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Synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of nucleobases

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Abstract—The synthesis of novel 3-pyrrolidinyl derivatives of nucleobases is described. Starting from malic acid, we improved the synthesis of both racemic and optically active *N*-benzyl-3-hydroxypyrrolidine-2,5-diones, which were transformed in four steps into *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines, the key synthons for the alkylation of purine and pyrimidine nucleobases. Alkylations of cesium salts of purines and sodium salts of pyrimidines with *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines proceeded smoothly, giving high yields of 9-substituted purine derivatives and moderate yields of 1-substituted pyrimidine derivatives. Using (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine as the same intermediate for the synthesis of both enantiomeric *N*-Boc-3-pyrrolidinyladenines, and considering the results obtained on chiral HPLC analysis of the products, we proved that nucleophilic displacement of the mesyloxy group proceeded with inversion and not with retention of the configuration. Prepared compounds were tested for cytostatic and antiviral properties, but no significant activity was found.

1. Introduction

Sugar-modified nucleoside analogues form an important group of potential antimetabolites, and compounds exhibiting remarkable antiviral and anticancer properties were found among them.[1] Replacement of the sugar moiety in nucleosides by a pyrrolidine ring seems to be one of the interesting modifications reported in the literature. The synthesis of the first L-nucleoside analogues **1** bearing D-prolinol residue was published by Kaspersen.[2,3] From L-prolinol, Ng and Orgel[4] synthesized D-thymidine analogue **2**, which inhibited the growth of breast carcinoma (MCF-7M), colon carcinoma (HT-29), and SK-MES-1 lung carcinoma cell lines. Kaspersen and Pandit[3,5] published the synthesis of a series of pyrrolidine nucleosides **1**, **3**, **5**, **8a**–**8d**, **9a**, **9b** corresponding to L-nucleosides. The L-uridine analogue **3** exhibited a weak inhibition of Baby hamster kidney cell (BHK) growth. Also purine D-nucleosides with a L-prolinol ring, **4a**–**4d**, **5** prepared by Peterson and Vince,[6] as well as a series of thymidine analogues,[4,6] exhibited a weak inhibition activity in vitro on P388 mouse leukemia cells and HIV-1 and HSV-1 at the concentrations of about 100 μM. Adenine-containing analogue **4a** was used for the preparation of *N*-phosphonomethyl derivative as the nucleoside 3′-phosphate analogue.[7] Harnden[8,9] published the synthesis of L-prolinol nucleosides **6a**–**6c** with a nucleobase connected to the nitrogen atom of a pyrrolidine ring, and a series of phosphonomethoxy derivatives **7a**–**7e** related to 2′,3′-dideoxynucleoside 5′-phosphates (Fig. 1). Westwood et al.[10] reported the synthesis of 5-ethyluracil and *E*-5-(2-bromovinyl)uracil derivatives **8a**–**8d**, **9a**, **9b**. These compounds were not capable of inhibiting the replication of HIV-1 and HIV-2, vesicular stomatitis at sub-toxic concentrations, or phosphorylation of thymidine by HSV-1 TK, but 5-ethyluracil derivative **8d** was found to inhibit (IC_{50} 40 μM) vaccinia virus. Pyrrolidine analogues of oxetanocin A **10a**, **10b** prepared by Oohashi et al. as potential antivirals against HSV-1, HSV-2, and HIV-1 were found completely inactive.[11] Temple et al. reported the synthesis of several 9-pyrrolidin-1-yl-9*H*-purine derivatives (**11**), which were inactive toward L1210 leukemic cells implanted in mice (Fig. 2).[12] No significant biological activity was found in case of 4′-aza nucleosides **12a**–**12n** and **13a**–**13d**,[13–18] as well as in case of oxazolidine **14**[19] and isooxazolidine **15**[20] ring-containing nucleoside analogues (Fig. 3). Richichi et al. reported the preparation of (*R*)-3-(pyrimidin-1-yl)pyrrolidine nucleoside analogues **16a**, **16b** and **17a**, **17b** by Mitsunobu reaction of unprotected pyrimidine bases with appropriate (*S*)-*N*-benzyl-3-hydroxypyrrolidine.[21] Miyabe et al. reported the total synthesis of uridine, thymidine, and adenosine analogues **18a**–**18c** including construction of heterocyclic base (Fig. 4).[22] A pyrrolidine ring, as a sugar mimic, was introduced into modified oligonucleotides,[23–33] and we can also find it as an important part in

Keywords: Malic acid; Pyrrolidine derivatives; Nucleoside analogues; N-,O-alkylation; Inversion of configuration.
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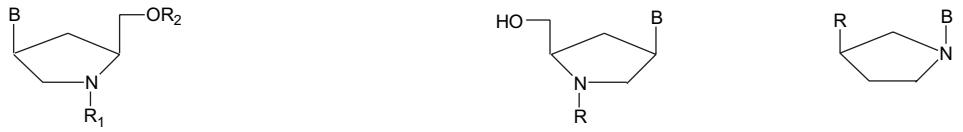
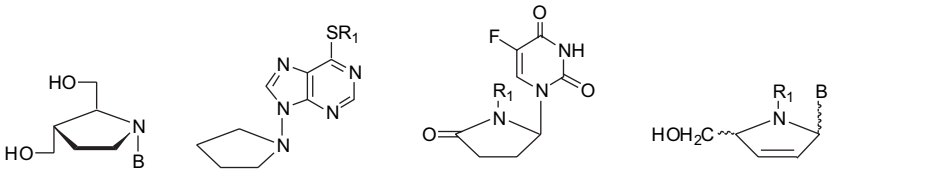


Comp.	B	R_1	R_2
1	2-Amino-6-chloropurin-9-yl	Ts	
3	Uracil-1-yl	H	
5	Guanin-9-yl	H	
8a	5-Ethyluracil-1-yl	Ts	*t*BDPS
8b	5-Ethyluracil-1-yl	Ts	Bz
8c	5-Ethyluracil-1-yl	H	H
8d	5-Ethyluracil-1-yl	Ts	Ac
9a	*E*-5-(2-bromovinyl)uracil-1-yl	Ts	Ac
9b	*E*-5-(2-bromovinyl)uracil-1-yl	Ts	H

Comp.	B	R
2	Thymin-1-yl	OH
4a	Adenin-9-yl	H
4b	Inosin-9-yl	H
4c	2,6-Diaminopurin-9-yl	H
4d	Guanin-9-yl	H

Comp.	B	R
6a	Cytosin-1-yl	CH_2OH
6b	Uracil-1-yl	CH_2OH
6c	Thymin-1-yl	CH_2OH
7a	Adenin-9-yl	$OCH_2P(O)(OH)_2$
7b	Hypoxanthin-9-yl	$OCH_2P(O)(OH)_2$
7c	Cytosin-1-yl	$OCH_2P(O)(OH)_2$
7d	Thymin-1-yl	$OCH_2P(O)(OH)_2$
7e	Uracil-1-yl	$OCH_2P(O)(OH)_2$

Figure 1.



10a B = Adenin-9-yl
10b B = Thymin-1-yl

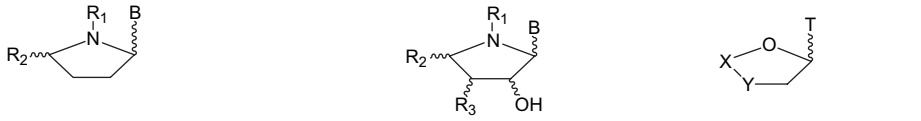
11 R_1 = H, CH_3, Ph_2CH

Comp.	R_1
12a	H
12b	C_4H_9
12c	$PhCH_2OCO$

Comp.	B	R_1
12d	Thymin-1-yl	Boc
12e	Uracil-1-yl	Boc
12f	Cytosin-1-yl	Boc
12g	Thymin-1-yl	Ac

Figure 2.

biologically active, non-nucleoside compounds.[34–44] In our previous paper,[45] we published the conditions for a reliable synthesis of pyrrolidine nucleosides **28d** and **28f** by nucleophilic displacement of the mesyloxy group in *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine by pyrimidine nucleobases, giving an excess of the desired 1-*N* regioisomer over the undesired 2-*O* isomer in a good overall yield. Herein, we report the synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of nucleobases **28a**–**28f** and **36**, **38**, respectively, as nucleoside analogues and also as the

