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The synthesis of piperidine nucleoside analogs—a comparison of several methods to access the introduction of nucleobases

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ABSTRACT

This work deals with the synthesis of piperidine and hydroxypiperidine analogs of nucleosides. Starting from commercially available 3-hydroxypiperidine, proline or 4-hydroxyproline, a series of piperidine derivatives of both purine and pyrimidine nucleobases was prepared. Various methods of nucleobase attachment were evaluated. The prepared compounds were tested for cytostatic, antibacterial, and antiviral properties but no significant activity was found.

1. Introduction

Azasugars (iminosugars) belong to a family of polyhydroxylated alkaloids. Many azafuranose and azapyranose analogs are potent α- and β-glycosidase inhibitors[1,2] and also have antidiabetic, anticancer, and antiviral properties.[3] *N*-Butyl-1-deoxynojirimycin **1** (Zavesca™) is used in Gaucher disease treatment. Another azasugar, Miglitol **2**, which is commercially available in the USA and Canada, is used for the treatment of type II diabetes (GLYSET™). The chemical and biological properties of iminosugars have been well reviewed in past years.[4–7]

Sugar-modified nucleosides represent an important group of antimetabolites that exhibit a variety of biological properties. First, azasugar nucleoside analog **3** was reported by Reist et al.[8] The ring nitrogen atom of this compound was acylated otherwise it would undergo spontaneous hydrolysis. Owing to the instability of iminonucleosides, most of the research has been focused on non-glycosidic or aza-C-nucleosides.[9–15] Aza-C-nucleosides **4** and **5** (D-immucillin-H and D-DADMe-immucillin-H) have been shown to be potent inhibitors of human purine nucleoside phosphorylase with K_i values of 56 and 16 pM, respectively.[16] These compounds are now in clinical trials for the treatment of T- and B-cell cancers and a variety of autoimmune diseases.[17] The synthesis of pyrrolidine nucleosides **6a**–**c** has been reported by our group.[18,19] Such compounds offer a site for the further modification of the pyrrolidine nitrogen atom. Thus, we prepared a series of nucleoside phosphonate analogs.[20,21] Phosphonate derivative **7** was found as a potent inhibitor of thymidine phosphorylase from spontaneous SD-rat lymphoma cells exhibiting IC_{50} of 11 nM.[22]

The synthesis of piperidine nucleoside analog **8** where the nucleobase is attached to the piperidine nitrogen atom was published by Pedersen et al.[23] Prukala[24] reported the synthesis of the piperidine derivative of cytosine **9**, where the cyclic amine was introduced through a methylene bridge at position 5 of the cytosine via a Mannich-type reaction. *N*-methyl-D-ribopyranuronamide nucleosides **10a**–**b** and **11a**–**b** were synthesized and evaluated in antiviral and cytotoxic assays, however, no activity was found.[25,26] Piperidine nucleoside **12** was prepared by Kim et al.,[27] and it seemed that oligonucleotides containing this modification exhibited a strong hybridization with RNA depending on the location and number of substitutions. Also, the increase of hydrophobicity in these modified oligonucleotides can be advantageous for cellular uptake.

Nucleobase attachment to the sugar-mimicking part represents the key step in the synthesis of a variety of nucleoside analogs. Sugar-modified nucleoside analogs, where the nucleobase is not attached via a glycosidic bond, are usually prepared by (i) the nucleophilic displacement of an activated hydroxyl with a nucleobase under Mitsunobu conditions, (ii) the nucleophilic displacement of mesyloxy, tosyloxy or halogen moieties with nucleobases, and (iii) nucleobase assembly on primary amino derivatives.

Mitsunobu nucleosidation usually consists of the reaction of a hydroxy compound with the nucleobase in the presence of triphenylphosphine and diethyl or diisopropyl azodicarboxylate in

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THF.[28–30] The nucleobases react as ambident nucleophiles, leading to mixtures of N^1/*O* isomers for pyrimidines and N^7/N^9 isomers for purines. The other disadvantage of this method is the complex reaction mixture rendering the isolation of the desired product difficult. Because of the low solubility of unprotected nucleobases in THF, and the tendency to form unwanted isomers, various modifications have been described. Concerning pyrimidines, the use of 3-*N*-benzoyluracil[31,32] and 4-*N*-benzoylcytosine[33,34] has been employed. 6-Chloropurine or 2-amino-6-chloropurine are frequently used to obtain derivatives of adenine or guanine, respectively.[35,36] Michael and Strazewski[37] used N^6-bis-Boc-protected adenine in a Mitsunobu reaction, during the synthesis of neplanocin A and obtained the desired product at a 98% yield.

The nucleophilic displacement of mesyloxy, tosyloxy or halogen groups with nucleobases is often used in the synthesis of nucleoside analogs.[38–42] The reaction is usually carried out in a polar aprotic solvent (e.g., DMF, DMSO) in the presence of cesium carbonate or sodium hydride as bases to generate the nucleobase anion. This reaction is often accompanied by the formation of unwanted regioisomers (mostly in a pyrimidine series) and a competing elimination reaction, thereby decreasing the yield of the desired product (Fig. 1).

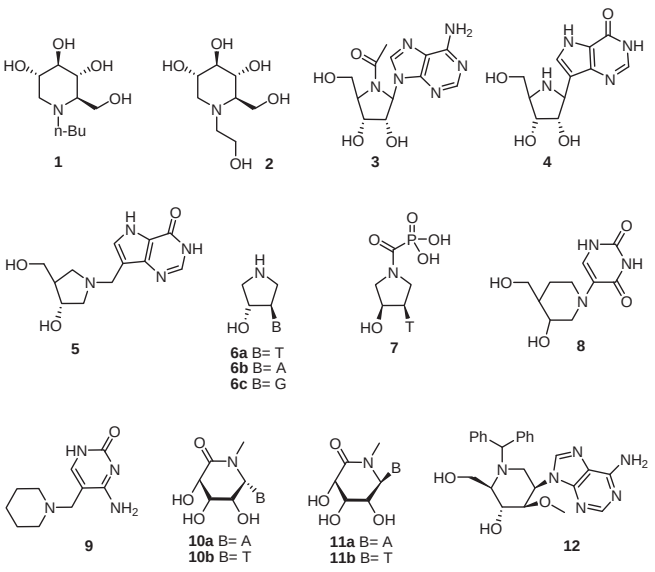


Fig. 1. Derivatives of iminosugars.

The last often used method is called the nucleobase build-up procedure. It consists of the reaction of primary amine with urea derivatives **13a**–**14b**[43–46] or 4,6-dichloropyrimidines **16**–**18**[47–50] (Fig. 2), forming an intermediate that undergoes a cyclization reaction to afford appropriate pyrimidine or purine derivatives, respectively. Recently, we described new reagents **15a**–**b** for the synthesis of N^1-substituted uracil and thymine, giving excellent results with a variety of structurally diverse amines.[51]

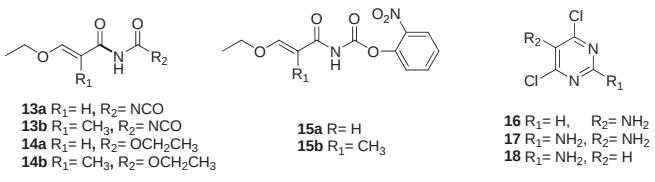


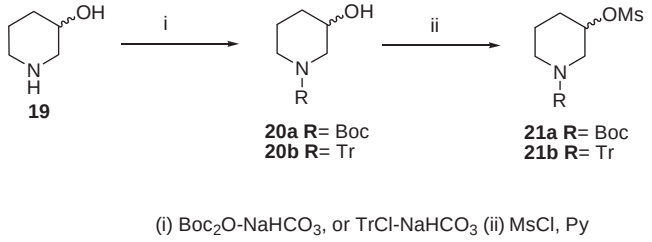
Fig. 2. Reagents for nucleobase construction.

2. Results and discussion

2.1. Optimization of the nucleosidation reaction and synthesis of the racemic piperidin-3-yl derivatives of nucleobases

Here, we report the synthesis of nucleoside analogs where the ribose moiety is replaced with a piperidine ring. According to our experiences with the synthesis of pyrrolidine nucleosides, the development of suitable strategies for nucleobase attachment to the protected piperidine ring has been the most challenging task. Thus, *N*-protected 3-hydroxypiperidine was selected as a model starting material, and various conditions for nucleobase attachment were evaluated.

Synthesis started from the commercially available (*RS*)-3-hydroxypiperidine (**19**). This compound was transformed into *N*-Boc (*tert*-butyloxycarbonyl) derivative **20a** (97%) and *N*-Tr (Trityl) derivative **20b** (30%), and these compounds were mesylated giving **21a** (85%) and **21b** (94%) (Scheme 1). Compounds **20a**,**b** and **21a**,**b** were used for the Mitsunobu reaction and nucleophilic displacement, respectively.

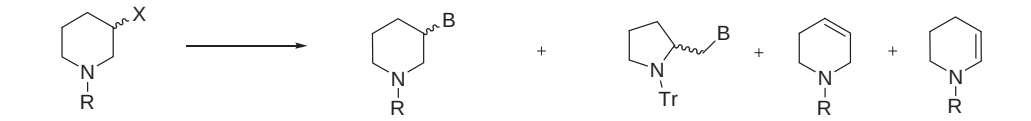


Scheme 1.

Boc-derivative **20a** and trityl derivative **20b** were treated with nucleobase under Mitsunobu conditions (Table 1). Reactions were performed in dioxane at 100 °C (according to Richichi[29]) or THF at 0–5 °C. It appeared that *N*-Boc-3-hydroxypiperidine **20a** was not a convenient substrate for Mitsunobu nucleosidation. In dioxane, it rapidly decomposed at high temperatures, and a mixture of compounds was obtained when treated with pyrimidine and purine bases. Also, the reactions in THF at low temperatures did not afford the expected pyrimidine or purine derivates of nucleobases. Only products of elimination, the 2,3 and 3,4 unsaturated compounds, were isolated at a yield of ~50% (entries 1–6). By contrast, we were able to isolate the 6-chloropurine and 6-chloro-2-aminopurine derivatives in 25% and 27% yields, respectively, when using *N*-trityl derivative **20b** as a starting material (entries 9 and 11). However, the reaction of **20b** with pyrimidines did not afford any desired product (entries 7 and 8). Similar results were obtained during the synthesis of pyrrolidine nucleosides described previously.[18]

It is necessary to note that the order of the addition of reagents and substrates might play an important role in the result of the Mitsunobu reaction. We obtained the best results when DIAD was first added dropwise to the stirred triphenylphosphine in THF, followed by the addition of **20a** or **20b** and nucleobase in THF. One drawback of the Mitsunobu reaction is the poor solubility of nucleobase in THF. Thus, to improve results, we attempted to use 6-*N*-bis(Boc)adenine[37] (entry 13). Unfortunately, no improvement was observed (Scheme 2).

For the alkylation reactions of the purine and pyrimidine nucleobases with 3-mesyloxy-*N*-protected piperidine, different combinations of solvents (DMSO, DMF) and bases (NaH, Cs_2CO_3) were investigated. Generally, nucleobases and bases were first allowed to react in DMSO (or DMF) at 120 °C to form the appropriate salt. Then, 3-mesyloxypiperidine in DMSO (DMF) was added dropwise into the reaction mixture.



20a R= Boc, X= OH
20b R= Tr, X= OH
21a R= Boc, X= OMs
21b R= Tr, X= OMs

22a R= Boc, B= thymine
22b R= Boc, B= 2-*O*-cytosine
22c R= Boc, B= cytosine
22d R= Boc, B= adenine
23a R= Tr, B= 6-chloropurine
23b R= Tr, B= 2-amino-6-chloropurine
23c R= Tr, B= adenine
23d R= Tr, B= 2-*O*-cytosine
23e R= Tr, B= thymine

24a B= adenine
24b B= thymine
24c B= 2-*O*-cytosine

25a R= Boc
25b R= Tr

26a R= Boc
26b R= Tr

Scheme 2.

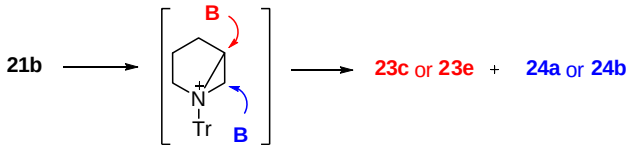
Table 1
Optimization of the nucleosidation reaction

	R	X	B[a]	Reagents	*T* (°C)	**22**/**23** Yield%	**24** Yield%	**25** Yield%	**26** Yield%
1	Boc	OH	T	THF, DIAD, PPh_3	0–5	0	—	25[b] (**25**+**26**)	
2	Boc	OH	T	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
3	Boc	OH	Cl-Pu	THF, DIAD, PPh_3	0–5	0	—	33[b] (**25**+**26**)	
4	Boc	OH	Cl-Pu	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
5	Boc	OH	Cl-G	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
6	Boc	OH	Bz-A	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
7	Tr	OH	T	THF, DIAD, PPh_3	0–5	0	—	18	22
8	Tr	OH	T	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
9	Tr	OH	Cl-Pu	THF, DIAD, PPh_3	0–5	25[d] (**23a**)	—	32 (**25**+**26**)	
10	Tr	OH	Cl-Pu	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
11	Tr	OH	Cl-G	THF, DIAD, PPh_3	0–5	27[d] (**23b**)	—	n.d	n.d.
12	Tr	OH	Cl-G	Dioxane, DIAD, PPh_3	100	0[c]	—	n.d.	n.d.
13	Boc	OH	Boc-Pu	THF, DIAD, PPh_3	0–5	0[c]	—	n.d.	n.d.
14	Boc	OMs	T	DMSO, Cs_2CO_3	120	16[d] (**22a**)	—	23	28
15	Boc	OMs	T	DMSO, NaH	120	0[c]	—	n.d.	n.d.
16	Boc	OMs	T	DMF, Cs_2CO_3	120	15[d] (**22a**)	—	n.d.	n.d
17	Boc	OMs	C	DMSO, NaH	120	0[e]	—	n.d.	n.d.
18	Boc	OMs	C	DMF, Cs_2CO_3	120	18[d] (**22c**)	—	n.d.	n.d.
19	Boc	OMs	A	DMF, Cs_2CO_3	120	16[d] (**22d**)	—	n.d.	n.d.
20	Boc	OMs	A	DMSO, Cs_2CO_3	120	18[d] (**22d**)	—	29 (**25**+**26**)	
21	Boc	OMs	U	DMSO, NaH	120	0[c]	—	n.d.	n.d.
22	Tr	OMs	A	DMSO, Cs_2CO_3	120	18[d] (**23c**)	18[d](**24a**)	n.d.	n.d.
23	Tr	OMs	A	DMF, Cs_2CO_3	120	35[g] (**23c**+**24a**)		n.d.	n.d.
24	Tr	OMs	Cl-G	DMSO, Cs_2CO_3	120	10[d] (**23b**)	—[f]	n.d.	n.d.
25	Tr	OMs	C	DMSO, Cs_2CO_3	120	28[g] (**23d**+**24c**)		n.d.	n.d.
26	Tr	OMs	T	DMSO, Cs_2CO_3	120	27[g] (**23e**+**24b**)		n.d.	n.d.
27	Tr	OMs	A	ECOENG212/DMF, Cs_2CO_3	120	38[g] (**23c**+**24a**)		n.d.	n.d.
28	Tr	OMs	T	ECOENG212/DMF, Cs_2CO_3	120	40[g] (**23e**+**24b**)		n.d.	n.d.
29	Tr	OMs	A	[BMIM]PF_6/DMF, Cs_2CO_3	120	45[g] (**23c**+**24a**)		n.d.	n.d.

[a] T=thymine, Cl-Pu=6-chloropurine, Cl-G=2-amino-6-chloropurine, Boc-Pu=6-*N*-bis-*tert*-butyloxycarbonyl purine, C=cytosine, A=adenine, U=uracil.
[b] Only products of elimination were isolated.
[c] TLC, complicated mixture.
[d] Isolated yield.
[e] *O*-Derivatives (29%) was isolated.
[f] Not isolated.
[g] Isolated yield of the mixture of piperidine and pyrrolidine derivatives.

The alkylation of thymine with **21a** in the presence of Cs_2CO_3 afforded a 16% yield of **22a** in DMSO and 15% yield of **22a** in DMF (entries 14 and 16). When NaH was used as a base in DMSO only a complex mixture of compounds was obtained (entry 15). The alkylation of cytosine led to a 29% yield of *O*-derivative **22b** when NaH was used as a base (entry 17), whereas when Cs_2CO_3 was used, the desired N^1-derivative **22c** was obtained in a 18% yield (entry 18). Adenine was alkylated in the presence of Cs_2CO_3 giving a 16% yield of **22d** in DMF and 18% yield in DMSO (entries 19 and 20). Uracil was attempted to react in DMSO using NaH as a base giving a complex mixture of products (entry 21). In all cases, the products of competing elimination reactions **25a** and **26a** were observed.

When treating *N*-trityl-3-mesyloxyderivative **21b** under alkylation conditions, we observed the formation of another by-product (besides the products of elimination **25b** and **26b**), which were identified as the appropriate pyrrolidine derivatives **24a**,**b**, the result of piperidine ring contraction[52–54] (entries 22–29). The ratio between the formed piperidine and pyrrolidine derivative was 1:1 (adenine derivatives **23c**/**24a**), 3:2 (thymine derivatives **23e**/**24b**), and 7:3 (2-*O*-cytosin derivatives **23d**/**24c**). We assume that the pyrrolidine derivatives **24a**–**c** were formed through the aziridinium intermediate (Scheme 3).

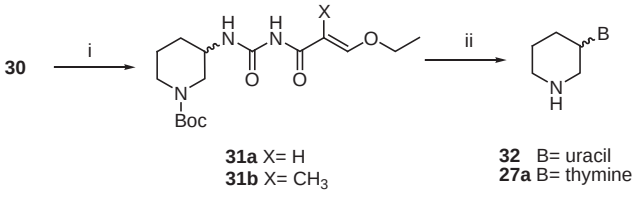


Scheme 3.

Ionic liquids have been reported as advantageous dipolar aprotic solvents ideal for alkylation reactions.[55,56] To our best knowledge, no article concerning nucleosidation in ionic liquids has been published so far. We performed alkylation in ECOENG212/DMF and [BMIM]PF_6/DMF (entries 27–29). Although the yield of the product increased, the removal of the ionic liquid seemed to be complicated, as well as the separation of the piperidine product from the pyrrolidine by-product.

