

3.5.1. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methylglycyl]-*N*-[2-(thymin-1-yl)ethyl]glycine (4b). The product **4b** was obtained as a white foam (82%) [Found: C, 58.19; H, 5.55; N, 10.18. $C_{27}H_{28}N_4O_7 \cdot 2H_2O$ requires: C, 58.27; H, 5.80; N, 10.07%]; ν_{max} (KBr): 1697 cm^{-1} (C=O), 765 and 743 (Fmoc); δ_H (300 Hz, d_6-DMSO) 7.79–7.37 (9H, m, Fmoc aromatic-C*H* and T–C*H*(6)), 3.94–3.48 (11H, m, Fmoc aliphatic C*H* and CH_2, TCH_2CH_2NCH_2CO), 2.67 (3H, brm, NCH_3), 1.71 (3H, brm, T–CH_3); ESI-MS *m/z* 521 (41, MH^+), 543 (100, MNa^+), 1041 (40, $2MH^+$), 1063 (100, $2MNa^+$).

3.5.2. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methylglycyl]-*N*-[2-(N^6-benzyloxycarbonyladenin-9-yl)ethyl]-glycine (6b). The product **6b** was obtained as a white foam (85%) [Found: C, 59.45; H, 5.58; N, 13.82. $C_{35}H_{33}N_7O_7 \cdot 2.5H_2O$ requires: C, 59.32; H, 5.40; N, 13.83%]; ν_{max} (KBr): 1706 and 1671 cm^{-1} (C=O), 761 and 742 (Fmoc); δ_H (300 MHz, d_6-DMSO) 10.72 and 10.65 (1H, 2×s, COO*H*), 8.66 and 8.62 (1H, 2×s, A–C*H*(2)), 8.49, 8.48, 8.42 and 8.40 (1H, 4×s, A–C*H*(8)), 7.91–7.25 (13H, m, phenyl and Fmoc aromatic-C*H*), 5.21 (2H, 2×s, CH_2Ph), 4.48–4.41 (2H, brm, ACH_2), 4.25–4.01 (5H, m, Fmoc aliphatic C*H* and CH_2 and NCH_2CO), 3.90–3.79 (4H, m, NCH_2CO and ACH_2CH_2), 2.62, 2.60 and 2.59 (3H, 3×s, NCH_3); ESI-MS *m/z*: 665 (100, MH^+), 687 (18, MNa^+).

3.5.3. *N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)-*N*-methylglycyl]-*N*-[2(2-amino-acetyl-guanine-9-yl)ethyl]glycine (7b). The product **7b** was obtained as a white foam (75%) [Found: C, 56.06, H, 5.72; N, 15.53. $C_{29}H_{29}N_7O_7 \cdot 2H_2O$ requires: C, 55.83; H, 5.33, N, 15.72%]; ν_{max} (KBr): 1683 cm^{-1} (C=O); δ_H (300 MHz, d_6-DMSO) 12.05 and 11.65 (2H, brm, G–N*H*(1),(2)), 8.06–7.29 (9H, m Fmoc aromatic-C*H* and G–C*H*(8)), 4.28–3.94 (7H, m, Fmoc aliphatic-C*H* and CH_2 and GCH_2NCH_2CO), 3.75–3.66 (4H, m, NCH_2CO and GCH_2CH_2), 2.73, 2.69, 2.68 and 2.64 (3H, 4×s, NCH_3), 2.17 and 2.15 (3H, 2×s, Ac–CH_3); ESI-MS *m/z*: 589 (100, MH^+), 1176 (63, $2MH^+$).

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References

1. Uhlman, E.; Reyman, A. *Chem. Rev.* **1990**, *90*, 544–584.
2. Bielinska, A.; Shivdasani, R. A.; Zhang, L. Q.; Nabel, G. J. *Science* **1990**, *250*, 997–1000.
3. Bock, L. C.; Griffin, L. C.; Latham, J. A.; Vermaas, E. H.; Joole, J. J. *Nature (London)* **1992**, *355*, 564–566.
4. (a) Stec, W. J.; Wilk, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *4*, 709–722. (b) Ramasamy, K. S.; Stoisavljevic, V. *Nucleosides Nucleotides* **1999**, *18*, 1845–1861. (c) Efimov, V. A.; Choob, M. V.; Kallinkina, A. L.; Chakhmakhoheva, O. G. *Nucleosides Nucleotides* **1997**, *16*, 1475–1480. (d) Rana, V.; Kumar, V.; Ganesh, K. *Bio. Med. Lett.* **1997**, *7*, 2637–2642.
5. Nielsen, P. E.; Egholm, M.; Berg, R. H.; Buchardt, O. *Science* **1991**, *254*, 1497–1500.
6. (a) Egholm, M.; Buchardt, O.; Nielsen, P. E.; Berg, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 1895–1897. (b) Egholm, M.; Buchardt, O.; Nielsen, P. E.; Berg, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9677–9678.
7. Kim, S. K.; Nielsen, P. E.; Egholm, M.; Buchardt, O.; Berg, R. H.; Norden, B. *J. Am. Chem. Soc.* **1993**, *115*, 6477–6481.
8. (a) Efimov, V. A.; Choob, M. V.; Buryakova, A. A.; Chakhmakhcheva, V. G. *Nucleosides Nucleotides* **1999**, *18*, 1425–1426, 1427–1428. (b) Bermann, F.; Bannuwarth, W.; Tam, S. *Tetrahedron Lett.* **1995**, *36*, 6823–6826.
9. Wu, Y.; Xu, J. C. *Chin. Chem. Lett.* **2000**, *11*, 771–774.
10. Lowe, G.; Vilaivan, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 539–546.
11. Jenny, T. F.; Previsani, N.; Benner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029–7032.
12. Howarth, N. M.; Wakelin, L. P. G. *J. Org. Chem.* **1997**, *62*, 5441–5450.
13. Dueholm, K. L.; Egholm, M.; Behnens, C.; Christensen, L.; Hansen, H. F. *J. Org. Chem.* **1994**, *59*, 5767–5773.
14. Warkins, B. E.; Kiely, J.; Papoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 5702–5708.
15. Jenny, T. F.; Schneider, K. C.; Benner, S. A. *Nucleosides Nucleotides* **1992**, *11*, 1257–1261.