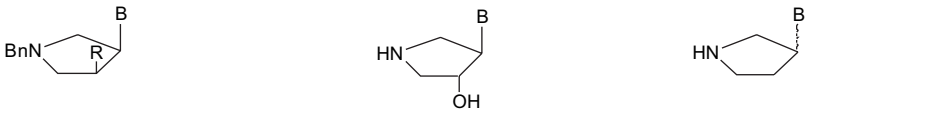


Comp.	B	R_1	R_2
12h	Thymin-1-yl	Boc	CH_2OH
12i	Uracil-1-yl	Boc	CH_2OH
12j	Cytosin-1-yl	Boc	CH_2OH
12k	Thymin-1-yl	Boc	CH_2OH
12l	Uracil-1-yl	Boc	H
12m	Thymin-1-yl	BnOCO	CH_2OH
12n	Thymin-1-yl	Ac	CH_2OH

Comp.	B	R_1	R_2	R_3
13a	Thymin-1-yl	Ac	CH_2OH	H
13b	Thymin-1-yl	Ac	CH_2OH	OH
13c	Thymin-1-yl	Ac	CH_3	OH
13d	Uracil-1-yl	Boc	CH_2OH	OH

14 X = CHOH, Y = NCOO-L-Menthyl
15 X = NH, Y = CH_2

Figure 3.



16a B = Thymin-1-yl; R = H
16b B = Uracil-1-yl; R = H
17a B = Thymin-1-yl; R = OH
17b B = Uracil-1-yl; R = OH

18a B = Thymin-1-yl
18b B = Uracil-1-yl
18c B = Adenin-9-yl

28a B = Adenin-9-yl
28b B = Guanin-9-yl
28c B = 2,6-Diaminopurin-9-yl
28d B = Thymin-1-yl
28e B = Uracil-1-yl
28f B = Cytosin-1-yl

Figure 4.

compounds for potential further derivatization. In addition, an improved preparation of starting (*RS*)- and (*S*)-*N*-protected-3-pyrrolidinol derivatives is described in detail.

2. Results and discussion

2.1. Improvement of the synthesis of 3-pyrrolidinols

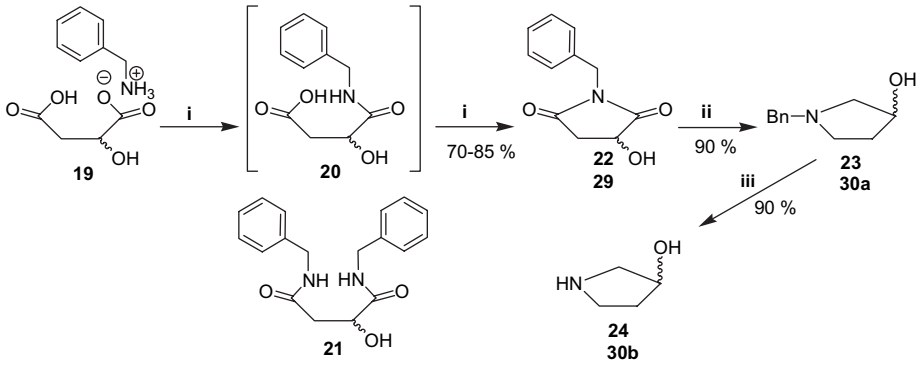
There are several approaches for the synthesis of *N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**) described in the literature (Schemes 1 and 3). Currently used procedures for the synthesis of *N*-benzyl-3-hydroxypyrrolidine-2,5-diones (**22**, **29**)[46–54] consist of azeotropic removal of water from the mixture of malic acid (**19**) and benzylamine in refluxing xylene[46,53] or in ethanol at 160 °C.[47–49,52,54] We repeated the 'xylene' procedure several times with varying yields of **22**. We observed that under experimental conditions, benzylamine distilled with xylene and the heterogeneous reaction mixture turned dark. The addition of benzylamine, to compensate for any loss during the azeotropic distillation, did not improve the yield of *N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**). An excess of benzylamine in the reaction mixture caused a drop in the yield of **22** due to the formation of dibenzylamide **21** as undesired product. Undoubtedly, the five-membered benzylimide ring of **22** was readily opened by benzylamine to form compound **21**. A similar ring-opening reaction of *N*-benzylsuccinimide, but with ammonia, has already been described by Werner.[55]

Concerning the mechanism of the benzylimide ring closure, a two-step reaction seems to be plausible. The first, rate-limiting step of the whole reaction involves thermal dehydration of the monobenzylammonium salt of malic acid **19**, resulting in formation of benzylamide **20**, which then undergoes a ring closure to yield benzylimide **22**. If the acid and benzylamine are mixed in xylene, a suspension is obtained, and monobenzylammonium salt **19** is formed very slowly. Concerning these observations, we elaborated a procedure giving consistently high yields of benzylimide **22**. Thus, first the monobenzylammonium salt of racemic or (*S*)-malic acid was prepared in aqueous methanol and then heated in refluxing xylene in the Dean–Stark apparatus. In contrast to the original procedure,[46,53] a clear homogeneous solution was obtained within several minutes of heating. Further heating (24 h) followed by crystallization of **22** (or **29**) from hot benzene afforded pure product in ~70% yield.

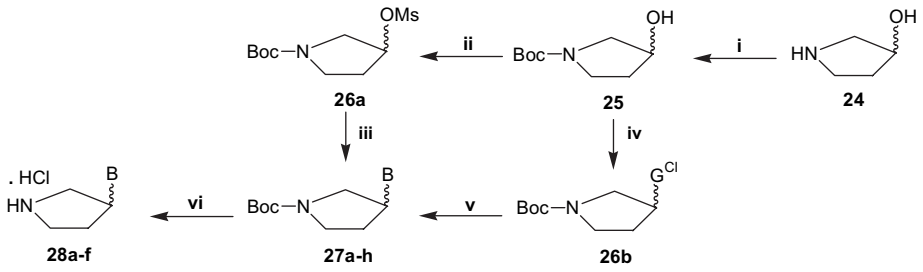
The reduction of benzylimide **22** and **29** to benzylamide **23** and **30a**, respectively, proceeded smoothly by treatment with diborane generated in situ from $NaBH_4$ and iodine in THF.[56] Desalting of *N*-benzyl-3-pyrrolidinol (**23**, **30a**) on Dowex 50W (H^+) followed by removal of *N*-benzyl group using catalytic hydrogenation afforded pure 3-pyrrolidinol (**24** and **30b**) (Schemes 1 and 3).

2.2. Synthesis of racemic 3-pyrrolidinyl derivatives of nucleobases

3-Pyrrolidinol **24** was first transformed into *N*-Boc derivative **25** and this compound was mesylated to derivative **26a**, which was used for the reaction with nucleobases (Scheme 2). For alkylation reactions of purine and pyrimidine nucleobases with **26a**, we selected DMSO as a solvent providing better yields of pyrrolidine derivatives of nucleobases than DMF. Thus, the alkylation of adenine and 2,6-diaminopurine with **26a** proceeded smoothly in the presence of Cs_2CO_3 as a base providing high yields of the desired 9-substituted compounds **27a** and **27c**. In contrast, the alkylation of sodium salts of pyrimidine nucleobases in DMSO led to a mixture of the desired 1-*N* substituted compounds **27e**–**27g** and the undesired 2-*O*-substituted derivatives as side products.[45] The Mitsunobu reaction of 2-amino-6-chloropurine with *N*-*tert*-butoxycarbonyl-3-pyrrolidinol (**25**) provided higher yield of **26b** than the alkylation of the same nucleobase with mesyl derivative **26a**. The obtained 2-amino-6-chloro-purine derivative **26b** was hydrolyzed in aqueous NaOH to afford guanine compound **27b**. The alkylation of sodium salt of cytosine by mesyl derivative **26a** in DMSO provided high overall yields of 1-*N*- and 2-*O*-substituted derivatives **27f** and **27g** (Scheme 2). The deprotection of *N*-*tert*-butoxycarbonyl derivatives **27a**–**27f** was accomplished by treatment with 20% TFA in dichlormethane and the crude products **28a**–**28f** were deionized on Dowex 50W. The obtained pyrrolidine nucleosides **28a**–**28f** were transformed into stable hydrochlorides.



Scheme 1. Synthesis of 3-pyrrolidinol.