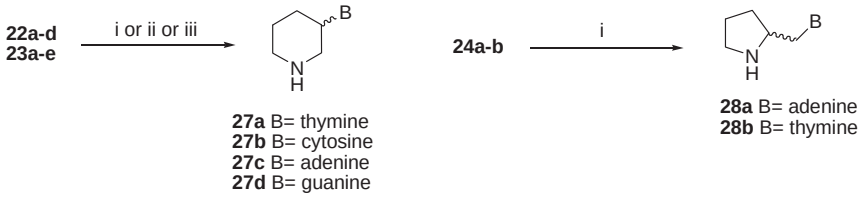
The final nucleosides **27a**,**b** and **28b** were obtained after treatment with TFA in DCM for thymine derivatives. Derivatives **23a**,**b** were treated with ammonia in ethanol and NaOH to obtain the adenine **27c** and guanine **27d** derivatives, respectively (Scheme 4). After treatment with TFA, the obtained free piperidine nucleosides were deionized on a Dowex 50 in H^+ form, and finally purified by a preparative reversed phase HPLC.

The reaction of aminopiperidine **30** with 2-nitrophenyl 3-ethoxyacryloylcarbamate (**15a**) and 2-nitrophenyl 3-ethoxy-2-methylacryloylcarbamate (**15b**)[51] proceeded smoothly within 10 min at room temperature (rt; Scheme 6). Products **31a** and **31b** were purified by flash chromatography and then cyclized by heating with a Dowex 50H^+ in dioxane at 80 °C, which also caused Boc group removal. The final purification of free nucleosides was performed using preparative HPLC. Both pyrimidine derivatives were obtained in excellent overall yields: 78% for the uracil derivative **32a** and 70% for the thymine derivative **27a**.



i. **15a** or **15b**, dioxane r.t.; ii. Dowex 50 H^+, dioxane, 80 °C

Scheme 6.

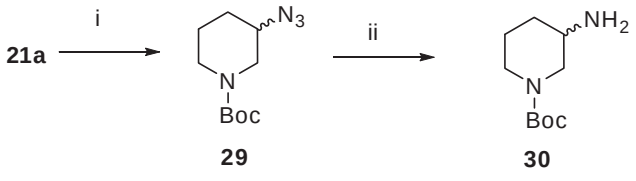


i. 20% TFA/DCM; ii. 1. NH_3/EtOH, 2. 20% TFA/DCM; iii. 1. NaOH, dioxane/H_2O, 2. 20% TFA/DCM

Scheme 4.

Since neither Mitsunobu coupling nor direct alkylation afforded satisfactory results, we were forced to look for another approach to piperidine nucleoside synthesis. Thus nucleobase assembly on primary amines was evaluated.

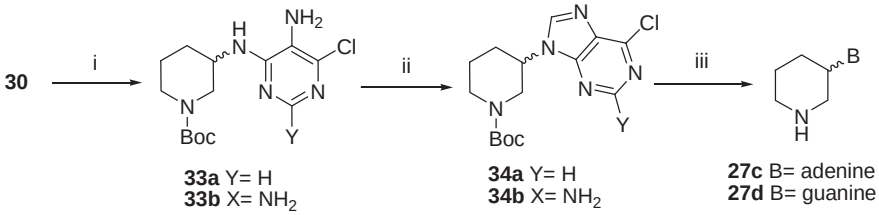
We prepared (*R*,*S*)-3-amino-1-*N*-*tert*-butyloxycarbonyl-piperidine (**30**) in two steps starting from (*R*,*S*)-*N*-Boc-3-mesyloxy-piperidine (**21a**). Mesyl derivative **21a** was first transformed into 3-azido derivative **29** by reaction with sodium azide in DMF in a 95% yield, which was then treated with H_2, Pd/C in ethanol to obtain aminopiperidine **30** in a 90% yield (Scheme 5).



i. NaN_3, DMF; ii. H_2, Pd/C, EtOH

Scheme 5.

A purine nucleobase on the piperidine skeleton was constructed according to Hřebabecký et al.[47] The reaction of (*R*,*S*)-3-amino-1-*N*-*tert*-butyloxycarbonylpiperidine (**30**) with 5-amino-4,6-dichloropyrimidine (**16**) or 2,5-diamino-4,6-dichloropyrimidine (**17**) afforded compounds **33a** (70%) and **33b** (56%), respectively (Scheme 7), which upon reaction with neat diethoxymethyl acetate[57] provided 6-chloropurine derivatives **34a** and **34b**, respectively. In the case of compound **33b**, only 1.1 M equiv of diethoxymethyl acetate were used and the reaction was carried out in DMF. Otherwise, the formylation of the exocyclic 2-amino group occurred. The final treatment of **34a** and **34b** with ammonia and 1 M NaOH, followed by Boc group removal with TFA, afforded good yields of the desired adenine **27c** (58%) and guanine **27d** (64%) derivatives, respectively.

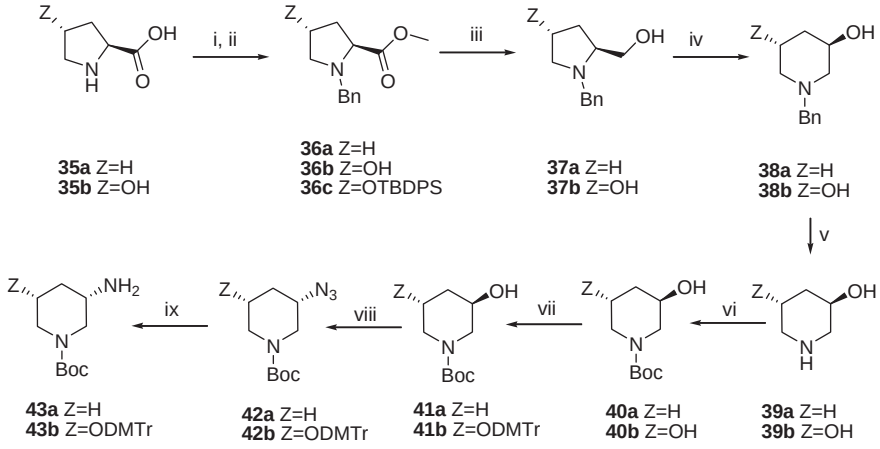


(i) **17** or **16**, Et_3N, n-butanol, 120 °C, pressure vessel; (ii) 1. diethoxymetylacetate, DMF, 100 °C; (iii) 1. NaOH or NH_3; 2. 20 % TFA in DCM, R.T

Scheme 7.

2.2. Synthesis of enantiomeric piperidin-3-yl and (3*R*,5*S*)-3-hydroxypiperidin-5-yl derivatives of nucleobases

Compounds **40a** and **40b** (hydroxy- and dihydroxypiperidine) were prepared from the appropriate prolinols according to the procedure published by Cossy et al.[58] (Scheme 8). First, the prolines **36a** and **36b** were converted to methyl esters by reaction with $MeOH/SOCl_2$, and these compounds were benzylated on nitrogen atom to obtain **37a** and **37b**. The compound **37b** was then treated with TBDPSCl to protect the secondary hydroxy group (compound **37c**). The ester functions of the proline derivatives **37a**–**c** were easily reduced with $LiAlH_4$ in the next step. However, the work-up of the reaction mixture of **37c** resulted in TBDPS group removal. This observation is in contrast to published results.[58] The authors reported a 90% yield and observed no TBDPS group deprotection during reaction work-up. The rearrangement of prolinol derivatives **38a** and **38b** to the corresponding piperidine compounds **39** was performed by reaction with trifluoroacetic anhydride and triethylamine in THF. The following saponification led to hydroxypiperidine **39a** (51%) and dihydroxypiperidine **39b** (49%). Although the ring expansion did not proceed completely, we were able to separate the prolinol and piperidine derivatives using flash chromatography on a silica gel, and thereby recover the starting material.



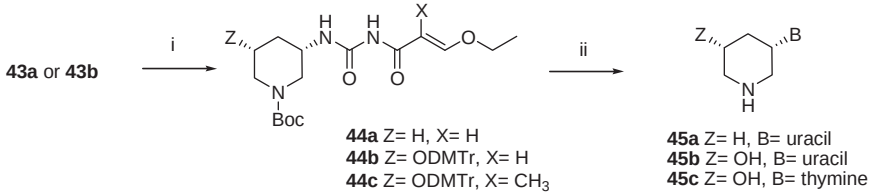
(i) 1. $SOCl_2$, MeOH; 2. BnBr, K_2CO_3; (ii)1. $SOCl_2$, MeOH; 2. BnBr, K_2CO_3; 3. TBDPSCl; (iii) $LiAlH_4$; (iv) $(CF_3CO)_2O$, Et_3N; (v) H_2, Pd/C; (vi) Boc_2O, $NaHCO_3$; (vii) DMTrCl, py; (viii) 1. MsCl, DMAP; 2. NaN_3, DMF; (ix) H_2, Pd/C

Scheme 8.

The *tert*-butyloxycarbonyl group was first introduced onto **39a** and **39b** followed by the partial dimethoxytritylation of **39b**, which afforded the monoprotected piperidine **41b** in a 35% yield. The bis-dimethoxytrityl derivative was also obtained, and we succeeded in the regeneration of **40b** by the treatment of the bis-DMTr derivative with 1.5% TFA in DCM for 15 min at rt followed by neutralizing the reaction mixture with a solid sodium hydrogencarbonate (the Boc group was not cleaved under these conditions). The 3-hydroxy derivatives **41a** and **41b** were transformed into 3-amino compounds **43a** and **43b** in two steps via the 3-mesyloxy and 3-azido derivatives **42a**,**b**. The nucleophilic displacement of the mesyloxy group for azido one proceeded as expected with the inversion of configuration. The reduction of azido compounds to the amino derivatives proceeded smoothly in 86% (**43a**) and 72% (**43b**) by hydrogenation under a Pd/C catalysis. The hydrogenation of the dimethoxytrityl derivative **42b** should be checked thoroughly because of the possibility of DMTr group removal. After observing the complete azido group reduction, the reaction needed to be worked up immediately.

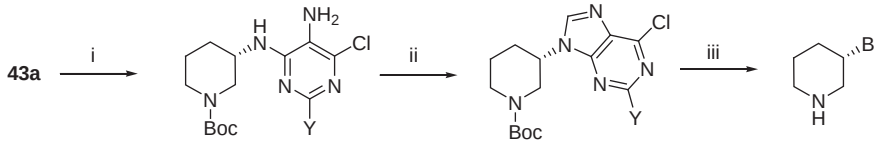
Thymine and uracil nucleobases were constructed on amino moieties of **43a** and **43b** using reagents **15a** and **15b** (Scheme 9). The smooth reaction in dioxane within 15 min resulted in the formation of **44a**–**c**, which were isolated in 80% (**44a**), 98% (**44b**), and 95% (**44c**) yields. The ureido intermediates **45a**–**c** were then cyclized by heating with a Dowex 50 in H^+ form in dioxane at 80 °C for 30 min. Under these conditions, both the Boc and DMTr groups were removed, and the fully deprotected nucleosides **45a**–**c** were obtained at 84% (**45a**, uracil derivative), 75% (**45b**, uracil derivative), and 81% (**46c**, thymine derivative) yields.

Purine nucleobases were constructed on the amino derivative **43a** (Scheme 10). The reaction of **43a** with 4,6-dichloropyrimidines **16** or **17** was carried out in *n*-butanol at 120 °C in a pressure vessel for 3–4 days, providing products **46a** and **46b** in 68% and 72% yields, respectively. The reaction of **46a** and **46b** with diethoxymethyl acetate provided **47a** (68%, 6-chloropurine derivative) and **47b** (72%, 2-amino-6-chloropurine derivative), respectively. Final nucleosides were obtained, after NaOH (guanine derivative) or NH_3 (adenine derivative) treatment followed by the deprotection of the *tert*-butoxycarbonyl group, in 65% (**48a**, adenine derivative) and 68% (**48b**, guanine derivative) yields.



(i) **15a** or **15b**, dioxane, r.t.; (ii) DOWEX 50 H^+, dioxane, 80 °C

Scheme 9.



(i) **17** or **16**, Et_3N, n-butanol, 120 °C, pressure vessel; (ii) 1. diethoxymetylacetate, DMF, 100 °C; (iii) 1. NaOH or NH_3 2. 20 % TFA in DCM, R.T

Scheme 10.

3. Conformation of piperidine derivatives

Protected piperidine derivatives had broad signals in NMR spectra at rt. This is not surprising in the case of Boc-protected compounds because it is well known that the C–N bond in amides has a partially double bond character, and free rotation around this bond is slowed down. The slow interconversion of the C–N rotamers causes the broadening of NMR signals and, therefore, we usually measured the ^1H and ^{13}C NMR spectra of these compounds at elevated temperatures where the rotation around the C–N bond is faster and sharp averaged signals can be observed. The broadening of NMR signals of trityl-protected piperidines was, by contrast, surprising, and a more detailed study had to be carried out to explain this behavior. When samples of compounds **21b**, and **23b** in $CDCl_3$ were heated to 323 K, the signals became narrower, and when they were cooled to 240 K the spectra split into two sets of signals with different integral intensities, corresponding to the piperidine derivatives with the substituent in position 3 in the axial or equatorial positions, respectively. Both forms had a chair conformation, and the axial/equatorial conformers were easily identified from the ^1H coupling patterns. In the equatorial conformer, the hydrogen in position 3 is axial and appears as a multiplet with big coupling constants because of the axial–axial interaction (10.8 Hz) to the H4-axial and H2-axial. The broadening of the signals at rt is caused by the slow interconversion between these two conformers by ring inversion with simultaneous nitrogen inversion. From the ratio between the two conformers of compound **21b** at 240 K we could calculate the free energy difference between them (0.36 kcal/mol), which is very close to the 0.56 kcal/mol difference found between the two conformers of the mesyloxycyclohexane derivative.[59,60] This supports the previous observation that the steric demands of a nitrogen lone pair in piperidine is only slightly lower than that of hydrogen in cyclohexane (Fig. 3).[61]

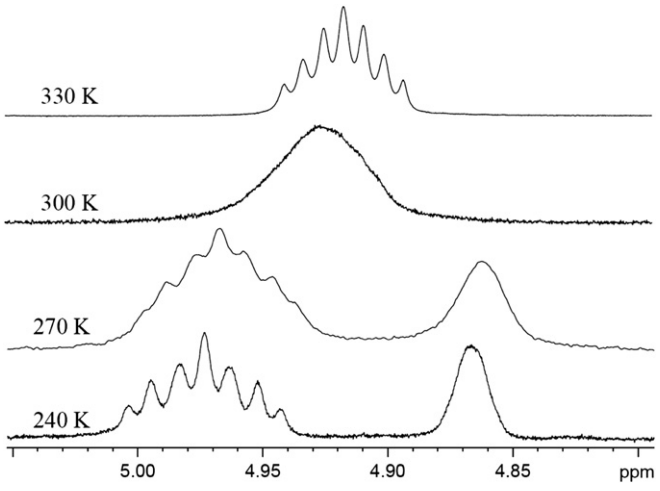


Fig. 3. Temperature dependence of hydrogen H-3 signal of compound **21b**.

The two signals are apparent at low temperatures. The signal in the lower field corresponds to the H-3 axial (triplet of triplets, $J_{3,2ax}=J_{3,4ax}=10.8$, $J_{3,2eq}=J_{3,4eq}=4.4$). At higher temperatures the signals are averaged and H-3 appears as triplet of triplets ($J_{3,2a}=J_{3,4a}=8.1$, $J_{3,2b}=J_{3,4b}=3.8$).

4. Conclusions

Various approaches for the introduction of nucleobases onto the piperidine skeleton were investigated. The nucleobase assembly on primary amine seemed to be the method of choice. Using this method a series of racemic and enantiomeric piperidine analogs of nucleosides was prepared. When comparing two synthetic ways for (thymin-1-yl)piperidine **27a** preparation, the strategy via nucleobase build-up provides **27a** in a 49% overall yield (from 3-hydroxypiperidine, over six steps), whereas via alkylation **27a** it was isolated in a 10% overall yield (from 3-hydroxypiperidine, over four steps). (Uracil-1-yl)piperidine **32** was prepared via nucleobase build-up at a 54% overall yield (over six steps) starting from 3-hydroxypiperidine. Attempts for the direct alkylation of **21a** with uracil failed, when only *O*-derivatives and products of elimination were formed.

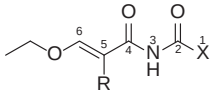
The prepared compounds **27a**–**d**, **28a**,**b**, **32**, **45a**–**c**, and **48a**,**b** offer further possibility for derivatization at the piperidine nitrogen atom, thereby providing the chance to prepare other types of structurally diverse compounds, e.g., phosphonate pyrrolidine nucleotides, and consequently, enlarge the area of potentially biologically active compounds. This makes these compounds interesting, although no significant cytostatic (L1210, HL60, HeLa S3, CCRF-CEM), antibacterial (*Enterococcus faecalis* CCM 4224, *Staphylococcus aureus* CCM 4223, *Escherichia coli* CCM 3954, *Pseudomonas aeruginosa* CCM 3955 *Bacillus subtilis*, *Streptococcus agalactiae*), and antiviral activities (HIV, HCV, RSV) of the prepared compounds were observed.