In formulae **27** and **28**
a = Adenin-9-yl
b = Guanin-9-yl
c = 2,6-Diaminopurin-9-yl
d = Thymin-1-yl
e = Uracil-1-yl
f = Uracil-2,4-di-*O*-yl
g = Cytosin-1-yl
h = Cytosin-2-*O*-yl

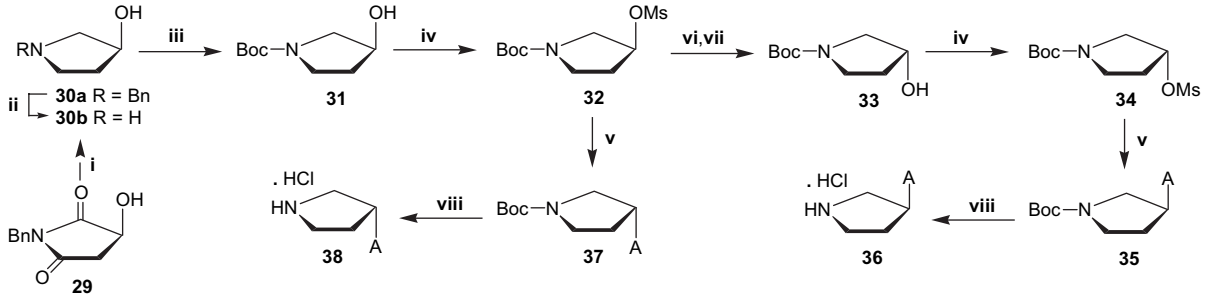
(**i**) Di(*tert*-butyl)dicarbonate, $NaHCO_3$ in *aq* dioxane;
(**ii**) MsCl, pyridine, DCM;
(**iii**) DMSO, NaH or Cs_2CO_3, base;
(**iv**) 2-amino-6-chloropurine, Ph_3P, DIAD, THF;
(**v**) 2-amino-6-chloro-purine derivative **26b**, 1M NaOH in *aq* dioxane;
(**vi**) a) 20% TFA in DCM, b) 1M HCl in diethylether

Scheme 2. Synthesis of racemic 3-pyrrolidinyl derivatives of nucleobases.

2.3. Synthesis of enantiomeric 3-pyrrolidinyl derivatives of adenine

Starting from (*S*)-malic acid (Fluka; information on enantiomeric purity is unavailable), we prepared (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**32**) via intermediates **30b** and **31** (Scheme 3). Inversion of the configuration on the C3-atom of **32**, bearing the mesyloxy group, was achieved by heating with sodium acetate in DMF. Treatment of the product with methanolic ammonia afforded 3-hydroxypyrrolidine derivative **33**, and its mesylation provided (*R*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**34**). Both mesyl derivatives **32** and **34** were subjected to the reaction with adenine in DMSO in the presence of Cs_2CO_3. The obtained (*S*)- and (*R*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) and (**37**), respectively, were deprotected to afford the derivatives **36** and **38**.

The enantiomeric purity of compounds **35** and **37** was checked on the cyclodextrin chiral HPLC column (ChiraDex, Merck). The results of analysis of the enantiomers **35** and **37** are shown in Figures 5 and 6, respectively, while Figure 7 shows the HPLC pattern of a mixture of the enantiomers **35** and **37**. Since the preparation of adenine compounds **35** and **37** started from the same chiral precursor **32**, and the reaction pathways to **35** and **37** included two nucleophilic displacements in the former case and one in the latter, we can conclude that the nucleophilic displacement of the mesyloxy group in compounds **32** and **34** must proceed with inversion, not retention of the configuration. In the latter case we would have obtained identical peaks on chiral HPLC. For the double inversion (**32**→**33** and **34**→**35**; Fig. 5) and for the single inversion (**32**→**37**; Fig. 6) of the configuration we found about 85% and 90% enantiomeric purities of the products **35** and **37**, respectively. Since there is 5% difference in the content of minor enantiomer, one can conclude that the increased amount of the minor enantiomer in compound **35** has to come from the displacement of the mesyloxy group for acetate moiety in the reaction **32**→**33** (Scheme 3). If this reaction is accompanied by a partial racemization then also the



(**i**) $NaBH_4$, I_2, THF;
(**ii**) Pd/C, Acetic acid, H_2 (*g*);
(**iii**) Di(*tert*-butyl)dicarbonate, $NaHCO_3$ in *aq* dioxane;
(**iv**) MsCl, pyridine, DCM;
(**v**) DMSO, Cs_2CO_3;
(**vi**) AcONa, DMF;
(**vii**) sat. NH_3 in MeOH;
(**viii**) a) 20% TFA in DCM, b) 1M HCl in diethylether

Scheme 3. Synthesis of enantiomeric 3-pyrrolidinyl derivatives of adenine.

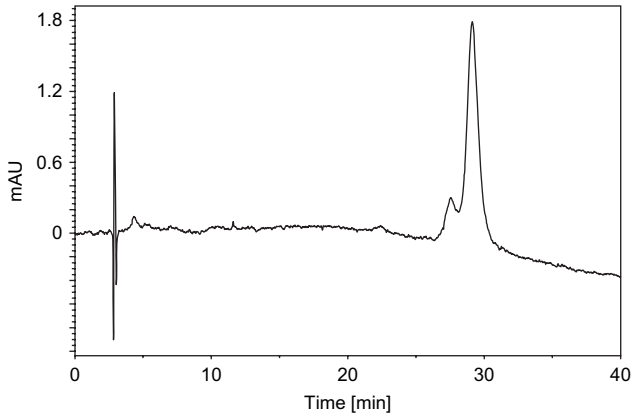


Figure 5. Chiral HPLC analysis: enantiomeric purity of (*S*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) (double inversion **32**→**33** and **34**→**35**).

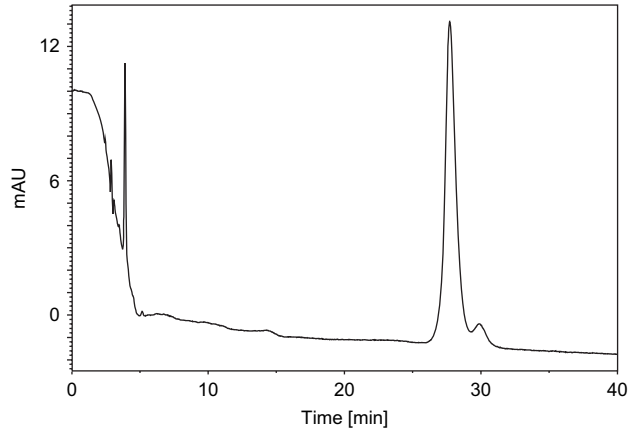


Figure 6. Chiral HPLC analysis: enantiomeric purity of (*R*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**37**) (single inversion **32**→**37**).

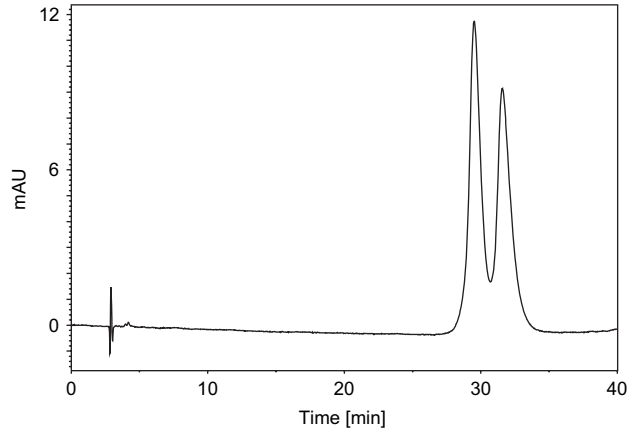


Figure 7. Chiral HPLC analysis: resolution of a mixture of **35** and **37** (the same pattern was obtained for racemic mixture **27**).

displacement of the mesyloxy group for adenine moiety in both reactions **32**→**37** and **34**→**35** should proceed with partial racemization but to the identical extent for both reactions. Nevertheless, potential presence of small amount of (*R*)-enantiomer in the starting (*S*)-malic acid (which cannot be excluded) and/or C3 racemization during thermal dehydration of benzylammonium salt of (*S*)-malic acid to dione **22** (Scheme 2) cannot influence, in any case, this 5% difference in the content of minor enantiomers (Figs. 5 and 6). This analysis suggests that mainly both nucleophilic displacements are responsible for found extent of racemization.

2.4. Biological activity

The cytostatic activity of analogues **28a–28f**, **32**, **34** was examined on L1210, L929, and HeLa S3 cell lines. The antiviral activity against DNA viruses was evaluated using infected E_6SM, HeLa, and Vero cell cultures. No significant activity was found.

3. Conclusion

In this paper, we report the synthesis of racemic and enantiomeric 3-pyrrolidinyl derivatives of purine and pyrimidine nucleobases as novel nucleoside analogues **28a–28f**, **36**, and **38**. These can be used for further derivatization at the pyrrolidine nitrogen atom in an attempt to modulate their potential biological activity. We have improved the synthesis of racemic and enantiomeric *N*-benzyl-3-pyrrolidinols with respect to reproducibility and high yields of these compounds. The racemic, as well as both enantiomeric *N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidines **26a**, **32**, **34** as key synthons for alkylation of nucleobases have been prepared in high yields after five steps. We have elaborated conditions providing acceptable yields for both 1-substituted pyrimidine and 9-substituted purine compounds. Using the same chiral precursor **32** for the preparation of enantiomeric adenine compounds **35** and **37**, which provided two different peaks on chiral HPLC, we proved that the nucleophilic displacement of 3-mesyloxy group in *N*-Boc-3-mesyloxypyrrolidines proceeded with inversion, not retention of the configuration. Concerning the cytostatic and antiviral properties of novel 3-pyrrolidinyl derivatives of nucleobases **28a–28f**, **36**, **38**, no significant activities were found.

4. Experimental

4.1. General

Unless stated otherwise, all solvents were evaporated at 13 kPa. Products were dried over P_2O_5 at 13 Pa. All chemicals were obtained from commercial suppliers and all used solvents were anhydrous. Chiral HPLC analysis was performed on Alliance HPLC system (Waters) with DAD detector using ChiraDex® column (Merck, 254×4 mm, 5 μm), isocratically in 10% aqueous acetonitrile at flow rate 1 mL/min. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance 400 and Bruker Avance 500 spectrometers (^{1}H at 400 and 500 MHz, ^{13}C at 100.6 and 125.8 MHz, respectively) in DMSO-d_6 and were referenced to the residual solvent signal (δ_H=2.50 ppm, δ_C=39.7 ppm). 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.

4.1.1. (*RS*)-*N*-Benzyl-3-hydroxypyrrolidine-2,5-dione (22). Benzylamine (160.7 mL, 1.5 mol) was slowly added to a stirred suspension of racemic malic acid (201.1 g;

1.5 mol) in 50% aqueous methanol (300 mL), and the resulting mixture was stirred at 50 °C until clear solution was obtained. The viscous solution was concentrated in vacuo, xylene (4 L) was added, and the mixture was refluxed in Dean–Stark apparatus at 190 °C in an oil bath for 24 h. During this time, xylene was added in two portions (2×500 mL). The dark brown solution was concentrated in vacuo, the residue was co-evaporated with ethanol (2×500 mL) to remove remaining xylene, and dissolved in refluxing benzene (1000 mL). Then the solution was concentrated in vacuo until crystallization took place. The suspension was left to crystallize overnight in the refrigerator. White crystals were filtered off, washed with cold benzene (2×100 mL), and the filtrates were concentrated for the next crystallization. Yield, 224.6 g (74%, white crystals) of **22**. (*Note: Mother liquor can provide additional 10–15% of the pure product* **22**.) Mp 105–109 °C.

HRMS: for $C_{11}H_{12}NO_3$ $(M+H)^+$ calcd 206.0817, found 206.0815.

^{1}H NMR (400 MHz, DMSO-d_6): 2.48 (dd, 1H, J_{gem}=17.8, $J_{4'b,3'}$=4.4, H-4′b); 3.05 (dd, 1H, J_{gem}=17.8, $J_{4'a,3'}$=8.3, H-4′a); 4.55 (s, 2H, NCH_2); 4.57 (ddd, 1H, $J_{3',4'}$=8.3, 4.4, $J_{3',OH}$=6.7, H-3′); 6.15 (d, 1H, $J_{OH,3'}$=6.7, OH); 7.20–7.40 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, DMSO-d_6): 38.03 (CH_2-4′); 41.36 (NCH_2); 66.51 (CH-3′); 127.60, 127.71 and 128.66 (CH–Ph); 136.29 (*i*-C–Ph); 174.98 (C-5); 178.25 (C-2).

4.1.2. (*RS*)-*N*-Benzyl-3-pyrrolidinol (23). A solution of iodine (95.2 g, 375 mmol) in THF (450 mL) was added dropwise under argon to an ice-cooled, vigorously stirred suspension of $NaBH_4$ (28.4 g, 750 mmol) in a solution of (*RS*)-*N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**22**) (co-evaporated with THF) (30.8 g, 150 mmol) in THF (700 mL). After completion of iodine addition, the reaction mixture was stirred at rt for 5 d, then cooled to 0 °C, and the excess $NaBH_4$ was decomposed by slowly adding 3 M HCl (143 mL). (*Note: Vigorous gas evolution*.) The reaction mixture was concentrated to about 150 mL and carefully basified with aqueous 2 M NaOH to pH 10 at 0 °C. DCM (500 mL) was added, and the aqueous phase was saturated with solid K_2CO_3 under vigorous stirring. The organic layer was separated, and the aqueous phase extracted once again with DCM (300 mL). The combined organic layers were concentrated in vacuo, and the residue was deionized on Dowex 50W (500 mL) in H^+ form. (*Note: Column of Dowex was first washed with EtOH to remove color impurities*.) The elution with 3% aqueous ammonia afforded a TLC pure compound (detection with ninhydrin), which was co-evaporated with ethanol (2×100 mL) to give 24.7 g (93%) of product **23** as light brown oil.

HRMS: for $C_{11}H_{16}NO$ $(M+H)^+$ calcd 178.1232, found 178.1233.

^{1}H NMR (500 MHz, DMSO-d_6): 1.53 (dddd, 1H, J_{gem}=12.9, $J_{4'b,5'}$=7.8, 5.6, $J_{4'b,3'}$=3.4, H-4′b); 1.98 (ddt, 1H, J_{gem}=12.9, $J_{4'a,5'}$=7.8, 6.5, $J_{4'a,3'}$=7.8, H-4′a); 2.29 (dd, 1H, J_{gem}=9.6, $J_{2'b,3}$=3.8, H-2′b); 2.38 (ddd, 1H, J_{gem}=8.9, $J_{5'b,4'}$=7.8, 5.6, H-5′b); 2.54 (dt, 1H, J_{gem}=8.9, $J_{5'a,4'}$=7.8, 6.5, H-5′a); 2.65 (dd, 1H, J_{gem}=9.6, $J_{2'a,3'}$=6.2, H-2′a); 3.50 and 3.56 (2×d, 2×1H, J_{gem}=13.0, CH_2–Ph); 4.18 (ddt, 1H, $J_{3',4'}$=7.8, 3.4, $J_{3',2'}$=6.2, 3.8, H-3′); 4.54 (br s, 1H, OH); 7.20–7.35 (m, 5H, Ph). ^{13}C NMR (125.8 MHz, DMSO-d_6) for **23a**: 34.64 (CH_2-4′); 52.61 (CH_2-5′); 59.95 (CH_2–Ph); 62.80 (CH_2-2′); 69.59 (CH-3′); 126.91, 128.29 and 128.66 (CH–Ph); 139.44 (*i*-C–Ph).

4.1.3. (*RS*)-3-Pyrrolidinol (24). A solution of *N*-benzyl-3-hydroxypyrrolidine **23a** (26.6 g, 150 mmol) in concentrated acetic acid (900 mL) was treated at rt with hydrogen gas (10 psi) in the presence of 10% palladium on charcoal (2 g) under vigorous stirring for 5 d. The suspension was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was co-evaporated with ethanol (2× 100 mL) and dried in vacuo over P_2O_5 to afford 12.0 g (92%) of product **24** as yellow oil.

EI$^+$: for C_4H_9NO (M^+) calcd 87.0684, found 87.0685.