5. Experimental

5.1. General

Unless stated otherwise, all used solvents were anhydrous. Reagents **15a**,**b** were prepared according to Ref. [51]. The final products were lyophilized from water, and dried over phosphorus pentoxide at 50–70 °C and 13 Pa. TLC was performed on a silica gel pre-coated aluminium plates silica gel/TLC-cards, UV 254 (Fluka), and compounds were detected by UV light (254 nm), by heating (the detection of dimethoxytrityl group; orange color), by spraying with a 1% ethanolic solution of ninhydrin to visualize amines and by spraying with a 1% solution of 4-(4-nitrobenzyl)pyridine in ethanol followed by heating and treating with gaseous ammonia (blue color detection of alkylating agents e.g., mesyl derivatives). Preparative column chromatography was carried out on a silica gel (40–60 μm; Fluka), and elution was performed at the flow rate of 40 ml/min. Analytical RP HPLC was performed on an LC5000 Liquid

Chromatograph (INGOS-PIKRON, CR) using a Luna C18 (2) column (4.6×150 mm) at a flow rate of 1 ml/min by a gradient elution of methanol in 0.1 M TEAB pH 7.5 (*A*=0.1 M TEAB; *B*=0.1 M TEAB in 50% aqueous methanol; C=methanol). Preparative RP HPLC was performed on an LC5000 Liquid Chromatograph (INGOS-PIKRON, CR) using a Luna C18 (2) column (250×21.2 mm) at a flow rate of 10 ml/min by a gradient elution of methanol in 0.1 M TEAB pH 7.5 (*A*=0.1 M TEAB; *B*=0.1 M TEAB in 50% aqueous methanol; C=methanol). All final compounds were lyophilized from water. Melting points were determined on a Stuart SMP model 3 and are uncorrected. Optical rotation values were measured on a polarimeter AUTOPOL IV (Rudolph Research Analytical, USA) for the sodium D line at 20 °C. Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV; glycerol and thioglycerol were used as matrices) and on an LTQ Orbitrap XL (Thermo Fisher Scientific) using ESI ionization. NMR spectra were measured on Bruker AVANCE 400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz), Bruker AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) and/or Bruker AVANCE 600 (^{1}H at 600.1 MHz, ^{13}C at 150.9 MHz) spectrometers. Chemical shifts (in ppm, δ scale) were referenced to TMS as the internal standard; coupling constants (*J*) are given in hertz. The complete assignment of protons and carbons was done by the analysis of correlated homonuclear 2D-COSY and heteronuclear ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. Relative configuration was checked using the DPFGSE-NOE and 2D-ROESY techniques. Nucleobase atom numbering was also used in the case of linear intermediates.



General method A: DIAD (3 mmol) was slowly added to the solution of *N*-protected-3-hydroxypiperidine (1 mmol), PPh_3 (3 mmol), and nucleobase (1 mmol) in 15 ml of refluxing dioxane. This mixture was stirred at 100 °C for 1 h and then concentrated under reduced pressure and purified by flash chromatography on a silica gel.

General method B: Triphenylphosphine (3.0 mmol) was added to the stirred mixture of DIAD (3.0 mmol) in dry THF at 0 °C. After 30 min, nucleobase (1.0 mmol) and *N*-protected-3-hydroxypiperidine in THF was added dropwise to the solution of DIAD and triphenylphosphine. The product was purified by flash chromatography on a silica gel.

General method C: Nucleobase (1.5 mmol) and base (1.5 mmol) were heated at 100 °C in dry DMF/DMSO (15 ml). Mesyl derivative (1 mmol) dissolved in dry DMF/DMSO (10 ml) was then added dropwise and the mixture was heated at 120 °C for 3 h. The solvent was evaporated and product purified on a silica gel using flash chromatography.

General method D: *N*-Boc/*N*-trityl derivative (1.0 mmol) was treated overnight with 20% TFA in DCM (30 ml). The mixture was extracted with water and then the aqueous phase was applied to a column of the Dowex 50 in H^+ form (20 ml). The column was washed with 50% aqueous ethanol (~200 ml) and the product was eluted with 2.5% NH_3 in H_2O (~100 ml). Final purification was performed on preparative RP HPLC.

General method E: Compounds **15a** (1.1 mmol) or **15b** (1.3 mmol) was added to the solution of amine (1 mmol) in dioxane (10 ml/mmol). The reaction mixture was stirred at rt for 30 min. The solvent was then evaporated and the product was purified on a silica gel.

General method F: Dowex 50 in H^+ form (2 g/mmol) was added to the solution of urea derivatives (1 mmol) in dioxane (10 ml/mmol). The reaction mixture was heated to 90 °C for 30 min. Then the mixture was filtered, and the Dowex was subsequently washed with dioxane (~25 ml), ethanol (~25 ml), water (~25 ml), and product was eluted with 2.5% NH_3 in H_2O (~100 ml). The final purification was achieved with RP HPLC.

*5.1.1. (RS)-1-N-tert-Butyloxycarbonyl-3-hydroxypiperidine (**20a**).* 3-Hydroxypiperidine (20.20 g, 0.2 mol) was dissolved in 1 L of H_2O/EtOH (1:1, v/v). Then, $NaHCO_3$ was added (100.80 g, 1.6 mol), stirring at rt, followed by the addition of Boc_2O (52.30 g, 0.24 mol). The reaction was completed in 4.5 h (TLC in 10% EtOH/$CHCl_3$, ninhydrin detection). The mixture was filtered and the filtrate was evaporated. The crude product was then purified by flash chromatography on a silica gel by a linear gradient of ethanol in $CHCl_3$ (0→10%). The product was obtained in a 97% (39.30 g, 0.195 mol) yield as a colorless oil, which crystallized in the fridge (mp=71.2–73.4 °C).

ν_{max} (KBr) 3468 (vs), 2981 (s), 2943 (s), 2864 (s), 1695 (vs), 1670 (vs), 1481 (s), 1472 (s), 1459 (s), 1450 (s), 1432 (vs), 1393 (vs), 1367 (vs), 1259 (vs), 1241 (vs), 1169 (vs), 1154 (vs), 1104 (m), 1073 (vs), 1024 (m), 1003 (w), 460 (w); δ_H ($CDCl_3$, 400.1 MHz) 3.78–3.82 (2H, m, J_{gem} 12.9 Hz, H-2a), 3.68–3.73 (1H, m, H-3), 3.56–3.61 (1H, m, H-6a), 2.98 (2H, dd, J_{gem} 12.9 Hz, $J_{2b\text{-}3}$ 7.9 Hz, H-2b), 2.99–3.06 (1H, m, H-6b), 1.89–1.93 (1H, m, H-4a), 1.72–1.77 (1H, m, H-5a), 1.38–1.54 (11H, m, (CH_3)$_3$, H-4b, H-5b); δ_C ($CDCl_3$, 100.6 MHz) 155.1 (CO), 79.7 (*C*(CH_3)), 66.0 (C-3), 50.5 (C-2), 44.0 (C-6), 32.5 (C-4), 28.4 (CH_3), 22.5 (C-5); HRMS (FAB) $C_{10}H_{20}NO_3$ $(M+H)^+$ calcd 202.1447, found 202.1443.

*5.1.2. (RS)-3-Hydroxy-1-N-tritylpiperidine (**20b**).* 3-Hydroxypiperidine (18.16 g, 0.18 mol) and $NaHCO_3$ (76.00 g, 0.9 mol) were suspended in 1 L of H_2O/dioxane (1:1, v/v). Tritylchloride (60 g, 0.22 mol) in 500 ml of dioxane was added to this stirred mixture at rt. After 2 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on a silica gel by a linear gradient of ethyl acetate in toluene (0→100%). The product was obtained as a light yellow amorphous solid in a 30% yield (20.00 g, 58 mmol).

ν_{max} (KBr) 3571 (w), 3493 (w), 3470 (w), 3082 (w), 3054 (w), 3029 (w), 3019 (w), 2999 (w), 1595 (w), 1580 (w), 1489 (m), 1447 (m), 1447 (m), 1284 (w), 1213 (m), 1157 (w), 1088 (w), 1078 (w), 1072 (w), 1066 (w), 1033 (w), 1001 (w), 934 (w), 908 (w), 846 (vw), 761 (m), 750 (s), 710 (vs), 701 (s), 631 (m), 544 (vw); δ_H (DMSO, 499.8 MHz, 80 °C) 7.39–7.42 (6H, m, H_o–Tr), 7.26–7.30 (6H, m, H_m–Tr), 7.16 (3H, m, H_p–Tr), 3.76–7.79 (1H, m, H-3), 2.88–3.00 (1H, m, H-2b), 2.70 (1H, m, H-6b), 1.83 (1H, m, H-4b), 1.62–1.70 (2H, m, H-5), 1.37 (1H, m, H-6a), 1.27 (1H, m, H-2a), 0.95 (1H, m, H-4a); δ_C (DMSO, 125.7 MHz, 80 °C) 143.1 (C-1′), 129.3 (C-2′), 127.9 (C-3′), 126.3 (C-4′), 77.3 (*C*–Ph_3), 67.1 (C-3), 56.7 (C-2), 48.7 (C-6), 34.3 (C-4), 23.8 (C-5); HRMS (FAB) $C_{24}H_{26}NO$ $(M+H)^+$ calcd 344.201440, found 344.202339.

*5.1.3. (RS)-1-N-tert-Butyloxycarbonyl-3-mesyloxypiperidine (**21a**).* Hydroxypiperidine **20a** (20.10 g, 0.1 mol) and DMAP (61.08 g, 0.5 mol) were co-evaporated with anhydrous dichloromethane (DCM) and suspended in 1 L DCM. The mixture was cooled to 0 °C and mesyl chloride (38 ml, 0.5 mol) was added dropwise under cooling and vigorous stirring. After 2 h TLC (10% EtOH/$CHCl_3$, ninhydrin detection) showed the complete consumption of the starting material. Water (20 ml) was added to the mixture and stirring continued for an additional 10 min. The mixture was extracted with saturated $NaHCO_3$ (3×), and the combined organic phases were dried over anhydrous Na_2SO_4. Sodium sulfate was filtered off and the filtrate was evaporated. The product was purified by flash chromatography on a silica gel using a linear of gradient ethyl acetate in toluene. The product was obtained as a white amorphous solid in a 85% yield (23.90 g, 85.5 mmol).

ν_{max} (KBr) 1693 (vs), 1463 (s), 1428 (s), 1245 (s), 1391 (m), 1365 (s), 1351 (vs), 1179 (vs), 976 (s), 938 (s), 929 (s), 904 (s), 543 (s), 524

(s); δ_H (DMSO, 499.8 MHz, 50 °C) 4.70 (1H, m, H-3), 3.60–3.64 (2H, m, H-2), 3.42 (1H, ddd, J_{gem} 13.4 Hz, $J_{6b\text{-}5}$ 7.2 and 3.9 Hz, H-6b), 3.34 (1H, ddd, J_{gem} 13.4 Hz, $J_{6a\text{-}5}$ 7.6 and 3.8 Hz, H-6a), 3.03 (3H, s, CH_3SO_2), 1.97 (1H, m, H-4b), 1.89 (1H, m, H-4a), 1.82 (1H, m, H-5b), 1.54 (1H, m, H-5a), 1.46 (9H, s, $C(CH_3)_3$)); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 154.7 (COO), 80.1 ($C(CH_3)_3$), 75.3 (C-3), 47.9 (C-2), 43.5 (C-6), 38.8 (SO_2CH_3), 30.5 (C-4), 28.3 ($C(CH_3)_3$), 21.7 (C-5); HRMS (FAB) $C_{11}H_{22}NO_5S$ $(M+H)^+$ calcd 280.1212, found 280.1223.

*5.1.4. (RS)-3-Mesyloxy-1-N-tritylpiperidine (**21b**).* Piperidine derivative **20b** (16.61 g, 48 mmol) and DMAP (29.32 g, 0.241 mmol) were co-evaporated with anhydrous DCM and suspended in 1 L DCM. The mixture was cooled to 0 °C and mesyl chloride (18.5 ml, 0.241 mmol) was added dropwise under cooling and vigorous stirring. After 2 h TLC showed the complete consumption of the starting material. Water (20 ml) was added to the mixture a stirring continued for 10 min. The mixture was extracted with saturated $NaHCO_3$ (3×), and the combined organic phases were dried over Na_2SO_4. Sodium sulfate was filtered and the filtrate was evaporated. The product was purified by flash chromatography on a silica gel using a linear gradient of ethyl acetate in toluene. The product was obtained as a light yellow foam in a 94% yield (18.90 g, 43.6 mmol).

ν_{max} (KBr) 3082 (m), 3066 (m), 3029 (m), 3019 (m), 2990 (m), 2946 (m), 2921 (m), 2850 (m), 1596 (m), 1583 (w), 1488 (s), 1448 (s), 1419 (w), 1352 (vs), 1330(s), 1316 (m), 1213 (m), 1173 (vs), 1159 (s), 1115 (m), 1086 (w), 1033 (m), 1003 (m), 982 (vs), 951 (vs), 938 (s), 909 (s), 840 (m), 775 (m), 762 (s), 744 (s), 708 (vs), 698 (vs), 641 (m), 629 (m), 539 (s), 523 (s); δ_H (DMSO, 499.8 MHz, 50 °C) 7.46 (6H, m, H_o–Tr), 7.25 (6H, m, H_m–Tr), 7.14 (3H, m, H_p–Tr), 4.92 (1H, m, H-3), 2.94 (3H, m, CH_3SO_2), 2.90 (1H, br s, H-2a), 2.50 (1H, br s, H-6a), 2.1 (1H, br s, H-5a), 1.69–2.04 (4H, m, H-2b, H-6b, H-5b, H-5a), 1.56 (1H, m, H-4b); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 142.3 (*C*–Tr), 129.2 (CH_o–Tr), 127.6 (CH_m–Tr), 126.2 (CH_p–Tr), 78.2 (C-3), 77.3 ($C(Ph)_3$), 53.4 (C-2), 48.2 (C-6), 38.6 (CH_3–Ms), 31.3 (C-4), 23.1 (C-5); HRMS (FAB) $C_{25}H_{28}NO_3S$ $(M+H)^+$ calcd 422.1790, found 422.1768.

*5.1.5. (RS)-1-N-tert-Butyloxycarbonyl-3-(thymin-1-yl)piperidine (**22a**).* Thymine derivative **22a** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), thymine (339 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO, according to general procedure C in a 16% yield (88 mg, 0.284 mmol) as a white foam.

ν_{max} (KBr) 3167 (w), 2979 (w), 1701 (s), 1684 (vs), 1651 (m), 1519 (vw), 1470 (w), 1430 (m), 1422 (m), 1391 (w), 1366 (w), 1313 (w), 1274 (m), 1259 (w), 1244 (m), 1155 (m), 862 (w), 758 (w), 466 (vw); δ_H (DMSO, 499.8 MHz) 11.24 (1H, s, NH-3′), 7.57 (1H, s, H-6′), 4.18 (1H, m, H-3), 3.85 (2H, m, H-2a, H-6a), 2.90 (1H, br s, H-2b), 2.66 (1H, m, H-6b), 1.75 (6H, m, H-4a, H-4b, H-5a, CH_3), 1.40 (1H, m, H-5b), 1.36 (9H, s, $(CH_3)_3$); δ_c (DMSO, 125.7 MHz) 163.8 (C-4′), 154.0 (*C*=O), 150.9 (C-2′), 137.7 (C-6′), 109.1 (C-5′), 79.2 ($C(CH_3)_3$), 50.9 (C-3), 46.5 (C-2), 43.2 (C-6), 28.2 (C-4), 28.1 ($C(CH_3)_3$), 24.5 (C-5), 12.2 (CH_3); HRMS (ESI) $C_{15}H_{24}O_4N_3$ $(M+H)^+$ calcd 310.1761, found 310.1760.

*5.1.6. (RS)-1-N-tert-Butyloxycarbonyl-3-(cytosin-2-O-yl)piperidine (**22b**).* Cytosine *O*-derivative **22c** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), cytosine (297 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO, according to general procedure C in a 29% yield (150 mg, 0.519 mmol) as a white amorphous solid.

ν_{max} (KBr) 3390 (m), 3330 (m), 3244 (w, sh), 3180 (m, br), 3005 (w), 2971 (m), 1678 (s), 1644 (s), 1592 (s), 1559 (s),1479 (m), 1462 (m), 1428 (s), 1407 (vs), 1365 (s), 1340 (m), 1280 (m), 1256 (m), 1241 (m), 1173 (m), 1146 (s), 1094 (m), 1075 (w), 859 (w), 811 (w), 769 (w); δ_H (DMSO, 600.1 MHz) 7.86 (1H, d, $J_{6'\text{-}5'}$ 6.2 Hz, H-6′), 7.46 (2H, br s, NH_2), 6.14 (1H, d, $J_{5'\text{-}6'}$ 6.2 Hz, H-5′), 4.85 (1H, br s, H-3), 3.95 (1H, br s, H-2b), 3.63 (1H, br s, H-6b), 3.25 (1H, m, H-2a), 3.00 (1H, m, H-6a), 1.77–1.82 (2H, br s, H-4a, H-4b), 1.68 (1H, m, H-5b), 1.10–1.46 (10H, m, H-5a, CH_3); δ_c (DMSO, 150.9 MHz) 165.8 (C-4′), 162.0 (C-2′), 154.2 (C=O), 152.2 (C-6′), 99.7 (C-5′), 78.6 ($C(CH_3)_3$), 70.1 (C-3), 46.5 (C-2), 43.1 (C-6), 28.7 (C-4), 28.0 (CH_3), 20.7 (C-5); HRMS (ESI) $C_{14}H_{23}O_3N_4$ $(M+H)^+$ calcd 295.1765, found 295.1765.

*5.1.7. (RS)-1-N-tert-Butyloxycarbonyl-3-(cytosin-1-yl)piperidine (**22c**).* Nucleoside derivative **22c** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), cytosine (297 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 18% yield (94 mg, 0.322 mmol) as a white amorphous solid.

ν_{max} ($CHCl_3$) 3392 (vs), 3212 (s), 2980 (m), 2954 (m), 2934 (m), 2865 (m), 1673 (vs), 1656 (vs), 1602 (s), 1532 (m), 1500 (s), 1480 (m), 1455 (m), 1429 (m), 1410 (m), 1394 (m), 1369 (m), 1349 (m), 1271 (s), 1247 (s), 1155 (m), 860 (w); δ_H (DMSO, 499.8 MHz, 80 °C) 7.59 (1H, d, $J_{6'\text{-}5'}$ 7.4 Hz, H-6′), 6.84 (2H, br s, NH_2), 5.72 m (1H, d, $J_{5'\text{-}6'}$ 7.4 Hz, H-5′), 4.32 (1H, m, H-3), 3.86–3.92 (2H, m, H-2b, H-6b), 2.89 (1H, m, H-2a), 2.73 (1H, m, H-6a), 1.73–1.82 (3H, m, H-4a, H-4b, H-5b), 1.46 (1H, m, H-5a), 1.41 (9H, s, H-3, $(CH_3)_3$); δ_c (DMSO, 125.7 MHz, 80 °C) 165.1 (C-4′), 155.2 (C-2′), 153.8 (C=O), 142.0 (C-6′), 93.4 (C-5′), 78.9 ($C(CH_3)_3$), 51.4 (C-3), 47.0 (C-2), 43.1 (C-6), 28.3 (C-4), 27.9 (CH_3), 24.17 (C-5); HRMS (ESI) $C_{12}H_{22}O_3N_4Na$ $(M+Na)^+$ calcd 317.1584, found 317.1584.