^{1}H NMR (500 MHz, DMSO-d_6): 1.58 (m, 1H, H-4′b); 1.75 (ddt, 1H, J_{gem}=13.1, $J_{4'a,5'}$=8.6, 8.3, $J_{4'a,3'}$=5.8, H-4′a); 2.67 (ddd, 1H, J_{gem}=11.5, $J_{2'b,3'}$=2.4, $J_{2'b,NH}$=1.0, H-2′b); 2.78 (ddd, 1H, J_{gem}=10.8, $J_{5'b,4'}$=8.6, 4.5, H-5′b); 2.81 (dd, 1H, J_{gem}=11.5, $J_{2'a,3'}$=4.8, H-2′a); 2.93 (dt, 1H, J_{gem}= 10.8, $J_{5'a,4'}$=8.3, 7.8, H-5′a); 4.19 (ddt, 1H, $J_{3',4'}$=5.8, $J_{3',2'}$=4.8, 2.4, H-3′); 4.49 (br s, 2H, NH+OH). ^{13}C NMR (125.8 MHz, DMSO-d_6): 35.11 (CH_2-4′); 44.61 (CH_2-5′); 54.83 (CH_2-2′); 70.60 (CH-3′).

4.1.4. (*RS*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (25). Boc anhydride (36.0 g, 165 mmol) was added to a vigorously stirred suspension of (*RS*)-3-pyrrolidinol (13.1 g, 150 mmol) (**24**) and sodium hydrogen carbonate (126.1 g, 1.5 mol) in 50% aqueous dioxane (750 mL) at rt. After the completion of reaction, the mixture was concentrated, the solids were filtered off, and the filtration cake was washed with ethanol. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (elution with a linear gradient of ethyl acetate in toluene). Yield, 26.4 g (94%, white solid) of **25**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 188.1280.

^{1}H NMR (500 MHz, DMSO-d_6, a mixture of amide isomers, 1:1): 1.39 (s, 9H, *t*-Bu); 1.72 (br m, 1H, H-4′b); 1.84 (br m, 1H, H-4′a); 3.10 (br d, 1H, J_{gem}=11.5, H-2′b); 3.22–3.32 (m, 3H, H-2′a and H-5′); 4.21 (br m, 1H, H-3′); 4.86 (d, 1H, $J_{OH,3'}$=6.5, OH-3′). ^{13}C NMR (125.8 MHz, DMSO-d_6): 28.33 (CH_3–*t*-Bu); 33.04 and 33.80 (CH_2-4′); 43.68 and 43.92 (CH_2-5′); 53.98 and 54.23 (CH_2-2′); 68.59 and 69.43 (CH-3); 78.15 (C–*t*-Bu); 153.82 (CO).

4.1.5. (*RS*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (26a). Mesylchloride (74.4 mL, 961.5 mmol) was added dropwise to a solution of (*RS*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**25**) (24 g, 128.2 mmol) and pyridine (77.4 mL, 961.5 mmol) in DCM (300 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h. The reaction was quenched by pouring onto an ice (100 g), and the organic layer was washed twice with 1 M HCl and saturated solution of sodium hydrogen carbonate. The organic phase was concentrated and the crude product was purified by flash chromatography on silica gel (elution with a linear gradient of

ethyl acetate in toluene). Yield, 29.2 g (85%, yellow foam) of **26a**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1066.

^{1}H NMR (400 MHz, 80 °C, DMSO-d_6, a mixture of amide isomers A:B, 3:2): 1.43 (s, 18H, *t*-Bu-A and *t*-Bu-B); 2.13 (m, 2H, H-4′bA and H-4′bB); 2.18 (dd, 1H, J_{gem}=8.9, $J_{4'a,3'}$=4.6, H-4′aA); 2.21 (dd, 1H, J_{gem}=9.2, $J_{4'a,3'}$=4.6, H-4′aB); 3.19 (s, 6H, CH_3–SO_2–); 3.31 (dd, 1H, J_{gem}=8.4, $J_{5'b,4'b}$=7.0, H-5′bB); 3.34 (dd, 1H, J_{gem}=11.7, $J_{5'b,4'b}$=7.3, H-5′bA); 3.41 (dd, 1H, J_{gem}=11.7, $J_{5'a,4'b}$=3.5, H-5′aA); 3.44 (dd, 1H, J_{gem}=8.4, $J_{5'a,4'b}$=3.6, H-5′aB); 3.49 (dd, 1H, J_{gem}=12.8, $J_{2'b,3'}$=1.8, H-2′bB); 3.50 (dd, 1H, J_{gem}=12.8, $J_{2'b,3'}$=1.8, H-2′bA); 3.55 (dd, 1H, J_{gem}=12.8, $J_{2'a,3'}$=4.3, H-2′aA and H-2′aB); 5.23 (tt, 2H, $J_{3',4'a}$=4.6, 2.4, $J_{3',2'a}$=4.3, 1.8, H-3′A and H-3′B). ^{13}C NMR (100.6 MHz, DMSO-d_6): 27.51 (CH_3–Boc); 31.11 and 31.94 (CH_2-4′); 37.82 (CH_3–SO_2–); 43.44 and 43.63 (CH_2-5′); 51.97 and 52.20 (CH_2-2′); 78.92 (C–Boc); 80.33 and 81.11 (CH-3′); 153.49 and 153.60 (CO).

4.2. General method for alkylation reactions

Prior to use, the nucleobases were dried in vacuo at 50–100 °C for 16 h. A suspension of the nucleobase and Cs_2CO_3 (1.5 equiv for purine nucleobases) or NaH (1.5 equiv for pyrimidine nucleobases) in DMSO (5 mL/mmol) was stirred under argon atmosphere at 100 °C for 20 min. Then, mesyl derivative **26a** (1 equiv) in DMSO (5 mL/mmol) was added and the mixture was stirred at 110 °C. After completion of reaction (~18 h) the mixture was concentrated under vacuum on an oil pump, adsorbed onto column of silica gel and purified by flash chromatography (elution with a linear gradient of ethanol in chloroform) to afford the compounds **27a**–**27f**.

4.2.1. (*RS*)-2-Amino-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-6-chloropurine (26b). *Method A*. A mixture of (*RS*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**25**) (4.3 g, 23 mmol), 2-amino-6-chloro-purine (4.48 g, 29 mmol), and triphenyl phosphine (10.9 g, 41.4 mmol) was co-evaporated twice with THF and suspended in THF (115 mL) under an argon atmosphere at 0 °C. Then, DIAD (10.3 mL, 53 mmol) was added under stirring. The suspension became clear within 5 min. The solution was concentrated, adsorbed onto a column of silica gel, and the compound was eluted with a linear gradient of ethanol in chloroform to afford crude product **26b** (ca. 70%, yellow solid), which was used directly for the preparation of guanine derivative **27b**.

Method B. The 2-amino-6-chloro-purine derivative **26b** was prepared from (*RS*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (0.8 g, 3 mmol) and 2-amino-6-chloropurine (0.8 g, 4.5 mmol) according to the general method for alkylation, but DMF was used instead of DMSO. Yield, 0.340 g (33%, yellow foam).

HRMS: for $C_{14}H_{20}ClN_6O_2$ $(M+H)^+$ calcd 339.1336, found 339.1327.

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C, a mixture of amide isomers, 1:1): 1.48 (s, 9H, *t*-Bu); 2.36–2.49 (m, 2H, H-4′); 3.45 and 3.58 (2×m, 2×1H, H-5′); 3.71 (dd, 1H, J_{gem}=12.0, $J_{2'b,3'}$=6.9, H-2′b); 3.89 (dd, 1H, J_{gem}=12.0, $J_{2'a,3'}$=6.5, H-2′a); 5.01 (p, 1H, $J_{3',2'}$=6.9, 6.5, $J_{3',4'}$=6.4, H-3′); 5.08 (br s, 2H, NH_2); 7.74 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, $CDCl_3$): 28.42 (CH_3–Boc); 30.54 and 31.48 (CH_2-4′); 43.95 (CH_2-5′); 50.01 and 50.62 (CH_2-2′); 53.22 and 53.85 (CH-3′); 80.30 (C–Boc); 125.47 (C-5); 139.84 (CH-8); 151.59 (C-4); 153.55 (CO); 154.22 (C-6); 158.91 (C-2).

4.2.2. (*RS*)-9-(*N*-*tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (27a). The title compound was prepared from (*RS*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (3.7 g, 14 mmol) and adenine (2.8 g, 20.7 mmol) according to the general method for alkylations provided above. Yield, 3 g (71%, yellow foam).