*5.1.8. (RS)-3-(Adenin-9-yl)-1-N-tert-butyloxycarbonylpiperidine (**22d**).* Nucleoside derivative **22d** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), adenine (362 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 18% yield (102 mg, 0.322 mmol) as a white amorphous solid.

ν_{max} ($CHCl_3$) 3526 (w), 3414 (w), 2981 (m), 2957 (m), 2930 (m), 2866 (w), 1688 (s), 1630 (vs), 1587 (m), 1575 (w), 1507 (w), 1471 (m), 1456 (m), 1425 (m), 1416 (m), 1394 (m), 1368 (m), 1346 (w), 1328 (w), 1300 (w), 1268 (m), 1245 (s), 1162 (m), 1151 (m), 860 (w), 649 (w); δ_H (DMSO, 499.8 MHz) 8.21 (1H, s, H-8′), 8.14 (1H, s, H-2′), 7.23 (2H, br s, NH_2), 4.39 (1H, m, H-3), 4.10 (1H, vbr s, H-2a), 3.89 (1H, br m, H-6a), 2.94 (1H, vbr s, H-2b), 2.20 (1H, m, H-4a), 2.07 (1H, m, H-4b), 1.77 (1H, m, H-5a), 1.53 (1H, m, H-5b), 1.36 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz) 156.2 (C-6′), 153.9 (C=O), 152.5 (C-2′), 149.4 (C-4′), 139.1 (C-8′), 119.0 (C-5′), 79.3 ($C(CH_3)_3$), 50.7 (C-3), 47.7 (C-2), 43.5 (C-6), 29.2 (C-4), 28.1 ($C(CH_3)_3$), 23.9 (C-5); HRMS (ESI) $C_{15}H_{23}O_2N_6$ $(M+H)^+$ calcd 319.1877, found 319.1877.

*5.1.9. (RS)-3-(6-Chloropurin-9-yl)-1-N-tritylpiperidine (**23a**).* 6-Chloropurine derivative **23a** was prepared from hydroxy derivative **20b** (343 mg, 1 mmol), 6-chloropurine (154 mg, 1 mmol), DIAD (0.59 ml, 3 mmol), and PPh_3 (786 mg, 3 mmol) according to general procedure B (THF) in a 25% yield (84 mg, 0.25 mmol) as a light yellow foam.

ν_{max} (KBr) 3285 (s), 3251 (s), 3085 (vw), 3056 (w), 3033 (m), 1738 (vs), 1691 (vs), 1591 (m), 1558 (m), 1526 (s), 1490 (m), 1448 (m), 1438 (w), 1336 (m), 1314 (m), 1219 (m), 1146 (m), 1086 (w), 1035 (m), 1004 (w), 936 (w), 902 (w), 793 (w), 763 (m), 747 (m), 710 (m), 700 (w), 649 (w), 636 (m); δ_H ($CDCl_3$, 499.9 MHz, 320 K) 8.70 (1H, s, H-2′), 8.09 (1H, br s, H-8′), 7.12–7.48 (15H, m, C–H–Tr), 5.09 (1H, m, H-3); 3.40 (1H, m, $H\text{-}2_{eq}$); 3.06 (1H, m, $H\text{-}6_{eq}$); 2.26 (1H, m, $H\text{-}4_{eq}$); 2.05 (1H, m, $H\text{-}5_{ax}$); 1.94 (1H, m, $H\text{-}5_{eq}$); 1.57–1.88 (3H, m, $H\text{-}2_{ax}$, $H\text{-}4_{ax}$, $H\text{-}6_{ax}$); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 152.3 (C-4′), 151.9 (C-2′), 151.0 (C-6′), 145.6 (C-8′), 144.6 (*C*–trityl), 131.6 (C-5′), 129.0 (C_o–trityl), 127.6 (C_m–trityl), 126.3 (C_p–trityl), 77.4 (*C*–Ph_3), 54.2 (C-2), 53.2 (C-3), 48.4 (C-6), 30.4 (C-4), 24.6 (C-5); HRMS (ESI) $C_{29}H_{27}N_5Cl$ $(M+H)^+$ calcd 480.1950, found 480.1950.

*5.1.10. (RS)-3-(2-Amino-6-chloropurin-9-yl)-1-N-tritylpiperidine (**23b**).* 2-Amino-6-chloropurine derivative **23b** was prepared from hydroxy derivative **20b** (343 mg, 1.0 mmol), 6-chloro-2-aminopurine (169 mg, 1.0 mmol), DIAD (0.59 ml, 3 mmol), and PPh_3

(786 mg, 3 mmol) according to general procedure B (in THF) in a 27% yield (95 mg, 0.27 mmol) as a light yellow foam.

ν_{max} (KBr) 3492 (vs), 3440 (vs), 3082 (vw), 3056 (w), 3030 (vw), 3020 (vw), 2939 (w), 2862 (vw), 1611 (vs), 1563 (s), 1506 (m), 1490(m), 1457 (m), 1449 (m), 1440 (w), 1403 (w), 1287 (w), 1213 (m), 1185 (w), 1112 (vw), 1086 (w), 1032 (w), 1003 (w), 937 (vw), 910 (m), 848 (vw), 786 (w), 776 (w), 745 (m), 710 (s), 699 (m), 639 (m), 632 (m); δ_H ($CDCl_3$, 499.9 MHz, 320 K) 7.67 (1H, s, H-8′), 7.02–7.47 (15H, m, C–H–Tr), 5.52 (2H, br s, NH_2), 4.85 (1H, m, H-3), 3.56 (1H, dm, J_{gem} 10.5 Hz, H-2_{eq}), 3.23 (1H, dm, J_{gem} 11.4 Hz, H-6_{eq}), 2.24 (1H, dm, J_{gem} 11.3 Hz, H-4_{eq}), 2.04 (1H, m, H-5_{ax}), 1.86 (1H, dm, J_{gem} 12.8 Hz, H-5_{eq}), 1.62 (1H, qd, J_{gem}=$J_{4ax\text{-}3}$=$J_{4ax\text{-}5ax}$ 11.3 Hz, H-4_{ax}), 1.51 (1H, t, $J_{2ax\text{-}3}$=J_{gem} 10.7 Hz, H-2_{ax}), 1.42 (1H, t, $J_{6ax\text{-}5ax}$=J_{gem} 12.0 Hz, H-6_{ax}); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 158.93 (C-2′), 153.73 (C-4′), 151.23 (C-6′), 144.85 (*C*–trityl), 142.05 (C-8′), 129.15 (C_o–trityl), 127.58 (C_m–trityl), 126.23 (C_p–trityl), 125.48 (C-5′), 77.45 (*C*–Ph_3), 53.92 (C-2), 52.68 (C-3), 48.46 (C-6), 30.16 (C-4), 24.66 (C-5); HRMS (ESI) $C_{29}H_{28}N_6Cl$ $(M+H)^+$ calcd 495.2058, found 495.2058.

*5.1.11. (RS)-3-(Adenin-9-yl)-1-N-tritylpiperidine (**23c**) and 2-(adenin-9-yl)methyl-1-N-tritylpyrrolidine (**24a**).* Adenine derivatives **23c** and **24a** were prepared from **21b** (753 mg, 1.79 mmol), adenine (362 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMF (25 ml) according to general procedure C in a 35% yield (410 mg, 0.895 mmol) as a light yellow foam (mixture of **23a** and **24a**).

NMR data for **23c**: δ_H ($CDCl_3$, 499.9 MHz, 320 K): 8.34 (1H, br s, H-2′), 7.77 (1H, br s, H-8′), 7.44 (6H, m, H_o–Tr), 7.22 (6H, m, H_m–Tr), 7.14 (3H, m, H_p–Tr), 5.61 (2H, br s, NH_2), 5.00 (1H, m, H-3), 3.34 (1H, br m, H-2_{eq}), 3.05 (1H, br m, H-6_{eq}), 2.24 (1H, br m, H-4_{eq}), 2.03 (1H, br m, H-5_{ax}), 1.91 (1H, br m, H-5_{eq}), 1.64–1.87 (3H, br m, H-2_{ax}, H-4_{ax}, H-6_{ax}); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 155.3 (C-6′), 152.8 (C-2′), 150.1 (C-4′), 144.9 (C_i–trityl), 141.0 (C-8′), 129.1 (C_o–trityl), 127.6 (C_m–trityl), 126.2 (C_p–trityl), 119.7 (C-5′), 77.4 (*C*–Ph_3), 54.3 (C-2), 52.3 (C-3), 48.5 (C-6), 30.7 (C-4), 24.7 (C-5).

NMR data for **24a**: δ_H ($CDCl_3$, 499.9 MHz, 320 K) 8.32 (1H, br s, H-2′), 7.73 (1H, br s, H-8′), 7.52 (6H, m, H_o–Tr), 7.22 (6H, m, H_m–Tr), 7.16 (3H, m, H_p–Tr), 5.62 (2H, br s, NH_2), 4.29 (1H, dd, J_{gem} 13.9 Hz, J_{vic} 5.4 Hz, C$H_a$$H_b$N), 4.26 (1H, dd, J_{gem} 13.9 Hz, J_{vic} 7.0 Hz, CH$_a$$H_b$N), 3.78 (1H, m, H-2), 3.18 (1H, ddd, J_{gem} 12.5 Hz, $J_{5a,3}$ 8.5, 6.9 Hz, H-5a), 2.97 (1H, ddd, J_{gem} 12.5 Hz, $J_{5b,4}$ 8.7 , 5.1 Hz, H-5b), 1.36 (1H, m, H-4a), 1.26 (1H, m, H-3a), 0.84 (1H, m, H-3b), 0.73 (1H, m, H-4b); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 155.3 (C-6′), 153.0 (C-2′), 150.7 (C-4′), 144.9 (C_i–trityl), 141.0 (C-8′), 129.6 (C_o–trityl), 127.6 (C_m–trityl), 126.3 (C_p–trityl), 119.4 (C-5′), 77.9 (*C*–Ph_3), 61.4 (C-2), 50.0 (C-5), 48.2 (CH_2N), 28.7 (C-3), 23.7 (C-4); HRMS (ESI) $C_{29}H_{29}N_6$ $(M+H)^+$ calcd 461.2448, found 461.2449.

*5.1.12. (RS)-3-(Cytosin-2-O-yl)-1-N-tritylpiperidine (**23d**) and 2-(cytosin-2-O-yl)methyl-1-N-tritylpyrrolidine (**24c**).* Cytosine derivatives **23d** and **24c** were prepared from mesyl derivative **21b** (753 mg, 1.79 mmol), cytosine (297 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 28% yield (218 mg, 0.501 mmol) as a white foam (mixture of **23d** and **24c**).

NMR data for **23d**: δ_H ($CDCl_3$, 499.9 MHz, 320 K) 7.89 (1H, d, $J_{6',5'}$ 5.7 Hz, H-6′), 7.48 (6H, m, H_o–Tr), 7.20 (6H, m, H_m–Tr), 7.08 (3H, m, H_p–Tr), 5.93 (1H, d, $J_{5',6'}$ 5.7 Hz, H-5′), 5.22 (1H, m, H-3), 5.04 (1H, br s, NH_2), 3.28 (1H, br m, H-2_{eq}), 2.90 (1H, br m, H-6_{eq}), 1.50–2.10 (6H, br m, H-2_{ax}, H-5, H-4, H-6_{ax}); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 164.8 (C-2′), 164.6 (C-4′), 157.1 (C-6′), 145.2 (C_i–trityl), 129.1 (C_o–trityl), 127.1 (C_m–trityl), 125.7 (C_p–trityl), 98.9 (C-5′), 77.1 (*C*–Ph_3), 72.2 (C-2), 52.4 (C-3), 48.5 (C-6), 30.1 (C-4), 23.4 (C-5).

NMR data for **24c**: δ_H ($CDCl_3$, 499.9 MHz, 320 K) 7.90 (1H, d, $J_{6',5'}$ 5.7 Hz, H-6′), 7.60 (6H, m, H_o–Tr), 7.20 (6H, m, H_m–Tr), 7.10 (3H, m, H_p–Tr), 5.94 (1H, d, $J_{5',6'}$ 5.7 Hz, H-5′), 5.01 (1H, br s, NH_2), 4.57(1H, dd, J_{gem} 10.1 Hz, J_{vic} 4.3 Hz, C$H_a$$H_b$O), 3.16 (1H, t, J_{gem}=J_{vic} 10.1 Hz, CH$_a$$H_b$O), 3.72 (1H, m, H-2), 3.28 (1H, ddd, J_{gem} 12.4 Hz, $J_{5a,3}$ 8.5 , 6.4 Hz, H-5a), 2.97 (1H, ddd, J_{gem} 12.4 Hz, $J_{5b,4}$ 8.5 , 5.0 Hz, H-5b), 1.50 (1H, m, H-3a), 1.45 (1H, m, H-4a), 0.75 (2H, m, H-3b, H-4b); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 165.1 (C-2′), 164.7 (C-4′), 157.0 (C-6′), 145.2 (C_i–trityl), 129.4 (C_o–trityl), 127.3 (C_m–trityl), 125.8 (C_p–trityl), 99.0 (C-5′), 77.58 (*C*–Ph_3), 68.8 (CH_2O), 59.1 (C-2), 49.8 (C-5), 27.7 (C-3), 23.7 (C-4); HRMS (ESI) $C_{28}H_{29}N_4O$ $(M+H)^+$ calcd 437.2335, found 437.2339.

*5.1.13. (RS)-3-(Thymin-1-yl)-1-N-tritylpiperidine (**23e**) and 2-(thymin-1-yl)methyl-1-N-tritylpyrrolidine (**24b**).* Thymine derivatives **23e** and **24b** were prepared from mesyl derivative **21b** (753 mg, 1.79 mmol), thymine (339 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 27% yield (217 mg, 0.482 mmol) as a white foam (mixture of **23e** and **24b**).

NMR data for **23e**: δ_H ($CDCl_3$, 499.9 MHz, 320 K) 9.60 (1H, br s, N3′-H), 7.46 (6H, m, H_o–Tr), 7.25 (6H, m, H_m–Tr) 7.12 (3H, m, H_p–Tr), 6.83 (1H, br s, H-6′), 4.98 (1H, m, H-3), 3.28 (1H, m, H-2_{eq}), 3.11 (1H, m, H-6_{eq}), 1.95 (1H, m, H-5_{ax}), 1.94 (1H, m, H-4_{eq}), 1.79 (3H, d, ^4J 1.0 Hz, CH_3), 1.76 (1H, m, H-5_{eq}), 1.44 (1H, m, H-2_{ax}), 1.39 (1H, m, H-6_{ax}), 1.30 (1H, m, H-4_{ax}); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 163.6 (C-4′), 150.9 (C-2′), 144.8 (C_i–trityl), 136.2 (C-6′), 129.0 (C_o–trityl), 127.5 (C_m–trityl), 126.0 (C_p–trityl), 110.1 (C-5′), 77.3 (*C*–Ph_3), 53.1 (C-2), 52.5 (C-3), 48.2 (C-6), 29.4 (C-4), 24.6 (C-5), 12.2 (CH_3).

NMR data for **24b**: δ_H ($CDCl_3$, 499.9 MHz, 320 K) 9.60 (1H, br s, N3′-H), 7.52 (6H, m, H_o–Tr), 7.21 (6H, m, H_m–Tr) 7.14 (3H, m, H_p–Tr), 6.73 (1H, q, ^4J 1.1 Hz, H-6′), 3.93 (1H, dd, J_{gem} 13.5 Hz, J_{vic} 8.2 Hz, CH_aH$_b$N), 3.64 (1H, dd, J_{gem} 13.5 Hz, J_{vic} 8.8 Hz, CH$_a$$H_b$N), 3.66 (1H, m, H-2), 3.26 (1H, ddd, J_{gem} 12.5 Hz, $J_{5a,3}$ 8.8 , 5.8 Hz, H-5a), 2.97 (1H, ddd, J_{gem} 12.5 Hz, $J_{5b,4}$ 8.3 , 5.8 Hz, H-5b), 1.87 (3H, d, ^4J 1.1 Hz, CH_3), 1.50 (1H, m, H-3a), 1.26 (1H, m, H-4a), 0.82 (2H, m, H-3b, H-4b); δ_C ($CDCl_3$, 125.7 MHz, 320 K) 164.2 (C-4′), 151.3 (C-2′), 144.8 (C_i–trityl), 140.7 (C-6′), 129.4 (C_o–trityl), 127.5 (C_m–trityl), 126.2 (C_p–trityl), 110.3 (C-5′), 77.5 (*C*–Ph_3), 60.3 (C-2), 51.0 (CH_2N), 49.5 (C-5), 27.9 (C-3), 23.7 (C-4), 12.0 (CH_3); HRMS (ESI) $C_{29}H_{28}O_2N_3$ Na $(M+Na)^+$ calcd 474.2152, found 474.2150.

*5.1.14. 1-N-tert-Butyloxycarbonyl-1,2,3,6-tetrahydropyridine (**25a**).* Tetrahydropyridine derivative **25a** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), thymine (339 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 23% yield (75 mg, 0.009 mmol) as a white amorphous solid.

ν_{max} (KBr) 3072 (vw), 3039 (w), 2981 (s), 2930 (s), 2845 (m), 1686 (vs), 1654 (s), 1477 (m), 1467 (m), 1451 (s), 1425 (vs), 1391 (s), 1367 (s), 1340 (m), 1285 (s), 1250 (s), 1244 (s), 1171 (vs), 1150 (s), 859 (w), 701 (w); δ_H ($CDCl_3$, 500.0 MHz) 5.82 (1H, m, H-4), 5.64 (1H, m, H-3), 3.87 (2H, m, H-2), 3.48 (2H, br t, H-6), 2.13 (2H, m, H-5), 1.47 (9H, s, $(CH_3)_3$); δ_C ($CDCl_3$, 125.7 MHz) 154.9 (C=O), 125.1 (C-4), 124.3 (C-3), 79.3 (*C*–$(CH_3)_3$), 43.3 (br s, C-2), 40.8 and 39.3 (C-6), 28.4 (CH_3), 25.0 (C-5); HRMS (FAB) $C_{24}H_{23}N$ $(M+H)^+$ calcd 326.1909, found 326.1901.

*5.1.15. 1-N-Trityl-1,2,3,6-tetrahydropyridine (**25b**).* Tetrahydropyridine derivative **25a** was prepared from hydroxy derivative **20b** (343 mg, 1 mmol), 6-chloropurine (154 mg, 1 mmol), DIAD (0.59 ml, 3 mmol), and PPh_3 (786 mg, 3 mmol) according to general procedure B (THF) in a 32% yield (104 mg, 0.32 mmol) as a light yellow foam.