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1724.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (s, 9H, *t*-Bu); 2.35–2.53 (m, 2H, H-4′); 3.42 (dt, 1H, J_{gem}=10.9, $J_{5'b,4'}$=7.6, H-5′b); 3.56 (ddd, 1H, J_{gem}=10.9, $J_{5'a,4'}$=8.0, 5.5, H-5′a); 3.65 (dd, 1H, J_{gem}=11.1, $J_{2'b,3'}$=6.1, H-2′b); 3.81 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=7.0, H-2′a); 5.08 (p, 1H, $J_{3',2'}$=7.0, 6.1, $J_{3'4'}$=6.0, H-3′); 7.11 (br s, 2H, NH_2); 8.12 (s, 1H, H-8); 8.15 (s, 1H, H-2).

^{13}C NMR (100.6 MHz, DMSO-d_6, 50 °C): 28.16 (CH_3–Boc); 29.99 (CH_2-4′); 44.11 (CH_2-5′); 50.05 (CH_2-2′); 53.12 (CH-3′); 78.73 (C–Boc); 119.20 (C-5); 138.97 (CH-8); 149.53 (C-4); 152.38 (CH-2); 153.54 (CO); 156.09 (C-6).

4.2.3. (*RS*)-9-(*N*-*tert*-Butoxycarbonyl-3-pyrrolidinyl)-guanine (27b). The crude mixture of (*RS*)-2-amino-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-6-chloropurine (**26b**) (prepared by *Method A*) was treated with 600 mL of 1 M NaOH in 30% aqueous dioxane. After 5 d of stirring, the mixture was mixed with Dowex 50 (Et_3NH^+) (500 mL), the suspension was filtered, the resin was washed with ethanol, and the combined filtrates were concentrated. The residue was adsorbed onto silica gel (100 g) and the dried sorbent was transferred onto dry silica gel column, which was eluted with a linear gradient of ethanol in chloroform to give the title compound as a white foam. Yield, 2.6 g (35% calculated for compound **25** from *Method A*).

HRMS: for $C_{14}H_{21}N_6O_3$ $(M+H)^+$ calcd 321.1675, found 321.1678.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.38 and 1.41 (2×s, 9H, *t*-Bu); 2.26–2.42 (m, 2H, H-4′); 3.35 (m, 1H, H-5′b); 3.45–3.57 (m, 2H, H5′a and H-2′b); 3.72 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=6.8, H-2′a); 4.82 (m, 1H, H-3′); 6.49 (br s, 2H, NH_2); 7.70 (s, 1H, H-8); 10.25 (br s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.30 (CH_3–Boc); 29.50 and 30.43 (CH_2-4′); 44.08 and 44.28 (CH_2-5′); 50.15 and 50.40 (CH_2-2′); 52.38 and 53.04 (CH-3′); 78.95 (C–Boc); 117.10 (C-5); 135.33 and 135.44 (CH-8); 151.29 (C-4); 153.64 (CO and C-6); 156.09 (C-2).

4.2.4. (*RS*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)-2,6-diaminopurine (27c). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (1.3 g, 5 mmol) and 2,6-diaminopurine (1.1 g, 7.5 mmol) according to the general method for alkylation. Yield, 1.2 g (76%, white foam).

HRMS: for $C_{14}H_{22}N_7O_2$ $(M+H)^+$ calcd 320.1835, found 320.1845.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (s, 9H, *t*-Bu); 2.27–2.48 (m, 2H, H-4′); 3.40 (m, 1H, H-5′b); 3.51 (ddd, 1H, J_{gem}=11.0, $J_{5'a,4'}$=8.0, 5.5, H-5′a); 3.58 (dd, 1H, J_{gem}=11.0, $J_{2'b,3'}$=6.2, H-2′b); 3.74 (dd, 1H, J_{gem}=11.0, $J_{2'a,3'}$=7.0, H-2′a); 4.86 (br p, 1H, $J_{3',2'}$=7.0, 6.2, $J_{3',4'}$=6.0, H-3′); 5.69 and 6.57 (2×br s, 2×2H, NH_2); 7.69 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.33 (CH_3–Boc); 29.39 and 30.37 (CH_2-4′); 44.16 and 44.36 (CH_2-5′); 50.00 and 50.32 (CH_2-2′); 52.22 and 52.90 (CH-3′); 78.94 (C–Boc); 113.10 (C-5); 135.45 and 135.54 (CH-8); 151.88 (C-4); 153.71 (CO); 156.38 (C-6); 160.37 (C-2).

4.2.5. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)thymine (27d). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**26a**) (6.0 g, 22.6 mmol) and thymine (4.3 g, 34 mmol) according to the general method for alkylation. Yield, 2.6 g (40%, yellow foam).

HRMS: for $C_{14}H_{22}N_3O_4$ $(M+H)^+$ calcd 296.1610, found 296.1612.

^{1}H NMR (500 MHz, DMSO-d_6, 30 °C, a mixture of amide isomers, 1:1): 1.40 (br s, 9H, *t*-Bu); 1.77 (d, 3H, *J*=1.2, CH_3-5); 2.13 (br m, 2H, H-4′); 3.22–3.31 (br m, 2H, H-5′b and H-2′b); 3.46 (dt, 1H, J_{gem}=10.8, $J_{5'a,4'}$=6.3, H-5′a); 3.58 (br m, 1H, H-2′a); 4.92 (br m, 1H, H-3′); 7.50 (br m, 1H, H-6); 11.23 (br s, 1H, NH).

^{13}C NMR (125.8 MHz, DMSO-d_6): 12.20 (CH_3-5); 28.25 and 28.33 (CH_3–Boc); 29.29 (CH_2-4′); 43.68 and 43.92 (CH_2-5′); 48.51 and 48.77 (CH_2-2′); 53.27 and 53.80 (CH-3′); 78.80 (C–Boc); 109.43 (C-5); 137.56 (CH-6); 151.08 (C-2); 153.55 (CO); 163.79 (C-4).

4.2.6. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)uracil (27e) and (*RS*)-2,4-bis-*O*-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)uracil (27f). The title compound was prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxy-pyrrolidine (**26a**) (7.4 g, 28 mmol) and uracil (4.7 g, 42 mmol) according to the general method for alkylation. Yield, 2.6 g (32%, yellow foam) of **27e** and 1.3 g (10%, yellow foam) of **27f**.

27e: HRMS: for $C_{13}H_{20}N_3O_4$ $(M+H)^+$ calcd 282.1454, found 282.1452.

^{1}H NMR (400 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (br s, 9H, *t*-Bu); 2.06–2.23 (br m, 2H, H-4′); 3.24–3.37 (br m, 2H, H-5′b and H-2′b); 3.44 (ddd, 1H, J_{gem}=13.4, $J_{5'a,4'}$=7.9, 5.1, H-5′a); 3.61 (dd, 1H, J_{gem}=11.3, $J_{2'a,3'}$=7.4, H-2′a); 4.90 (br p, 1H, $J_{3',2'}$=7.4, 7.0, $J_{3'4'}$=7.0, H-3′); 5.57 (d, 1H, $J_{5,6}$=8.0, H-5); 7.56 (d, 1H, $J_{6,5}$=8.0, H-6); 11.18 (br s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.31 (CH_3–Boc); 28.94 and 29.45 (CH_2-4′); 44.00 and 44.27 (CH_2-5′); 48.82 and 49.06 (CH_2-2′); 53.82 and 54.47 (CH-3′); 78.90 (C–Boc); 101.81 (CH-5); 142.15 (CH-6); 151.19 (C-2); 153.61 (CO); 163.32 (C-4).

27f: HRMS: for $C_{22}H_{35}N_4O_6$ $(M+H)^+$ calcd 451.2557, found 451.2556.