ν_{max} (KBr) 3082 (w), 3056 (w), 3028 (w), 1655 (w), 1596 (w), 1488 (m), 1466 (w), 1448 (m), 1439 (w), 1319 (w), 1213 (w), 1177 (w), 1159 (vw), 1082 (w), 1033 (w), 999 (w), 936 (w), 902 (w), 843 (w), 773 (w), 751 (m), 744 (s), 710 (vs), 699 (m), 642 (w), 629 (s); δ_H ($CDCl_3$, 600.1 MHz) 7.49 (6H, m, H_o–Tr), 7.22 (6H, m, H_m–Tr) 7.11 (3H, m, H_p–Tr), 5.68 (1H, m, H-4), 5.62 (1H, m, H-3), 2.83 (2H, m, H-2), 2.34 (2H, br s, H-6), 2.23 (2H, br s, H-5); δ_C ($CDCl_3$, 150.9 MHz) 142.6 (*C*–trityl), 129.2 (C_o–trityl), 127.3 (C_m–trityl), 126.5 (C-3), 125.8

(C_p—trityl), 124.9 (C-4), 77.0 (*C*—Ph_3), 47.0 (C-2), 45.5 (C-6), 27.2 (C-5); HRMS (FAB) $C_{24}H_{23}N$ $(M+H)^+$ calcd 326.1909, found 326.1901.

*5.1.16. 1-N-tert-Butyloxycarbonyl-1,2,3,4-tetrahydropyridine (**26a**).* Tetrahydropyridine derivative **26a** was prepared from mesyl derivative **21a** (500 mg, 1.79 mmol), thymine (339 mg, 2.68 mmol), and Cs_2CO_3 (873 mg, 2.68 mmol) in DMSO according to general procedure C in a 28% yield (92 mg, 0.28 mmol) as a white amorphous solid. All spectral data recorded were in accordance with the literature data.[62]

*5.1.17. (RS)-3-(Thymin-1-yl)piperidine (**27a**).* Nucleoside **27a** was prepared according to general method F from ureido derivative **31b** (355 mg, 1 mmol) in a 80% yield (167 mg, 0.8 mmol) as a white amorphous solid.

ν_{max} (KBr) 3424 (m), 3301 (w), 3194 (w), 3059 (w), 1687 (vs), 1468 (m), 1445 (m), 1389 (w), 1337 (w), 1260 (m), 1116 (w), 1101 (w), 888 (w), 811 (w), 765 (w); δ_H (DMSO, 600.1 MHz) 7.63 (1H,q, $J_{6'\text{-}CH3}$ 1.2 Hz, H-6′), 4.26 (1H, m, H-3), 2.82 (2H, m, H-2b, H-6b), 2.60 (1H, t, J_{gem}=$J_{2a\text{-}3}$ 10.2 Hz, H-2a), 2.38 (1H, m, H-6a), 1.76 (3H, d, $J_{CH3\text{-}6'}$ 1.2 Hz, CH_3), 1.65–1.76 (3H, m, H-4a, H-4b, H-5b), 1.45 (1H, m, H-5a); δ_C (DMSO, 150.9 MHz) 163.9 (C-4′), 151.1 (C-2′), 138.1 (C-6′), 108.8 (C-5′), 52.2 (C-3), 49.9 (C-2), 45.3 (C-6), 29.3 (C-4), 26.5 (C-5), 12.3 (CH_3); HRMS (ESI) $C_{10}H_{16}O_2N_3$ $(M+H)^+$ calcd 210.1237, found 210.1238.

*5.1.18. (RS)-3-(Cytosin-1-yl)piperidine (**27b**).* Nucleoside **27b** was prepared according to general method D from cytosine derivative **22c** (294 mg, 1 mmol) in a 87% yield (168 mg, 0.87 mmol) as a white amorphous solid.

ν_{max} (KBr) 3420 (s), 3197 (m), 2947 (w), 2864 (vw), 1646 (vs), 1612 (s), 1574 (m), 1525 (m), 1489 (s), 1455 (m), 1399 (m), 1375 (m), 1331 (w), 1282 (m), 786 (m); δ_H (DMSO, 500.0 MHz) 7.66 (1H, bd, $J_{6'\text{-}5'}$ 6.8 Hz, H-6′), 7.04 (1H, br s) and 7.14, (1H, br s, NH_2), 5.70 (1H, bd, $J_{5'\text{-}6'}$ 7.2 Hz, H-5′), 4.57 (1H, m, H-3), 3.03–3.13 (2H, m, H-2b, H-6b), 2.85 (1H, m, H-2a), 2.62 (1H, m, H-6a), 1.74–1.85 (3H, m, H-4a, H-4b, H-5b), 1.52 (1H, m, H-5a); δ_C (DMSO, 125.7 MHz) 165.3 (C-4′), 155.5 (C-2′), 142.5 (C-6′), 94.0 (C-5′), 50.6 (C-3), 47.3 (C-2), 43.8 (C-6), 28.1 (C-4), 23.5 (C-5); HRMS (ESI) $C_9H_{15}ON_4$ $(M+H)^+$ calcd 195.1240, found 195.1240.

*5.1.19. (RS)-3-(Adenin-9-yl)piperidine (**27c**).* Nucleoside **27c** was prepared according to general method D from adenine derivative **22d** (318 mg, 1 mmol) in a 72% yield (156 mg, 0.72 mmol) as a white amorphous solid.

ν_{max} (KBr) 3504 (m), 3395 (m), 3313 (s), 3298 (s), 3260 (s), 3137 (s), 1657 (vs), 1642 (vs), 1634 (vs), 1598 (vs), 1571 (s), 1474 (s), 1449 (m), 1413 (m), 1327 (m), 1302 (m), 1205 (m), 1112 (m), 884 (w), 820 (w), 798 (m), 721 (m), 647 (m); δ_H (DMSO, 600.1 MHz) 8.27 (1H, s, H-8′), 8.13 (1H, s, H-2′), 7.22 (2H, br s, NH_2), 4.38 (1H, m, H-3), 3.10 (1H, dd, J_{gem} 11.6 Hz, $J_{2b\text{-}3}$ 4.3 Hz, H-2b), 2.89 (2H, m, H-2a, H-6b), 2.51 (1H, ddd, J_{gem} 12.0 Hz, $J_{6a\text{-}5a}$ 11.8 Hz, $J_{6a\text{-}5b}$ 2.8 Hz, H-6a), 2.04 (2H, m, H-4), 1.70 (1H, m, H-5b), 1.53 (1H, m, H-5a); δ_C (DMSO, 150.9 MHz) 156.2 (C-6′), 152.4 (C-2′), 149.4 (C-4′), 139.3 (C-8′), 119.0 (C-5′), 52.1 (C-3), 51.2 (C-2), 45.5 (C-6), 30.6 (C-4), 25.9 (C-5); HRMS (ESI) $C_{10}H_{15}N_6$ $(M+H)^+$ calcd 219.1353, found 219.1353.

*5.1.20. (RS)-3-(Guanin-9-yl)piperidine (**27d**).* Nucleoside **34b** (500 mg, 1.42 mmol) was treated with 1 M NaOH in 30% aqueous dioxane for 2 days. The reaction was treated with a Dowex 50 in trimethylammonium form. The Dowex was filtered and the filtrate evaporated to give a crude guanine derivative, which was then treated according to general procedure D and finally purified by reversed phase HPLC. The product was obtained in a 64% yield (203 mg, 0.87 mmol) as a white amorphous solid.

ν_{max} (KBr) 3413 (vs), 2974 (s), 2931 (m), 1687 (m), 1627 (m), 1577 (w), 1533 (w), 1475 (w), 1456 (w), 1450 (w), 1377 (w), 1089 (m), 1050 (s), 782 (w); δ_H (DMSO, 500.0 MHz) 10.4 (1H, vbr s, NH), 7.82 (1H, br s, H-8′), 6.46 (2H, br s, NH_2), 4.18 (1H, m, H-3), 3.10 (1H, dm, J_{gem} 11.8 Hz, H-2b), 2.90 (1H, dm, J_{gem} 12.2 Hz, H-6b), 2.83 (1H, dd, J_{gem} 11.8 Hz, $J_{2a\text{-}3}$ 9.9 Hz, H-2a), 2.52 (1H, td, J_{gem}=$J_{6a\text{-}5a}$ 11.9 Hz, $J_{6a\text{-}5b}$ 2.8 Hz, H-6a), 1.98 (1H, m, H-4b), 1.89 (1H, m, H-4a), 1.72 (1H, dm, J_{gem} 13.4 Hz, H-5b), 1.50 (1H, m, H-5a); δ_C (DMSO, 125.7 MHz) 157.0 (C-6′), 153.5 (C-2′), 150.9 (C-4′), 135.5 (C-8′), 116.6 (C-5′), 51.1 (C-3), 50.7 (C-2), 45.2 (C-6), 30.6 (C-4), 25.3 (C-5); HRMS (ESI) $C_{10}H_{15}ON_6$ $(M+H)^+$ calcd 235.1302, found 235.1302.

*5.1.21. 2-(Adenin-9-yl)methylpyrrolidine (**28a**).* Pyrrolidine nucleoside **28a** was prepared according to general method D from mixture of adenine derivatives **24a** and **23c** (159 mg, 0.500 mmol) in a 40% yield (47 mg, 0.216 mmol) as a white amorphous solid.

ν_{max} (KBr) 3445 (vs), 3279 (s), 3121 (m), 3118 (m), 2975 (m), 2955 (m), 2944 (m), 2870 (m), 2842 (w), 1668 (s), 1641 (s),1600 (s), 1573 (m), 1517 (w), 1484 (m), 1428 (m), 1420 (m), 1345 (m), 1299 (s), 1210 (w), 990 (w), 796 (w), 728 (w), 642 (w); δ_H (DMSO, 600.1 MHz) 8.12 (1H, s, H-2′), 8.11 (1H, s, H-8′), 7.20 (2H, br s, NH_2), 4.05 (1H, dd, J_{gem} 13.7 Hz, $J_{CH2\text{–}H2}$ 5.6 Hz, (CH_2)a–N), 3.97 (1H, dd, J_{gem} 13.7 Hz, $J_{CH2\text{–}H2}$ 7.4 Hz, (CH_2)b–N), 2.74 (2H, t, $J_{H6\text{-}H5}$ 6.7 Hz, H-5), 3.45 (1H, m, H-2), 1.70 (1H, m, H-3b), 1.61 (1H, m, H-4b), 1.54 (1H, m, H-4a), 1.34 (1H, m, H-3a); δ_C (DMSO, 150.9 MHz) 156.1 (C-6′), 152.4 (C-2′), 149.8 (C-4′), 141.5 (C-8′), 118.7 (C-5′), 57.4 (C-2), 48.0 (*C*H_2N), 46.1 (C-6), 29.1 (C-3), 25.5 (C-4); HRMS (ESI) $C_{10}H_{15}N_6$ $(M+H)^+$ calcd 219.1353, found 219.1352.

*5.1.22. 2-(Thymin-1-yl)methylpyrrolidine (**28b**).* Pyrrolidine nucleoside **28b** was prepared according to general method D from thymine derivative **24b** (254 mg, 0.500 mmol) in a 38% yield (39 mg, 0.183 mmol) as a white amorphous solid.

ν_{max} (KBr) 3173 (w), 3058 (w), 1688 (vs), 1471 (w), 1454 (w), 1438 (w), 1387 (w), 1348 (w), 1265 (w), 1201 (m), 1176 (m), 1130 (m); δ_H (DMSO) 7.47 (1H, q, $J_{6'\text{-}CH3}$ 1.2 Hz, H-6′), 3.66 (1H, dd, J_{gem} 13.3 Hz, $J_{CH2\text{-}2}$ 4.8 Hz, (CH_2)b–N), 3.34 (1H, dd, J_{gem} 13.3 Hz, $J_{CH2\text{-}2}$ 8.4 Hz, (CH_2)a–N), 3.26 (1H, m, H-2), 2.75 (2H, t, $J_{5\text{-}4}$ 6.8 Hz, H-5), 1.73 (3H, d, $J_{CH3\text{-}6'}$ 1.2 Hz, CH_3), 1.62–1.75 (2H, m, H-4b, H-3b), 1.56 (1H, m, H-4a), 1.28 (1H, m, H-3a); δ_C (DMSO) 164.6 (C-4′), 151.3 (C-2′), 142.7 (C-6′), 107.6 (C-5′), 56.8 (C-2), 52.0 (*C*H_2N), 45.9 (C-5), 28.98 (C-3), 25.5 (C-4), 12.2 (CH_3); HRMS (ESI) $C_{10}H_{16}O_2N_3$ $(M+H)^+$ calcd 210.1237, found 210.1237.

*5.1.23. (RS)-3-Azido-1-N-tert-butyloxycarbonylpiperidine (**29**).* Mesyl derivative **21a** (5.00 g, 17.9 mmol) and sodium azide (4.60 g, 71.6 mmol) were suspended in anhydrous DMF (50 ml) and heated to 100 °C. The reaction finished in 2 h. The DMF was evaporated, and the crude product dissolved in chloroform and extracted with saturated $NaHCO_3$. The organic phases were combined and dried over sodium sulfate. Na_2SO_4 was filtered and the product was purified by flash chromatography using a linear gradient of ethyl acetate in toluene. The product was obtained in a 87% yield (3.53 g, 15.6 mmol) as a light yellow oil.

ν_{max} (KBr) 2981 (s), 2949 (s), 2935 (s), 2863 (m), 2101 (vs), 1687 (vs), 1477 (s), 1467 (s), 1425 (vs), 1393 (s), 1368 (vs), 1345 (m), 1243 (vs), 1173 (vs), 1152 (vs), 556 (w); δ_H ($CDCl_3$, 400.1 MHz) 3.80 (1H, br m, H-2a), 3.58 (1H, br s, H-6a), 3.47 (1H, m, H-3), 3.15 (2H, br m, H-2b, H-6b), 1.97 (1H, br s, H-4b), 1.76 (1H, br m, H-5a), 1.42–1.64 (2H, m, H-5b, H-4b), 1.46 (9H, s, $(CH_3)_3$); δ_C ($CDCl_3$, 100.6 MHz) 154.6 (CO), 80.0 (*C*(CH_3)), 56.4 (br s, C-3), 47.8 (C-2), 43.7 (br s, C-6), 29.9 (C-4), 28.3 (CH_3), 22.6 (C-5); HRMS (ESI) $C_{10}H_{18}O_2N_4Na$ $(M+Na)^+$ calcd 249.1322, found 249.1322.

*5.1.24. (RS)-3-Amino-1-N-tert-butyloxycarbonylpiperidine (**30**).* Azido derivative **29** (3.53 g) and Pd/C catalyst (150 mg) were suspended in ethanol (150 ml). The mixture was hydrogenated at rt under atmospheric pressure for 12 h (TLC controlled, 50% ethyl

acetate/toluene, ninhydrin detection). The mixture was filtered through a layer of Celite for catalyst removal. The solvent was evaporated and the product was dried on an oil pump. The product was obtained in a 90% yield (2.82 g, 14 mmol) as a colorless liquid.

ν_{max} ($CHCl_3$) 3376 (w), 3316 (vw), 2981 (s), 2940 (s), 2861 (s), 1682 (vs), 1477 (s), 1467 (s), 1452 (s), 1427 (vs), 1393 (s), 1367 (vs), 1268 (vs), 1243 (vs), 1172 (vs), 1157 (vs), 860 (s), 464 (w); δ_H ($CDCl_3$, 400.1 MHz) 3.93 (1H, br s, H-2a), 3.82 (1H, br d, J_{gem} 13.0 Hz, H-6a), 2.81 (1H, ddd, J_{gem} 13.2 Hz, $J_{6b\text{-}5a}$ 3.3 Hz, $J_{6b\text{-}5a}$ 10.9 Hz, H-6b), 2.77 (1H, m, H-3), 2.58 (1H, br s, H-2b), 1.91 (1H, m, H-4a), 1.68 (1H, dm, J_{gem} 13.6 Hz, H-5a), 1.48 (1H, m, H-5b), 1.45 (9H, s, $(CH_3)_3$), 1.22 (1H, m, H-4b); δ_C ($CDCl_3$, 100.6 MHz) 154.8 (CO), 79.4 ($C(CH_3)$), 52.3 (br s, C-2), 47.6 (C-3), 43.9 (br s, C-6), 33.9 (br s, C-4), 28.4 (CH_3), 23.6 (C-5); HRMS (ESI) $C_{10}H_{21}O_2N_2$ $(M+H)^+$ calcd 201.1598, found 201.1597.

*5.1.25. 1-((RS)-1-N-tert-butyloxycarbonylpiperidin-3-yl)-3-((E)-3-ethoxyacryloyl)urea (**31a**).* Urea derivative **31a** was prepared according to general method E using reagent **15a** (753 mg, 2.69 mmol) from amino derivative **30** (490 mg, 2.45 mmol) in a 87% yield (740 mg, 2.17 mmol) as a light yellow foam.

ν_{max} (KBr) 3384 (w), 3233 (m), 3128 (m), 3096 (m), 2980 (s), 1708 (vs), 1690 (vs), 1677 (vs), 1632 (s), 1610 (s), 1553 (vs), 1498 (s), 1475 (s), 1465 (m), 1394 (m), 1381 (m), 1365 (s), 1242 (s), 1165 (vs), 1150 (vs), 970 (w); δ_H ($CDCl_3$, 500.0 MHz) 9.66 (1H, br s, H-3), 8.61 (1H, bd, $J_{1-3'}$ 7.7 Hz, H-1), 7.63 (1H, d, $J_{6\text{-}5}$ 12.3 Hz, H-6), 5.37 (1H, d, $J_{5\text{-}6}$ 12.2 Hz, H-5), 3.97 (2H, q, $J_{CH2-CH3}$ 7.1 Hz, OCH_2CH_3), 3.71–3.87 (2H, m, H-2′b, and H-3′), 3.56 (1H, ddd, J_{gem} 13.2 Hz, $J_{6'b\text{-}5'b}$ 3.4 Hz, $J_{6'b\text{-}5'a}$ 6.4 Hz, H-6′b), 3.14–3.24 (2H, m, H-2′a, H-6′a), 1.94 (1H, m, H-4′b), 1.71 (1H, m, H-5′b), 1.51–1.60 (2H, m, H-4′a, H-5′a), 1.44 (9H, br s, $(CH_3)_3$), 1.35 (3H, t, $J_{CH3-CH2}$ 7.1 Hz, OCH_2CH_3); δ_C ($CDCl_3$, 125.7 MHz) 168.2 (C-4), 162.6 (C-6), 154.7 and 154.7 (Boc-*C*=O), 154.5 (C-2), 97.9 (C-5), 79.6 ($C(CH_3)_3$), 67.4 (OCH_2CH_3), 48.2 (C-2′), 45.7 (C-3′), 43.4 (C-6′), 30.2 (C-4′), 28.3 (Boc-CH_3), 22.9 (C-5′), 14.4 (OCH_2CH_3); HRMS (ESI) $C_{16}H_{28}O_5N_3$ $(M+H)^+$ calcd 342.2023, found 342.2017.

*5.1.26. 1-((RS)-1-N-tert-Butyloxycarbonylpiperidin-3-yl)-3-((E)-3-ethoxy-2-methylacryloyl)urea (**31b**).* Urea derivative **31b** was prepared according to general method E using reagent **15b** (760 mg, 2.58 mmol) from amino derivative **30** (470 mg, 2.34 mmol) in a 82% yield (751 mg, 2.11 mmol) as a light yellow foam.

ν_{max} (KBr) 3288 (s), 2981 (s), 2938 (m), 2867 (m), 1764 (s), 1751 (s), 1691 (vs), 1677 (vs), 1652 (vs), 1620 (m), 1546 (s), 1527 (s), 1479 (s), 1468 (s), 1448 (s), 1424 (s), 1392 (s), 1367 (s), 1305 (s), 1268 (s), 1243 (s), 1211 (vs), 1175 (s), 1148 (vs), 1108 (s), 1096 (m), 861 (w), 765 (m), 656 (w); δ_H ($CDCl_3$, 500.0 MHz) 8.87 (1H, br m, NH-1), 8.04–8.33 (1H, br m, NH-3), 7.41 (1H, s, H-6), 4.06 (2H, m, OCH_2CH_3), 3.83 (1H, br s, H-3′), 3.71–3.87 (2H, m, H-2′b, and H-3′), 3.56 (1H, ddd, J_{gem} 13.2 Hz, $J_{6'b,5'}$ 3.4 Hz and 6.4 Hz, H-6′b), 3.14–3.24 (2H, m, H-2′a, and H-6′a), 1.94 (1H, m, H-4′b), 1.71 (1H, m, H-5′b), 1.51–1.60 (2H, m, H-4′a, H-5′a), 1.44 (9H, s, $(CH_3)_3$), 1.35 (3H, t, $J_{CH3-CH2}$ 7.1 Hz, OCH_2CH_3); δ_C ($CDCl_3$, 125.7 MHz) 169.8 and 169.8 (C-4), 157.4 and 157.4 (C-6), 154.7 (Boc-*C*=O), 153.7 and 153.6 (C-2), 107.3 (C-5), 79.6 ($C(CH_3)_3$), 70.1 (OCH_2CH_3), 48.7 (C-2′), 45.7 (C-3′), 43.2 (C-6′), 28.3 (Boc-CH_3), 22.8 (C-5′), 15.3 (OCH_2CH_3), 8.7 (CH_3); HRMS (ESI) $C_{17}H_{29}O_5N_3Na$ $(M+H)^+$ calcd 378.1999, found 378.1999.

*5.1.27. (RS)-3-(Uracil-1-yl)piperidine (**32**).* Nucleoside **32** was prepared according to general method F from urea derivative **31a** (730 mg, 2.14 mmol) in a 89% yield (371 mg, 1.9 mmol) as a white amorphous solid.

ν_{max} ($CHCl_3$) 3392 (m), 3173 (m), 2949 (s), 2862 (m), 2823 (m), 1755 (m), 1685 (vs), 1627 (m), 1462 (s), 1446 (s), 1439 (s), 1384 (s), 1360 (m), 1338 (m), 1259 (s); δ_H (DMSO, 499.9 MHz) 11.20 (1H, br s, NH), 7.78 (1H, d, $J_{6'\text{-}5'}$ 8.0 Hz, H-6′), 5.53 (1H, d, $J_{5'\text{-}6'}$ 8.0 Hz, H-5′), 4.26 (1H, m, H-3), 2.87 (1H, dm, J_{gem} 11.7 Hz, H-2_{eq}), 2.80 (1H, dm, J_{gem} 12.5 Hz, H-6_{eq}), 2.58 (1H, dd, J_{gem} 11.6 Hz, $J_{2'ax\text{-}3'}$ 10.6 Hz, H-2_{ax}), 2.38 (1H, td, J_{gem}=$J_{6'ax\text{-}5'ax}$ 12.1 Hz, $J_{6'ax\text{-}5'eq}$ 2.7 Hz, H-6_{ax}), 1.64–1.80 (3H, m, H-4, H-5_{eq}), 1.45 (1H, m, H-5_{ax}); δ_C (DMSO, 125.7 MHz) 163.3 (C-4′), 151.1 (C-2′), 142.5 (C-6′), 101.0 (C-5′), 52.4 (C-3), 49.9 (C-2), 45.30 (C-6), 29.3 (C-4), 26.3 (C-5); HRMS (ESI) $C_9H_{14}O_2N_3$ $(M+H)^+$ calcd 196.1081, found 196.1078.

*5.1.28. (RS)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-1-N-tert-butyloxycarbonylpiperidine (**33a**).* Amino derivative **30** (366 mg, 1.82 mmol), 5-amino-4,6-dichloropyrimidine **16** (600 mg, 3.65 mmol), and triethylamine (1.09 ml, 7.86 mmol) were suspended in ethanol (20 ml) and heated to 110 °C in a pressure vessel over 48 h. After the reaction was completed, the solvent was evaporated and residue chromatographed on a silica gel using a linear gradient of ethyl acetate in toluene. The product was obtained in a 70% yield (375 mg, 1.27 mmol) as a dark orange foam.

ν_{max} (KBr) 3468 (m), 3366 (s), 3330 (m), 3259 (w), 2983 (w), 2916 (w), 1692 (m), 1646 (vs), 1579 (vs), 1561 (s), 1494 (w), 1477 (m), 1439 (s), 1416 (s), 1390 (m), 1367 (m), 1170 (s), 1158 (s), 1104 (m), 923 (m), 769 (m), 461 (w); δ_H (DMSO, 499.8 MHz, 80 °C) 7.75(1H, s, H-2′), 6.32 (1H, br d, J_{NH-3} 6.4 Hz, NH), 4.88 (2H, br s, NH_2), 3.97 (1H, m, H-3), 3.89 (1H, m, H-2_{eq}), 3.63 (1H, m, H-6_{eq}), 2.92–3.03 (2H, m, H-2_{ax}, H-6_{ax}), 1.99 (1H, m, H-4_{eq}), 1.79 (1H, m, H-5_{eq}), 1.54 (1H, m, H-4_{ax}), 1.45 (1H, m, H-5_{ax}), 1.36 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz, 80 °C) 153.9 (COO), 151.4 (C-4′), 145.4 (C-2′), 137.5 (C-6′), 123.4 (C-5′), 78.4 ($C(CH_3)_3$), 47.6 (C-2), 46.9 (C-3), 43.4 (C-6), 29.5 (C-4), 27.8 ($C(CH_3)_3$), 22.9 (C-5); HRMS (ESI) $C_{14}H_{23}O_2N_5Cl$ $(M+H)^+$ calcd 328.1535, found 328.1536.

*5.1.29. (RS)-1-N-tert-Butyloxycarbonyl-3-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]piperidine (**33b**).* Amino derivative **30** (1.05 g, 5.24 mmol), 2,5-diamino-4,6-dichloropyrimidine **17** (1.03 g, 5.76 mmol), and triethylamine (3.1 ml, 22.53 mmol) were suspended in *n*-butanol (55 ml) and heated to 140 °C in a pressure vessel over 48 h. After the reaction was completed, the solvent was evaporated and the residue chromatographed on a silica gel using a linear gradient of ethyl acetate in toluene. The product was obtained in a 56% yield (1.00 g, 2.92 mmol) as a dark orange foam.

ν_{max} (KBr) 3493 (s), 3405 (s), 3213 (m), 2975 (m), 2934 (m), 2858 (w), 1688 (s), 1617 (s), 1571 (vs), 1502 (m), 1467 (s), 1430 (s), 1442 (s), 1392 (m), 1366 (m), 1308 (w), 1265 (m), 1242 (m), 1174 (m), 1153 (s), 860 (w), 773 (w); δ_H (DMSO, 499.8 MHz, 80 °C) 6.06 (1H, br d, J_{NH-3} 7.4 Hz, NH), 3.92 (1H, m, H-3), 5.35 (2H, br s, NH_2), 3.82 (1H, m, H-2_{eq}), 3.77 (2H, br s, NH_2), 3.63 (1H, m, H-6_{eq}), 2.94–3.01 (2H, m, H-2_{ax}, H-6_{ax}), 1.94 (1H, m, H-4_{eq}), 1.75 (1H, m, H-5_{eq}), 1.51 (1H, m, H-4_{ax}), 1.42 (1H, m, H-5_{ax}), 1.38 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz, 80 °C) 78.4 ($C(CH_3)_3$), 47.7 (C-2), 46.2 (C-3), 43.2 (C-6), 29.6 (C-4), 27.8 ($C(CH_3)_3$), 22.9 (C-5); HRMS (ESI) $C_{14}H_{24}O_2N_6Cl$ $(M+H)^+$ calcd 343.1644, found 343.1645.

*5.1.30. (RS)-1-N-tert-Butyloxycarbonyl-3-(6-chloropurin-9-yl)piperidine (**34a**).* Pyrimidine derivative **33a** (370 mg, 1.12 mmol) and diethoxymethyl acetate (10 ml, 61.22 mmol) were stirred at rt for 8 h and then heated to 120 °C for the next 24 h. After the reaction was completed, the solvent was evaporated and residue chromatographed on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$. The product was obtained in a 91% yield (345 mg, 1.022 mmol) as a light yellow foam.

ν_{max} ($CHCl_3$) 3122 (vw), 3067 (vw), 2983 (m), 2953 (m), 2933 (m), 2866 (m), 1689 (vs), 1591 (vs), 1562 (s), 1511 (w), 1487 (m), 1477 (m), 1468 (m), 1455 (m), 1443 (s), 1426 (s), 1406 (s), 1395 (s), 1368 (s), 1339 (s), 1259 (s), 1244 (s), 1194 (s), 1172 (s), 1150 (vs), 938 (m), 861 (m), 647 (w), 637 (m); δ_H (DMSO, 499.8 MHz, 100 °C) 8.74 (1H, s, H-2′), 8.65 (1H, s, H-8′), 4.62 (1H, t, $J_{3\text{-}2b}$=$J_{3\text{-}4a}$ 9.7 Hz, $J_{3\text{-}2a}$=$J_{3\text{-}4}$ 4.3 Hz, H-3), 4.17 (1H, ddt, J_{gem} 12.9 Hz, $J_{2a\text{-}3}$ 4.3 Hz, $J_{2a\text{-}4b}$=$J_{2a\text{-}6a}$ 1.4 Hz, H-2a), 3.52 (1H, dd, J_{gem} 12.9 Hz, $J_{2b\text{-}3}$ 9.7 Hz, H-2b), 3.06 (1H,

ddd, J_{gem} 13.3 Hz, $J_{6b\text{-}5b}$ 10.07 Hz, H-6b), 2.31 (1H, dddd, J_{gem} 13.3 Hz, $J_{4a\text{-}5b}$ 11.2 Hz, $J_{4a\text{-}3}$ 9.7 Hz, $J_{4a\text{-}5a}$ 4.3 Hz, H-4a), 2.22 (1H, br m, J_{gem} 13.1 Hz, $J_{4b\text{-}5a}$ 4.8 Hz, $J_{4b\text{-}3}$ 4.3 Hz, $J_{4b\text{-}5b}$ 3.7 Hz, H-4b), 1.87 (1H, m, J_{gem} 13.9 Hz, $J_{5b\text{-}4b}$ 4.8 Hz, $J_{5a\text{-}4a}$=$J_{5a\text{-}6a}$ 4.3 Hz, $J_{5a\text{-}6b}$ 3.3 Hz, H-5a), 1.63 (1H, m, J_{gem} 13.9 Hz, $J_{5b\text{-}4a}$ 11.2 Hz, $J_{5b\text{-}6b}$ 10.7 Hz, $J_{5b\text{-}6a}$ 4.3 Hz, $J_{5b\text{-}4a}$ 3.7 Hz, H-5b), 1.41 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz, 100 °C) 153.6 (CO), 151.5 (C-4′), 150.8 (C-2′), 149.1 (C-6′), 145.1 (C-8′), 130.9 (C-5′), 79.0 ($C(CH_3)_3$), 51.5 (C-3), 47.0 (C-2), 43.1 (C-6), 28.5 (C-4), 27.7 ($C(CH_3)_3$), 23.2 (C-5); HRMS (ESI) $C_{15}H_{21}O_2N_5Cl$ $(M+H)^+$ calcd 338.1378, found 338.1378.

*5.1.31. (RS)-3-(2-Amino-6-chloropurin-9-yl)-1-N-tert-butyloxycarbonylpiperidine (**34b**).* Pyrimidine derivative **33b** (370 mg, 1.12 mmol) and diethoxymethyl acetate (0.164 ml, 1.232) in DMF (20 ml) were stirred at rt for 6 h and then heated to 120 °C for the next 24 h. After the reaction was completed, the solvent was evaporated and the residue chromatographed on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$. The product was obtained in a 50% yield (190 mg, 0.562 mmol) as a light orange oil.

ν_{max} (KBr) 3500 (s), 3330 (m), 3215 (m), 2976 (w),1690 (s), 1612 (vs), 1563 (s), 1512 (m), 1466 (m), 1425 (m), 1406 (s), 1391 (m), 1367 (m), 1312 (w), 1244 (m), 1213 (w), 1173 (m), 1155 (m), 786 (w), 642 (w); δ_H (DMSO, 500.0 MHz, 50 °C) 7.87 (1H, s, H-8′), 5.01 (2H, vbr s, NH_2), 4.40 (1H, m, H-3), 4.19 (1H, m, J_{gem} 13.3 Hz, H-2_{eq}), 3.90 (1H, bdt, J_{gem} 13.5 Hz, $J_{6eq\text{-}5}$ 4.3 Hz, H-6_{eq}), 3.44 (1H, dd, J_{gem} 13.2 Hz, $J_{2ax\text{-}3}$ 9.3 Hz, H-2_{ax}), 3.09 (1H, ddd, J_{gem} 13.4 Hz, $J_{6ax\text{-}5ax}$ 10.4 Hz, $J_{6ax\text{-}5eq}$ 3.3 Hz, H-6_{ax}), 2.14–2.22 (2H, m, H-4), 1.81 (1H, m, H-5b), 1.67 (1H, m, H-5a), 1.47 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz, 50 °C) 158.8 (C-2′), 154.5 (CO), 153.5 (C-4′), 151.5 (C-6′), 140.4 (C-8′), 125.4 (C-5′), 80.5 ($C(CH_3)_3$), 51.6 (C-3), 47.7 (C-2), 43.7 (C-6), 29.8 (C-4), 28.4 (C $(CH_3)_3$), 23.7 (C-5); HRMS (ESI) $C_{15}H_{22}O_2N_6Cl$ $(M+H)^+$ calcd 353.1487, found 353.1489.

*5.1.32. (S)-1-N-Benzyl-2-methoxycarbonylpyrrolidine (**36a**).* Thionyl chloride (20 ml, 0.275 mol) was added dropwise to a stirred suspension of (*R*)-proline (**35a**) (26.20 g, 0.228 mol) in MeOH (900 ml) at 0 °C. After the consumption of the starting material, methanol was evaporated under reduced pressure. The resulting solid was suspended in DCM (500 ml), and Et_3N (127 ml, 0.915 mol) and BnBr (33 ml, 0.275 mol) were added. The mixture was refluxed for 10 h. The solvent was evaporated and the product purified by flash chromatography on a silica gel using a linear gradient of EtOH in $CHCl_3$. The product was obtained as a light yellow oil in a 75% yield (34.00 g, 0.159 mol). All spectral data recorded were in accordance with the literature data.[58]

*5.1.33. (2S,4R)-1-N-Benzyl-4-hydroxy-2-methoxycarbonylpyrrolidine (**36b**).* Thionyl chloride (20 ml, 0.275 mol) was added dropwise to a stirred suspension of (2*R*,4*R*)-4-hydroxyproline (**35b**) (30.00 g, 0.228 mol) in MeOH (900 ml) at 0 °C. After the consumption of the starting material, methanol was evaporated under reduced pressure. The resulting solid was suspended in DCM (500 ml), and Et_3N (127 ml, 0.915 mol) and BnBr (33 ml, 0.275 mol) were added. The mixture was refluxed for 10 h. The solvent was evaporated and the product purified by flash chromatography using a linear gradient of EtOH in $CHCl_3$. The product was obtained as a light yellow oil in a 70% yield (37.00 g, 0.160 mol). All spectral data recorded were in accordance with the literature data.[58]

*5.1.34. (S)-(1-N-Benzyl-pyrrolidin-2-yl)methanol (**37a**).* A solution of pyrrolidine derivative **36a** (26.84 g, 0.122 mol) in THF (150 ml) was added dropwise to a suspension of $LiAlH_4$ (18.58 g, 0.489 mol) in THF (400 ml). The mixture was stirred until the complete consumption of the product (~16 h). Water was carefully added at 0 °C (CAUTION! gas evolving), and the mixture was then filtered. Product **37a** was purified by flash chromatography on a silica gel using a linear gradient of EtOH in $CHCl_3$. The product was obtained in a 85% yield (20 g, 0.104 mol) as a light yellow liquid. All spectral data recorded were in accordance with the literature data.[58]

*5.1.35. (2S,4R)-(1-N-Benzyl-4-hydroxypyrrolidin-2-yl)methanol (**37b**).* A solution of pyrrolidine derivative **36b** (21.00 g, 0.085 mol) in THF (120 ml) was added dropwise to a suspension of $LiAlH_4$ (12.93 g, 0.34 mmol) in THF (300 ml). The mixture was stirred until the complete consumption of the product (~16 h). Water was carefully added at 0 °C (CAUTION! gas evolving), and the mixture was then filtered. Product **37b** was purified by flash chromatography on a silica gel using a linear gradient of EtOH in $CHCl_3$. The product was obtained in a 77% yield (13.50 g, 0.065 mmol) as an orange liquid. All spectral data recorded were in accordance with the literature data.[58]

*5.1.36. (S)-1-N-Benzyl-3-hydroxypiperidine (**38a**).* Trifluoroacetic anhydride (5.7 ml, 41.05 mmol) was added dropwise to a solution of pyrrolidine derivative **37a** (17.00 g, 88.8 mmol) in THF (900 ml), and then cooled to −78 °C. After 1 h, Et_3N (50 ml, 355 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 20 min at 0 °C and then heated at reflux for 60 h. After the addition of an aqueous 2.5 M NaOH solution (210 ml), the mixture was stirred for 2 h at rt and then extracted with ethyl acetate, dried with $MgSO_4$, and evaporated to dryness in a vacuum. The product was obtained by purification on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$ in a 51% yield (8.95 g, 45.2 mmol) as a colorless oil. All spectral data recorded were in accordance with the literature data.[58]

*5.1.37. (3R,5R)-1-N-Benzyl-3,5-dihydroxy-piperidine (**38b**).* Trifluoroaceticanhydride (5.7 ml, 41.05 mmol) was added dropwise to a solution of pyrrolidine derivative **37b** (7.70 g, 37.3 mmol) in THF (300 ml), and then cooled to 0 °C. After 1 h, Et_3N (23.08 ml, 166 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 20 min at 0 °C and then heated at reflux for 60 h. After the addition of an aqueous 2.5 M NaOH solution (210 ml), the mixture was stirred for 2 h at rt and then extracted with ethyl acetate, dried with $MgSO_4$, and evaporated to dryness in a vacuum. The product was obtained by purification on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$ in a 49% yield (3.70 g, 18.22 mmol) as a colorless oil. All spectral data recorded were in accordance with the literature data.[58]

*5.1.38. (R)-3-Hydroxypiperidine (**39a**)[63–65].* Hydroxypiperidine **38a** (7.25 g, 38.42 mmol) was hydrogenated in ethanol (200 ml) at an atmospheric pressure using Pd/C (150 mg) as a catalyst. After the reaction was finished, the mixture was filtered through Celite and the filtrate was evaporated. Product **39a** was obtained in a 90% yield (3.50 g, 34.6 mmol) as a light yellow oil.