^{1}H NMR (400 MHz, DMSO-d_6): 1.38 and 1.39 (2×br s, 2×9H, *t*-Bu); 2.00–2.25 (br m, 4H, H-4′); 3.25–3.48 (br m, 6H, H-2′b and H-5′); 3.52–3.64 (br m, 2H, H-2′a); 5.42 and 5.52 (2×br m, 2×1H, H-3′), 6.57 (d, 1H, $J_{5,6}$=5.7, H-5); 8.30 (d, 1H, $J_{6,5}$=5.7, H-6).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.39 (CH_3–Boc); 30.30 and 31.08 (CH_2-4′); 43.87, 43.93, 44.08 and 44.17 (CH_2-5′); 51.55, 51.71, 51.75 and 51.90 (CH_2-2′); 75.27, 75.76, 76.07 and 76.62 (CH-3′); 78.85 and 78.90 (C–Boc); 102.79 (CH-5); 153.79 (CO); 159.73 (CH-6); 163.90 (C-2); 170.09 (C-4).

4.2.7. (*RS*)-1-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)-cytosine (27g) and (*RS*)-2-*O*-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)cytosine (27h). The title compounds were prepared from (*RS*)-*N-tert*-butyloxycarbonyl-3-mesyloxy-pyrrolidine (**26a**) (8.7 g, 33 mmol) and cytosine (5.5 g, 50 mmol) according to the general method for alkylation. Yield, 5.0 g (54%, yellow foam) of **27g** and 3.6 g (39%, yellow foam) of **27h**.

27g: HRMS: for $C_{13}H_{21}N_4O_3$ $(M+H)^+$ calcd 281.1614, found 281.1610.

^{1}H NMR (500 MHz, DMSO-d_6, 50 °C, a mixture of amide isomers, 1:1): 1.41 (br s, 9H, *t*-Bu); 2.03–2.19 (br m, 2H, H-4′); 3.23 (dd, 1H, J_{gem}=11.2, $J_{2'b,3'}$=6.2, H-2′b); 3.32 (dt, 1H, J_{gem}=10.9, $J_{5'b,4'}$=7.5, H-5′b); 3.43 (ddd, 1H, J_{gem}=10.9, $J_{5'a,4'}$=8.2, 5.4, H-5′a); 3.60 (dd, 1H, J_{gem}=11.2, $J_{2'a,3'}$=7.4, H-2′a); 4.90 (p, 1H, $J_{3',4'}$=7.6, $J_{3',2'}$=7.4, 6.2, H-3′); 5.71 (d, 1H, $J_{5,6}$=7.4, H-5); 6.92 (br s, 2H, NH); 7.49 (d, 1H, $J_{6,5}$=7.4, H-6).

^{13}C NMR (125.8 MHz, DMSO-d_6, 50 °C): 28.14 (CH_3–Boc); 28.54 (CH_2-4′); 43.96 (CH_2-5′); 49.38 (CH_2-2′); 54.66 (CH-3′); 78.60 (C–Boc); 93.82 (CH-5); 142.17 (CH-6); 153.49 (CO); 155.58 (C-2); 165.40 (C-4).

27h: HRMS: for $C_{13}H_{21}N_4O_3$ $(M+H)^+$ calcd 281.1614, found 281.1623.

^{1}H NMR (500 MHz, DMSO-d_6, 50 °C): 1.40 (br s, 9H, *t*-Bu); 2.00 (br m, 2H, H-4′b); 2.11 (br m, 2H, H-4′a); 3.30–3.37 (br m, 2H, H-2′b and H-5′b); 3.41 (ddd, 1H, J_{gem}=10.5, $J_{5'a,4'}$=8.8, 3.2, H-5′a); 3.53 (br dd, 1H, J_{gem}=12.3, $J_{2'a,3'}$=4.6, H-2′a); 5.34 (br m, 1H, H-3′); 6.10 (d, 1H, $J_{5,6}$=5.7, H-5); 6.71 (br s, 2H, NH_2); 7.85 (d, 1H, $J_{6,5}$=5.7, H-6).

^{13}C NMR (125.8 MHz, DMSO-d_6, 50 °C): 28.16 (CH_3–Boc); 30.69 (CH_2-4′); 43.83 (CH_2-5′); 51.69 (CH_2-2′);

73.92 (CH-3′); 78.38 (C–Boc); 99.58 (CH-5); 153.61 (CO); 156.17 (CH-6); 164.17 (C-2); 165.46 (C-4).

4.2.8. (*RS*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (28a). (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**27a**) (3.0 g, 10 mmol) was treated with 20% (v/v) TFA in DCM (100 mL) for 1 d. Pyrrolidine derivative was deionized on Dowex 50 (H^+ form) as described previously, treated with 1 M HCl in MeOH (50 mL) for 30 min, and the solution was concentrated in vacuo. Obtained solid residue was co-evaporated several times with methanol and the compound was freeze-dried from aqueous solution to give dihydrochloride salt. Yield, 1.8 g (66%, white powder).

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1200.

ν_{max}(KBr) 3350 (m), 3301 (s), 3119 (s, br), 2746 (w), 1674 (vs), 1647 (s), 1600 (vs),1570 (s), 1535 (m), 1480 (s), 1421 (s), 1415 (s), 1373 (s), 1331 (s), 1307 (s), 1229 (m), 845 (m), 798 (m), 728 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 2.34 (dddd, 1H, J_{gem}=13.5, $J_{4'b,5'}$=8.1, 6.9, $J_{4'b,3'}$=5.6, H-4′b); 2.49 (dtd, 1H, J_{gem}=13.5, $J_{4'a,5'}$=8.2, 6.5, $J_{4'a,3'}$=7.9, H-4′a); 3.30 (ddd, 1H, J_{gem}=11.5, $J_{5'b,4'}$=8.2, 6.9, H-5′b); 3.51 (ddd, 1H, J_{gem}=11.5, $J_{5'a,4'}$=8.1, 6.5, H-5′a); 3.58 (dd, 1H, J_{gem}=12.3, $J_{2'b,3'}$=5.4, H-2′b); 3.64 (dd, 1H, J_{gem}=12.3, $J_{2'a,3'}$=7.4, H-2′a); 5.25 (tt, 1H, $J_{3',4'}$=7.9, 5.6, $J_{3',2'}$=7.4, 5.4, H-3′); 7.31 (br s, 2H, NH_2); 8.15 (s, 1H, H-2); 8.31 (s, 1H, H-8).

^{13}C NMR (100.6 MHz, DMSO-d_6): 30.69 (CH_2-4′); 44.48 (CH_2-5′); 49.10 (CH_2-2′); 53.26 (CH-3′); 119.28 (C-5); 139.81 (CH-8); 149.25 (C-4); 152.53 (CH-2); 156.30 (C-6).

4.2.9. (*RS*)-9-(3-Pyrrolidinyl)guanine dihydrochloride (28b). The title compound was prepared from (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-guanine (**27b**) (1.5 g, 4.7 mmol) according to the procedure described for compound **28a**. Yield, 1.2 g (84%, white powder).

HRMS: for $C_9H_{13}N_6O$ $(M+H)^+$ calcd 221.1151, found 221.1154.

ν_{max}(KBr) 3299 (m), 3112 (s, br), 2756 (m, br), 1720 (s), 1656 (vs), 1606 (s), 1536 (w), 1377 (m), 1162 (w), 766 (m), 732 (w), 674 (w).

^{1}H NMR (500 MHz, DMSO-d_6): 2.31 (dddd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.2, 6.4, $J_{4'b,3'}$=4.1, H-4′b); 2.54 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=8.6, 6.8, H-4′a); 3.32 (ddd, 1H, J_{gem}=11.9, $J_{5'b,4'}$=8.6, 6.4, H-5′b); 3.54–3.73 (m, 3H, H-4′ and H-5′a); 5.22 (tt, 1H, $J_{3',4'}$=8.8, 4.1, $J_{3',2'}$=7.4, 3.9, H-3′); 7.23 (br s, 2H, NH_2); 8.82 (s, 1H, H-8); 9.25, 9.83 and 11.56 (3×br s, 3×1H, NH).

^{13}C NMR (125.8 MHz, DMSO-d_6): 31.63 (CH_2-4′); 44.74 (CH_2-5′); 49.19 (CH_2-2′); 54.83 (CH-3′); 111.00 (C-5); 136.92 (CH-8); 149.81 (C-4); 154.77 (C-6); 155.25 (C-2).

4.2.10. (*RS*)-2,6-Diamino-9-(3-pyrrolidinyl)purine trihydrochloride (28c). The title compound was prepared from (*RS*)-9-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)-2,6-diaminopurine (**27c**) (2.3 g, 7.1 mmol) according to the procedure described for compound **28a**. Yield, 1.7 g (73%, white powder).