All NMR data of compound **39a** were in accordance with the NMR data published for its enantiomer, (*S*)-3-hydroxypiperidine.[66]

$[\alpha]_D^{20}$ +11.9 (*c* 0.345, EtOH); ν_{max} (KBr) 3409 (vs), 3301 (vs), 3112 (s), 2967 (s), 2935 (vs), 2899 (s), 2856 (s), 2825 (s), 1632 (m), 1554 (m), 1470 (m), 1443 (s), 1379 (w), 1360 (w), 1344 (w), 1329 (m); HRMS (ESI) $C_5H_{12}ON$ $(M+H)^+$ calcd 102.0913, found 102.0912.

*5.1.39. (3R,5R)-Dihydroxypiperidine (**39b**)[67,68].* Dihydroxypiperidine **38b** (2.93 g, 5.38 mmol) was hydrogenated in ethanol (70 ml) at an atmospheric pressure using Pd/C (100 mg) as a catalyst. After the reaction was finished, the mixture was filtered through Celite and the filtrate was evaporated. Product **39b** was obtained in a 79% yield (2.20 g, 4.24 mmol) as a colorless oil.

$[\alpha]_D^{20}$ +49.4 (*c* 0.245, EtOH); ν_{max} (KBr) 3410 (vs), 3354 (vs), 3313 (s), 3268 (vs), 3076 (s), 2941 (s), 2926 (vs), 2900 (s), 2854 (s), 2761 (s), 2707 (s), 2598 (m), 1632 (w), 1558 (w), 1477 (m), 1455 (m), 1443

(s), 1431 (s), 1418 (m), 1066 (s), 1008 (s), 995 (m), 867 (s); δ_H (DMSO, 500.0 MHz) 3.74 (2H, br s, OH), 3.68 (2H, m, H-3, H-5), 2.33 (2H, m) and 2.62 (2H, m, H-2, H-6), 1.57 (2H, br t, $J_{4\text{-}3}$ 5.5 Hz, H-4); δ_C (DMSO, 125.7 MHz) 64.48 (C-3, C-5), 52.64 (C-2, C-6), 41.04 (C-4); HRMS (ESI) $C_5H_{12}O_2N$ $(M+H)^+$ calcd 118.0863, found 118.0861.

*5.1.40. (3R,5R)-1-N-tert-Butyloxycarbonyl-3,5-dihydroxypiperidine (**40b**).* Boc_2O (4.58 g, 21.02 mmol) was added to a stirred suspension of dihydroxypiperidine **39b** (2.00 g, 17.52 mmol) and $NaHCO_3$ (7.35 g, 87.60 mmol) in 200 ml ethanol/water (1:1, v/v). After 2 h TLC (ethyl acetate/acetone/ethanol/water=4:1:1:1, v/v) showed the total consumption of the starting material. The mixture was then filtered through Celite and the product purified by flash chromatography on a silica gel using a linear gradient of (ethyl acetate/acetone/ethanol/water=4:1:1:1, v/v) in ethyl acetate. Product **40b** was obtained in a 92% yield (3.50 g, 16.10 mmol) as an orange oil.

$[\alpha]_D^{20}$ −3.2 (*c* 0.215, EtOH); ν_{max} (KBr) 3495 (s), 3273 (m), 2976 (m), 2930 (m), 1684 (vs), 1477 (m), 1462 (m), 1456 (m), 1439 (m), 1428 (s), 1414 (m), 1393 (m), 1368(m), 1335 (w), 1304 (w), 1245 (m), 1235 (s), 1169 (s), 1151 (s), 1061 (m), 984 (w), 465 (w); δ_H (DMSO, 499.8 MHz, 120 °C) 4.21 (2H, br s, OH), 3.83 (2H, m, H-3, H-5), 3.38 (2H, dd, J_{gem} 13.0 Hz, $J_{2b\text{-}3}$ 3.5 Hz, H-2b, H-6b), 3.10 (2H, J_{gem} 13.0 Hz, $J_{2a\text{-}3}$ 6.5 Hz, H-2a, H-6a), 1.65 (2H, t, $J_{4\text{-}3}$ 5.5 Hz, H-4), 1.42 (9H, s, $(CH_3)_3$); δ_C (DMSO, 125.7 MHz, 120 °C) 154.4 (CO), 77.9 ($C(CH_3)_3$), 62.6 (C-3, C-5), 49.6 (C-2, C-6), 40.0 (C-4), 27.8 (CH_3); HRMS (ESI) $C_{10}H_{19}O_4Na$ $(M+Na)^+$ calcd 240.1206, found 240.1206.

*5.1.41. (R)-1-N-tert-Butyloxycarbonyl-3-hydroxypiperidine (**41a**).* Hydroxypiperidine **39a** (3.72 g, 36.8 mmol) was dissolved in a mixture of H_2O/EtOH (250 ml, 1:1, v/v). Then, $NaHCO_3$ (15.40 g, 183.5 mmol) was added, followed by the addition of Boc_2O (9.63 g, 44.1 mmol). After the reaction was completed, the mixture was filtered and the filtrate was evaporated. The crude product was then purified by flash chromatography on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$. Product **41a** was obtained in a 97% yield (6.70 g, 33.51 mmol) as a colorless oil.

^1H NMR, ^{13}C NMR, and IR spectra were identical to those of **20a**. HRMS (ESI) $C_{10}H_{19}O_3NNa$ $(M+Na)^+$ calcd 224.12571, found 224.12563; $[\alpha]_D^{20}$ +16.6 (*c* 0.717, EtOH).

*5.1.42. (3R,5R)-5-Dimethoxytrityloxy-1-N-tert-butyloxycarbonyl-3-hydroxypiperidine (**41b**).* A solution of dimethoxytritylchloride (5.45 g, 16.1 mmol) in anhydrous pyridine (50 ml) was added dropwise to a stirred mixture of **40b** (3.5 g, 16.1 mmol) in pyridine (150 ml) under an argon atmosphere. After 7 h the reaction was quenched with water (10 ml) and evaporated. Product **41b** was obtained in a 36% (3.00 g, 5.7 mmol) yield as a light yellow foam after purification on a silica gel using a linear gradient of ethyl acetate in toluene.

$[\alpha]_D^{20}$ −8.0 (*c* 0.387, EtOH); ν_{max} (KBr) 3436 (m), 3057 (w), 3035 (vw), 3001 (w), 2974 (m), 2837 (w), 1691 (s), 1671 (s), 1608 (m), 1582 (w), 1509 (vs), 1492 (m), 1477 (m), 1463 (m), 1445 (m), 1392 (w), 1366 (m), 1301 (m), 1251 (vs), 1117 (w), 1064 (m), 1035 (s), 1011 (w), 1001 (vw), 945 (w), 913 (vw), 867 (w), 827 (w), 791 (w), 766 (w), 754 (w), 727 (w), 634 (vw); δ_H($CDCl_3$, 499.8 MHz, 50 °C) 7.49 (2H, m, H-2″), 7.36–7.41 (4H, m, H-2′), 7.19–7.28 (3H, m, H-3″, H-4″), 6.79–6.83 (4H, m, H-3′), 3.95 (1H, br s, H-3), 3.86 (1H, m, H-5), 3.78 (6H, s, OCH_3), 3.75 (1H, m, H-2b), 3.61 (1H, m, H-6b), 3.09 (1H, br d, J_{gem} 13.5 Hz, H-6a), 2.96 (1H, dd, J_{gem} 13.0 Hz, $J_{2a\text{-}3}$ 7.6 Hz, H-2a), 1.47 (9H, s $(CH_3)_3$), 1.01–1.13 (2H, m, H-4); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 158.5 and 158.5 (C-4′), 145.7 (C-1″), 136.7 and 136.9 (C-1′), 130.2 and 130.3 (C-2′), 128.2 and 128.3 (C-2″), 127.7 (C-3″), 126.7 (C-4″), 113.0 and 113.0 (C-3′), 86.3 (3-O–*C*), 79.8 ($C(CH_3)_3$), 66.4 (C-5), 64.4 (C-3), 55.1 (OCH_3), 49.7 (C-6, C-2), 38.7 (C-4), 28.4 ($C(CH_3)_3$); HRMS (ESI) $C_{31}H_{37}O_6NNa$ $(M+Na)^+$ calcd 542.2513, found 542.2511.

*5.1.43. (S)-3-Azido-1-N-tert-butyloxycarbonylpiperidine (**42a**).* Mesyl derivative **41a** (9.20 g, 32.9 mmol) and sodium azide (8.56 g, 131.7 mmol) were heated to 90 °C in DMF (200 ml) for 12 h. The solvent was then evaporated and the product was obtained in a 91% yield (6.77 g, 29.9 mmol) as a light yellow liquid after purification on a silica gel using a linear gradient of ethyl acetate in toluene.

^1H NMR, ^{13}C NMR, and IR spectra were identical to those of **29**. HRMS (ESI) $C_{10}H_{18}O_2N_4Na$ $(M+Na)^+$ calcd 249.1322, found 249.1320; $[\alpha]_D^{20}$ +19.3 (*c* 0.302, EtOH).

*5.1.44. (3S,5R)-3-Azido-1-N-tert-butyloxycarbonyl-5-dimethoxytrityloxypiperidine (**42b**).* Hydroxypiperidine derivative **41b** (3.00 g, 5.7 mmol) and DMAP (1.05 g, 8.6 mmol) were dissolved in DCM (100 ml). Mesyl chloride (1.6 ml, 8.6 mmol) was added dropwise to DCM (50 ml). The reaction was completed within 1 h (TLC controlled, 20% ethyl acetate/toluene). The mixture was cooled to 0 °C and the reaction was quenched with water (10 ml). The mixture was then washed with H_2O (150 ml) and the organic phase was evaporated. The crude product (4.00 g) was used in the next step without further characterization.

Crude (3*R*,5*R*)-*N-tert*-butyloxycarbonyl-5-dimethoxytrityloxy-3-mesyloxypiperidine (4.00 g) and sodium azide (1.40 g, 23.08 mmol) were heated to 90 °C in DMF (100 ml) for 12 h. The solvent was then evaporated and the product was obtained in a 93% yield (2.93 g, 5.37 mmol, over two steps) as a colorless oil after purification on a silica gel using a linear gradient of ethyl acetate in toluene.

$[\alpha]_D^{20}$ −10.0 (*c* 0.169, EtOH); ν_{max} (KBr) 2974 (m), 2837 (m), 2098 (s), 1697 (s), 1464 (m), 1446 (m), 1418 (m), 1366 (m), 1251 (vs), 1034 (m); δ_H ($CDCl_3$, 499.8 MHz, 50 °C) 7.47 (2H, m, H-2″), 7.35–7.39 (4H, m, H-2′), 7.28 (2H, m, H-3″), 7.21 (1H, m, H-4″), 6.80–6.85 (4H, m, H-3′), 4.04 (1H, br m, $H\text{-}2_{eq}$), 3.88 (1H, dd, J_{gem} 12.9 Hz, $J_{6eq\text{-}3}$ 4.7 Hz, $H\text{-}6_{eq}$), 3.78 (6H, s, OCH_3), 3.45 (1H, tt, $J_{5\text{-}6ax}=J_{5\text{-}4ax}$ 10.0 Hz, $J_{5\text{-}6eq}=J_{5\text{-}4eq}$ 4.5 Hz, H-5), 3.03 (1H, tt, $J_{3\text{-}4ax}=J_{3\text{-}2ax}$ 10.9 Hz, $J_{3\text{-}4eq}=J_{3\text{-}2eq}$ 4.5 Hz, H-3), 2.62 (1H, dd, J_{gem} 12.9 Hz, $J_{6ax\text{-}5}$ 10.0 Hz, $H\text{-}6_{ax}$), 2.45 (1H, br t, $J_{gem}=J_{2ax\text{-}3}$ 11.7 Hz, $H\text{-}2_{ax}$), 1.50 (1H, m, $H\text{-}4_{eq}$), 1.38 (9H, s, C$(CH_3)_3$), 1.27 (1H, ddd, J_{gem} 12.5 Hz, $J_{4ax\text{-}5}$ 11.4 Hz, $J_{4ax\text{-}3}$ 10.2 Hz, $H\text{-}4_{ax}$); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 158.8 and 158.8 (C-4′), 154.2 (COO), 145.6 (C-1″), 136.6 and 136.7 (C-1′), 130.2 and 130.2 (C-2′), 128.3 (C-2″), 127.8 (C-3″), 126.9 (C-4″), 113.2 and 113.2 (C-3′), 86.7 (5-O–*C*), 80.1 ($C(CH_3)_3$), 67.2 (C-5), 55.2 (OCH_3), 54.9 (C-3), 49.1 (C-6), 47.3 (C-2), 37.6 (C-4), 28.3 ($C(CH_3)_3$); HRMS (ESI) $C_{31}H_{36}O_5N_4Na$ $(M+Na)^+$ calcd 567.2578, found 567.2578.

*5.1.45. (S)-3-Amino-1-N-tert-butyloxycarbonylpiperidine (**43a**).* Azido derivative **42a** (6.77 g, 29.9 mmol) and Pd/C catalyst (150 mg) were hydrogenated in ethanol (200 ml) at an atmospheric pressure overnight. The catalyst was filtered through Celite and the solvent was evaporated. Product **43a** was obtained in a 90% yield (5.39 g, 26.9 mmol) as a colorless liquid without further purification.

^1H NMR, ^{13}C NMR, and IR spectra were identical to those of **30**. HRMS (ESI) $C_{10}H_{21}O_2N_2$ $(M+H)^+$ calcd 201.1598, found 201.1597; $[\alpha]_D^{20}$ +26.0 (*c* 0.308, EtOH).

*5.1.46. (3S,5R)-3-Amino-1-N-tert-butyloxycarbonyl-5-dimethoxytrityloxypiperidine (**43b**).* Azido derivative **42b** (2.93 g, 5.37 mmol) and Pd/C catalyst (100 mg) were hydrogenated in ethanol (100 ml) at an atmospheric pressure overnight. The catalyst was filtered through Celite and the solvent was evaporated. The product was obtained in a 79% yield (2.20 g, 4.24 mmol) as a white foam without further purification.

$[\alpha]_D^{20}$ +7.3 (*c* 0.328, EtOH); ν_{max} ($CHCl_3$) 3379 (vw), 3311 (vw), 3088 (vw), 3060 (vw), 2979 (m), 2960 (w), 2935 (m), 2859 (w),

2840 (w), 1683 (s), 1608 (m), 1583 (w), 1509 (vs), 1494 (w), 1478 (w), 1464 (m), 1457 (m), 1444 (m), 1425 (m), 1393 (w), 1367 (m), 1301 (m), 1253 (vs), 1176 (s), 1153 (m), 1117 (w), 1080 (w), 1036 (s), 1012 (w), 950 (vw), 912 (w), 861 (w), 831 (m), 709 (w), 702 (w), 640 (w), 615 (vw), 599 (w), 584 (w); δ_H ($CDCl_3$, 499.8 MHz, 80 °C) 7.42 (2H, m, H-2″), 7.28–7.32 (6H, m, H-2′, H-3″), 7.23 (1H, m, H-4″), 6.88 (4H, m, H-3′), 3.76 (6H, s, OCH_3), 3.70 (1H, m, H-2_{eq}), 3.56 (1H, dm, J_{gem} 12.7 Hz, H-6_{eq}), 3.34 (1H, m, H-5), 2.56 (1H, dd, J_{gem} 12.7 Hz, $J_{6ax\text{-}5}$ 9.5 Hz, H-6_{ax}), 2.28–2.31 (1H, m, H-3, H-2_{ax}), 1.55 (1H, m, H-4_{eq}), 1.32 (9H, s, $C(CH_3)_3$), 1.10 (1H, m, H-4_{ax}); δ_C ($CDCl_3$, 125.7 MHz, 80 °C) 158.1 (C-4′), 153.5 (COO), 145.6 (C-1″), 136.4 (C-1′), 129.6 and 129.6 (C-2′), 127.7 (C-2″), 127.3 (C-3″), 126.4 (C-4″), 113.0 (C-3′), 85.7 (5-O–*C*), 78.3 (*C*$(CH_3)_3$), 67.53 (C-5), 54.9 (OCH_3), 51.2 (C-2), 48.5 (C-6), 46.3 (C-3), 41.4 (C-4), 27.8 (C(*C*$H_3)_3$); HRMS (ESI) $C_{31}H_{38}O_5N_2Na$ $(M+Na)^+$ calcd 541.2673, found 541.2673.

*5.1.47. 1-((S)-1-N-tert-Butyloxycarbonylpiperidin-3-yl)-3-((E)-3-ethoxyacryloyl)urea (**44a**).* Urea derivative **44a** was prepared according to general method E from amino derivative **43a** (300 mg, 1.5 mmol) and reagent **15a** (420 mg, 1.5 mmol) in a 80% yield (410 mg, 1.2 mmol) as a light yellow foam.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **31a**. HRMS (ESI) $C_{16}H_{28}O_5N_3$ $(M+H)^+$ calcd 342.2023, found 342.2024; $[\alpha]_D^{20}$ +34.7 (*c* 0.305, EtOH).

*5.1.48. 1-((3S,5R)-3-Amino-1-N-tert-butyloxycarbonyl-5-dimethoxytrityloxypiperidin-3-yl)-3-((E)-3-ethoxyacryloyl)urea (**44b**).* Amino derivative **43b** (350 mg, 0.67 mmol) and reagent **15a** (189 mg, 0.67 mmol) were dissolved in anhydrous dioxane (30 ml). The reaction proceeded in 10 min. The crude product was purified on a silica gel using a linear gradient of ethyl acetate in toluene. Product **44b** was obtained in a 98% yield (440 mg, 0.653 mmol) as a light yellow foam.

$[\alpha]_D^{20}$ −24.2 (*c* 0.268, EtOH); ν_{max} (KBr) 3237 (w), 3089 (w), 2977 (m), 2837 (w), 1693 (vs), 1680 (vs), 1655 (m), 1629 (m), 1609 (s), 1578 (w), 1543 (s), 1509 (vs), 1475 (m), 1463 (m), 1446 (m), 1422 (m), 1394 (w), 1378 (w), 1366 (m), 1302 (m), 1250 (vs), 1224 (m), 1175 (vs), 1152 (s), 1080 (w), 1060 (w), 1034 (m), 1011 (w), 934 (vw), 912 (vw), 830 (m), 702 (w), 585 (w), 528 (vw); δ_H ($CDCl_3$, 499.8 MHz, 50 °C) 9.03 (1H, br s, H-3), 8.60 (1H, d, $J_{1\text{-}5'}$ 7.7 Hz, H-1), 7.52 (1H, d, $J_{6\text{-}5}$ 12.2 Hz, H-6), 7.48 (2H, m, H-2‴), 7.36–7.40 (4H, m, H-2″), 7.25 (2H, m, H-3‴), 7.18 (1H, m, H-4‴), 6.79–6.82 (4H, m, H-3″), 5.26 (1H, d, $J_{5\text{-}6}$ 12.2 Hz, H-5), 3.89–3.94 (2H, m, O*C*H_2CH_3), 3.77 (1H, m, H-6′b), 3.77 (6H, s, OCH_3), 3.49–3.59 (3H, m, H-2′b, H-3′, H-5′), 2.72–3.00 (2H, m, H-2′a, H-6′a), 1.40 (9H, s, C(*C*$H_3)_3$), 1.63 (1H, br m, H-4′b), 1.30 (3H, t, $J_{CH3-CH2}$ 7.1 Hz, OCH_2CH_3), 1.27 (1H, m, H-4′a); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 167.6 (C-4), 162.7 (C-6), 158.6 (C-4′), 154.3 and 154.5 (COO and C-2), 145.7 (C-1‴), 136.8 and 136.8 (C-1″), 130.3 (C-2″), 128.4 (C-2‴), 127.6 (C-3‴), 126.7 (C-4‴), 113.1 and 113.1 (C-3″), 98.0 (C-5), 86.8 (3′-O–*C*), 79.6 (*C*$(CH_3)_3$), 67.5 (O*C*H_2CH_3), 67.2 (C-3′), 55.1 (OCH_3), 49.3 (C-2′), 47.9 (C-6′), 44.9 (C-5′), 37.4 (C-4′), 28.3 (C(*C*$H_3)_3$), 14.4 (CH_2*C*H_3); HRMS (ESI) $C_{38}H_{47}O_8N_3Na$ $(M+Na)^+$ calcd 696.3255, found 696.3258.

*5.1.49. 1-((3S,5R)-3-Amino-1-N-tert-butyloxycarbonyl-5-dimethoxytrityloxypiperidin-3-yl)-3-((E)-3-ethoxy-2-methylacryloyl)urea (**44c**).* Amino derivative **43b** (350 mg, 0.67 mmol) and reagent **15b** (258 mg, 0.87 mmol) were dissolved in anhydrous dioxane (30 ml). The reaction proceeded in 30 min. The crude product was purified on a silica gel using a linear gradient of ethyl acetate in toluene. Product **44c** was obtained in a 95% yield (430 mg, 0.626 mmol) as a light yellow foam.

$[\alpha]_D^{20}$ −18.8 (*c* 0.069, EtOH); ν_{max} (KBr) 3360 (w), 3259 (w), 2977 (m), 2836 (w), 1697 (vs), 1677 (vs), 1650 (m), 1620 (m), 1609 (m), 1542 (m), 1475 (m), 1463 (m), 1446 (m), 1421 (m), 1392 (w), 1379 (w), 1366 (m), 1301 (m), 1251 (s), 1210 (s), 1177 (s), 1151 (s), 1081 (w), 1060 (w), 1035 (m), 1010 (w), 934 (vw), 912 (w), 755 (w), 701 (w), 600 (w), 585 (w), 529 (vw); δ_H ($CDCl_3$, 499.8 MHz, 50 °C) 8.65 (1H, d, $J_{1\text{-}5'}$ 7.9 Hz, H-1), 7.54 (1H, br s, H-3), 7.49 (2H, m, H-2‴), 7.37–7.40 (4H, m, H-2″), 7.27 (1H, br s, H-6), 7.24 (2H, m, H-3‴), 7.18 (1H, m, H-4‴), 6.79–6.83 (4H, m, H-3″), 4.03 (2H, q, $J_{CH2-CH3}$ 7.1 Hz, O*C*H_2CH_3), 3.82 (1H, br s, H-6′b), 3.78 (6H, s, OCH_3), 3.48–3.62 (3H, m, H-2′b, H-3′, H-5′), 2.74–3.02 (2H, m, H-2′a, H-6′a), 1.74 (3H, d, $J_{CH3\text{-}6}$ 1.2 Hz, 5-CH_3), 1.65 (1H, br m, H-4′b), 1.41 (9H, s, C($CH_3)_3$), 1.31 (3H, t, $J_{CH3-CH2}$ 7.1 Hz, OCH_2*C*H_3), 1.24 (1H, m, H-4′a); δ_C ($CDCl_3$, 125.7 MHz, 50 °C) 168.6 (C-4), 158.6 (C-4″), 157.2 (C-6), 154.5 (C-2), 154.0 (COO), 145.8 (C-1‴), 136.8 and 136.9 (C-1″), 130.4 (C-2″), 128.5 (C-2‴), 127.6 (C-3‴), 126.7 (C-4‴), 113.1 and 113.2 (C-3″), 106.5 (C-5), 86.8 (3′-O–*C*), 79.6 (*C*$(CH_3)_3$), 70.2 (O*C*H_2CH_3), 67.2 (C-3′), 55.1 (OCH_3), 49.2 (C-2′), 48.1 (C-6′), 44.9 (C-5′), 37.5 (C-4′), 28.3 (C(*C*$H_3)_3$), 15.3 (CH_2*C*H_3), 8.8 (5-CH_3); HRMS (ESI) $C_{37}H_{45}O_8N_3Na$ $(M+Na)^+$ calcd 682.3099, found 682.3102.

*5.1.50. (S)-3-(Uracil-1-yl)piperidine (**45a**).* Nucleoside **45a** was prepared according to general method F from **44a** (410 mg, 1.2 mmol) in a 84% yield (196 mg, 1.0 mmol) as a white amorphous solid.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **32**. HRMS (ESI) $C_9H_{14}O_2N_3$ $(M+H)^+$ calcd 196.1081, found 196.1081; $[\alpha]_D^{20}$ −52.5 (*c* 0.257, EtOH).

*5.1.51. (3S,5R)-5-Hydroxy-3-(uracil-1-yl)piperidine (**45b**).* Urea derivative **44b** (440 mg, 0.653 mmol) was treated with a Dowex H^+ (20 ml) in dioxane (50 ml) at 90 °C. After 30 min, the mixture was filtered and washed with ethanol (30 ml) and water (30 ml). The product was eluted with 2.5% NH_3 in H_2O (~50 ml) and further purified by reversed phase HPLC. The product was obtained as a white amorphous solid in a 75% yield (100 mg, 0.47 mmol).

$[\alpha]_D^{20}$ −28.3 (*c* 0.130, EtOH); ν_{max} (KBr) 3462 (vs), 3404 (m), 3286 (w), 2662 (w), 1696 (vs), 1656 (vs), 1640 (m), 1444 (m), 1429 (w), 1385 (m), 1276 (m), 1101 (w), 875 (w), 801 (w), 769 (w); δ_H (DMSO, 499.9 MHz) 11.25 (1H, NH), 7.73 (1H, d, $J_{6\text{-}5}$ 8.0 Hz, H-6), 5.52 (1H, d, $J_{5\text{-}6}$ 8.0 Hz, H-5), 4.91 (1H, d, $J_{OH\text{-}5'}$ 4.2 Hz, HO), 4.28 (1H, m, H-3′), 3.46 (1H, m, H-5′), 2.88 (1H, ddm, J_{gem} 11.8 Hz, $J_{6'eq,5'}$ 4.4 Hz, H-$6'_{eq}$), 2.78 (1H, ddm, J_{gem} 11.8 Hz, $J_{2'eq,3'}$ 4.1 Hz, H-$2'_{eq}$), 2.42 (1H, t, J_{gem}=$J_{2'ax,3'}$ 11.4 Hz, H-$2'_{ax}$), 2.12 (1H, dd, J_{gem} 12.1 Hz, $J_{6'ax,5'}$ 10.2 Hz, H-$6'_{ax}$), 1.95 (1H, dm, J_{gem} 11.1 Hz, H-$4'_{eq}$), 1.58 (1H, m, H-$4'_{ax}$); δ_C (DMSO, 125.7 MHz) 163.3 (C-4), 151.1 (C-2), 142.4 (C-6), 101.2 (C-5), 67.1 (C-5′), 52.8 (C-6′), 51.6 (C-3′), 48.7 (C-2′), 38.7 (C-4′); HRMS (ESI) $C_9H_{14}O_3N_3$ $(M+H)^+$ calcd 212.1030, found 212.1030.

*5.1.52. (3S,5R)-5-Hydroxy-3-(thymin-1-yl)piperidine (**45c**).* Urea derivative **44c** (430 mg, 0.626 mmol) was treated with a Dowex H^+ (20 ml) in dioxane (50 ml) at 90 °C. After 30 min, the reaction mixture was filtered and the Dowex was washed with ethanol (30 ml) and water (30 ml). The product was eluted with 2.5% NH_3 in H_2O (~50 ml) and further purified by reversed phase HPLC. The product was obtained as a white amorphous solid in a 81% yield (110 mg, 0.48 mmol).

$[\alpha]_D^{20}$ −66.1 (*c* 0.233, EtOH); ν_{max} (KBr) 3505 (w), 3470 (w), 3288 (w), 3145 (w), 3021 (w), 1682 (vs), 1657 (vs), 1639 (m), 1470 (m), 1429 (w), 1391 (w), 1374 (w), 1301 (w), 1277 (w), 1268 (w), 1118 (w), 1086 (w), 1065 (w), 1059 (w), 886 (w) 820 (w), 768 (w), 759 (w); δ_H (DMSO, 499.9 MHz) 11.21 (1H, br s, NH), 7.61 (1H, q, $J_{6\text{-}CH3}$ 1.2 Hz, H-6), 4.89 (1H, br s, OH), 4.28 (1H, m, H-3′), 3.46 (1H, m, H-5′), 2.76 (1H, ddd, J_{gem} 11.7 Hz, $J_{6'eq\text{-}5'}$ 4.6 Hz, $J_{6'eq\text{-}4'eq}$ 1.5 Hz, H-$6'_{eq}$), 2.76 (1H, ddd, J_{gem} 11.7 Hz, $J_{2'eq\text{-}3'}$ 4.5 Hz, $J_{2'eq\text{-}4'eq}$ 1.6 Hz, H-$2'_{eq}$), 2.44 (1H, t, J_{gem}=$J_{2'ax\text{-}3'}$ 11.5 Hz, H-$2'_{ax}$), 2.12 (1H, dd, J_{gem} 12.1 Hz, $J_{6'ax\text{-}5'}$ 10.2 Hz, H-$6'_{ax}$), 1.94 (1H, dm, J_{gem} 11.2, H-$4'_{eq}$), 1.76 (3H, d, $J_{CH3\text{-}6}$ 1.2 Hz, CH_3), 1.61 (1H, m, H-$4'_{ax}$); δ_C (DMSO, 125.7 MHz) 163.9 (C-4), 151.0 (C-2), 138.0 (C-6), 108.9 (C-5), 67.1 (C-5′), 52.8 (C-6′), 51.2 (C-3′), 48.7 (C-2′), 38.8 (C-4′), 12.2 (CH_3); HRMS (ESI) $C_{10}H_{16}O_3N_3$ $(M+H)^+$ calcd 226.1186, found 226.1186.

*5.1.53. (S)-1-N-tert-Butyloxycarbonyl-3-[(5-amino-6-chloropyrimidin-4-yl)amine]piperidine (**46a**).* Amino derivative **43a** (200 mg, 1.0 mmol), 5-amino-4,6-dichloropyrimidine **16** (179 mg, 1.1 mmol), and triethylamine (0.59 ml, 4.3 mmol) were suspended in ethanol (40 ml) and heated to 110 °C in a pressure vessel over 48 h. After the reaction was completed (TLC controlled 50% ethyl acetate/toluene), all the solvent was evaporated and the residue was chromatographed on a silica gel using a linear gradient of ethyl acetate in toluene. Product was obtained in 72% yield (235 mg, 0.72 mmol) as a dark orange foam.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **33a**. HRMS (ESI) $C_{14}H_{23}O_2N_5Cl$ $(M+H)^+$ calcd 328.1535, found 328.1536; $[\alpha]_D^{20}$ +3.4 (*c* 0.355, EtOH).

*5.1.54. (S)-1-N-tert-Butyloxycarbonyl-3-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]piperidine (**46b**).* Amino derivative **43a** (1.05 g, 5.24 mmol), 2,5-diamino-4,6-dichloropyrimidine **17** (1.03 g, 5.76 mmol), and triethylamine (3.1 ml, 22.53 mmol) were suspended in *n*-butanol (80 ml) and heated to 140 °C in a pressure vessel over 48 h. After the reaction was completed, the solvent was evaporated and the residue chromatographed on a silica gel using a linear gradient of ethyl acetate in toluene. The product was obtained in a 54% yield (969 mg, 2.82 mmol) as a light orange foam.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **33b**. HRMS (ESI) $C_{14}H_{24}O_2N_6Cl$ $(M+H)^+$ calcd 343.1644, found 343.1645; $[\alpha]_D^{20}$ −31.1 (*c* 0.106, EtOH).

*5.1.55. (S)-1-N-tert-Butyloxycarbonyl-3-(6-chloropurin-9-yl)piperidine (**47a**).* Pyrimidine derivative **46a** (370 mg, 1.12 mmol) and diethoxymethyl acetate (0.185 ml, 1.12 mmol) in DMF (25 ml) were stirred at rt for 8 h and then heated to 120 °C for the next 24 h. The solvent was evaporated and the residue was chromatographed on a silica gel using a linear gradient of 10% EtOH/$CHCl_3$ in $CHCl_3$. The product was obtained as a light orange foam in a 68% yield (258 mg, 0.764 mmol).

^{1}H NMR, ^{13}C NMR, HR-ESI, and IR spectra were identical to those of **34a**. $[\alpha]_D^{20}$ +15.3 (*c* 0.170, EtOH).

*5.1.56. (S)-1-N-tert-Butyloxycarbonyl-3-(2-amino-6-chloropurin-9-yl)piperidine (**47b**).* Pyrimidine derivative **46b** (680 mg, 1.98 mmol) and diethoxymethyl acetate (0.324 ml, 1.98 mmol) were stirred in DMF (40 ml) at rt and then heated to 120 °C for the next 24 h. The solvent was evaporated and the residue was chromatographed on a silica gel using a linear gradient of ethyl acetate in toluene. The product was obtained as a light yellow foam in a 72% yield (502 mg, 1.42 mmol).

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **47b**. HRMS (ESI) $C_{15}H_{22}O_2N_6Cl$ $(M+H)^+$ calcd 353.1487, found 353.1489; $[\alpha]_D^{20}$ −20.8 (*c* 0.139, EtOH).

*5.1.57. (S)-3-(Adenin-9-yl)piperidine (**48a**).* Nucleoside **48a** was prepared from **47a** (258 mg, 0.76 mmol) and aqueous NH_3. The reaction progress was controlled by RP HPLC. When the reaction was finished, the solvent was evaporated and the compound treated according to general procedure D. After the reaction was completed, the product was purified by preparative RP HPLC to give **48a** in a 65% yield (107 mg, 0.49 mmol) as a white amorphous solid.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **27c**. HRMS (ESI) $C_{10}H_{15}N_6$ $(M+H)^+$ calcd 219.1353, found 219.1353; $[\alpha]_D^{20}$ −6.4 (*c* 0.283, EtOH).

*5.1.58. (S)-3-(Guanin-9-yl)piperidine (**48b**).* Guanine derivative **47b** (502 mg, 1.42 mmol) was treated with 1 M NaOH in 30% dioxane/water (50 ml) for 2 days. After this time, the reaction was treated with a Dowex 50 in trimethylammonium form (100 ml) for 5 min. The Dowex was then filtrated off and the filtrate was evaporated to give a crude guanine derivative, which was then treated according to general procedure D and finally purified by reversed phase HPLC. The product was isolated in a 68% yield (216 mg, 0.92 mmol) as a white amorphous solid.

^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those of **27d**. HRMS (ESI) $C_{10}H_{15}ON_6$ $(M+H)^+$ calcd 235.1302, found 235.1301; $[\alpha]_D^{20}$ −22.9 (*c* 0.240, EtOH).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.029. These data include MOL files and InChiKeys of the most important compounds described in this article.

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