HRMS: for $C_9H_{14}N_7$ $(M+H)^+$ calcd 220.1311, found 220.1321.

ν_{max}(KBr) 3318 (s, br), 3099 (s, vbr), 2942 (s, vbr, sh), 2738 (m, br), 1705 (s), 1686 (s, sh), 1636 (vs), 1612 (s), 1593 (s, sh), 1570 (m, sh), 1532 (m, w), 1515 (w, sh), 1480 (m), 1414 (m), 1345 (m), 1205 (w), 790 (w), 658 (w).

^{1}H NMR (400 MHz, DMSO-d_6): 2.20 (dddd, 1H, J_{gem}=11.3, $J_{4'b,5'}$=8.2, 6.9, $J_{4'b,3'}$=4.4, H-4′b); 2.48 (dtd, 1H, J_{gem}=11.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=8.2, 6.6, H-4′a); 3.32 (br m, 1H, H-5′b); 3.55 (br m, 1H, H-5′a); 3.61 (br m, 2H, H-2′); 5.16 (tt, 1H, $J_{3',4'}$=8.8, 4.4, $J_{3',2'}$=6.8, 4.3, H-3′); 7.09 (br s, 2H, NH_2); 8.09 (s, 1H, H-8); 8.10 (br s, 2H, NH_2); 9.52 and 9.96 (2×br s, 2H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 31.03 (CH_2-4′); 44.43 (CH_2-5′); 49.06 (CH_2-2′); 53.20 (CH-3′); 112.20 (C-5); 138.89 (CH-8); 151.03 (C-4); 157.43 (C-6); 160.14 (C-2).

4.2.11. (*RS*)-1-(3-Pyrrolidinyl)thymine hydrochloride (28d). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)thymine (**27d**) (2.6 g, 8.8 mmol) according to the procedure described for compound **28a**. Yield, 1.2 g (73%, white powder).

HRMS: for $C_9H_{14}N_3O_2$ $(M+H)^+$ calcd 196.1086, found 196.1095.

ν_{max}(KBr) 3331 (m), 3064 (m), 1694 (vs), 1673 (vs), 1649 (vs), 1605 (m, sh), 1481 (s), 1438 (s, sh), 1398 (s), 1379 (m), 1275 (s), 760 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 1.78 (d, 3H, J=1.2, CH_3-5); 2.10 (dq, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.9, 7.4, $J_{4'b,3'}$=7.4, H-4′b); 2.31 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=7.8, 4.7, H-4′a); 3.17 (br m, 1H, H-5′b); 3.32 (br m, 1H, H-2′b); 3.40–3.53 (br m, 2H, H-2′a and H-5′a); 5.02 (tdd, 1H, $J_{3',2'}$=8.8, 6.3, $J_{3',4'}$=8.8, 7.4, H-3′); 7.77 (q, 1H, J=1.2, H-6); 7.48 (br s, 2H, +NH_2); 11.36 (s, 1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 12.19 (CH_3-5); 28.99 (CH_2-4′); 44.54 (CH_2-5′); 47.12 (CH_2-2′); 54.81 (CH-3′); 109.61 (C-5); 139.09 (CH-6); 151.13 (C-2); 164.03 (C-4).

4.2.12. (*RS*)-1-(3-Pyrrolidinyl)uracil hydrochloride (28e). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)uracil (**27e**) (1.2 g, 4.3 mmol) according to the procedure described for compound **28a**. Yield, 0.763 g (93%, yellow powder).

HRMS: for $C_8H_{12}N_3O_2$ $(M+H)^+$ calcd 182.0930, found 182.0939.

ν_{max}(KBr) 3339 (s), 3089 (m), 3054 (m), 1766 (m), 1695 (vs, vbr), 1625 (s), 1531 (m), 1408 (s), 992 (m).

^{1}H NMR (400 MHz, DMSO-d_6): 1.66 (dddd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.1, 6.8, $J_{4'b,3'}$=4.4, H-4′b); 2.11 (dtd, 1H, J_{gem}=13.3,

$J_{4'a,3'}$=8.9, $J_{4'a,5'}$=8.4, 5.5, H-4′a); 2.76 (ddd, 1H, J_{gem}=10.5, $J_{5'b,4'}$=8.4, 6.8, H-5′b); 2.77 (dd, 1H, J_{gem}=11.2, $J_{2'b,3'}$=3.8, H-2′b); 2.99 (ddd, 1H, J_{gem}=10.5, $J_{5'a,4'}$=8.1, 5.5, H-5′a); 3.00 (dd, 1H, J_{gem}=11.1, $J_{2'a,3'}$=7.4, H-2′a); 4.85 (ddt, 1H, $J_{3',4'}$=8.9, 4.4, $J_{3',2'}$=7.4, 3.8, H-3′); 5.56 (d, 1H, $J_{5,6}$=8.0, H-5); 7.70 (d, 1H, $J_{6,5}$=8.0, H-6).

^{13}C NMR (100.6 MHz, DMSO-d_6): 31.81 (CH_2-4′); 45.81 (CH_2-5′); 51.89 (CH_2-2′); 55.53 (CH-3′); 101.59 (CH-5); 142.81 (CH-6); 151.22 (C-2); 163.42 (C-4).

4.2.13. (*RS*)-1-(3-Pyrrolidinyl)cytosine dihydrochloride (28g). The title compound was prepared from (*RS*)-1-(*N*-*tert*-butoxycarbonyl-3-pyrrolidinyl)cytosine (**27g**) (5 g, 17.8 mmol) according to the procedure described for compound **28a**. Yield, 2.9 g (65%, white powder).

HRMS: for $C_8H_{13}N_4O$ $(M+H)^+$ calcd 181.1089, found 181.1087.

ν_{max}(KBr) 3350 (m, sh), 3294 (m), 3133 (m), 2753 (m), 1705 (s), 1671 (vs), 1645 (s, sh), 1628 (s, sh), 1526 (m), 1413 (m), 1300 (m), 1213 (w), 780 (w).

^{1}H NMR (400 MHz, DMSO-d_6): 2.15 (dtd, 1H, J_{gem}=13.3, $J_{4'b,5'}$=8.4, $J_{4'b,3'}$=6.6, H-4′b); 2.33 (dtd, 1H, J_{gem}=13.3, $J_{4'a,3'}$=8.8, $J_{4'a,5'}$=7.7, 5.0, H-4′a); 3.17 (dt, 1H, J_{gem}=11.2, $J_{5'b,4'}$=8.4, 7.7, H-5′b); 3.36 (dd, 1H, J_{gem}=12.5, $J_{2'b,3'}$=5.4, H-2′b); 3.45 (ddd, 1H, J_{gem}=11.2, $J_{5'a,4'}$=8.3, 5.0, H-5′a); 3.46 (dd, 1H, J_{gem}=12.5, $J_{2'a,3'}$=8.5, H-2′a); 4.96 (tt, 1H, $J_{3',4'}$=8.8, 6.6, $J_{3',2'}$=8.5, 5.4, H-3′); 5.97 (d, 1H, $J_{5,6}$=7.6, H-5); 8.01 (d, 1H, $J_{6,5}$=7.6, H-6); 8.08, 8.74, 9.47 and 9.60 (4×br s, 4×1H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): 28.95 (CH_2-4′); 44.67 (CH_2-5′); 47.43 (CH_2-2′); 57.36 (CH-3′); 94.12 (CH-5); 146.68 (CH-6); 151.40 (C-2); 162.49 (C-4).

4.2.14. (*S*)-*N*-Benzyl-3-hydroxypyrrolidine-2,5-dione (29). The title compound was prepared from (*S*)-malic acid (201.1 g; 1.5 mol) according to the procedure described for compound **22**. Yield, 223 g (73%, white crystals) of **29**. Mp 94–97 °C.

HRMS: for $C_{11}H_{12}NO_3$ $(M+H)^+$ calcd 206.0817, found 206.0808.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **22**.

4.2.15. (*S*)-*N*-Benzyl-3-pyrrolidinol (30a). The title compound was prepared from (*S*)-*N*-benzyl-3-hydroxypyrrolidine-2,5-dione (**29**) (30.8 g, 150 mmol) according to the procedure described for compound **23**. Yield, 24.4 g (92%, yellowish oil) of **30a**.

HRMS: for $C_{11}H_{16}NO$ $(M+H)^+$ calcd 178.1232, found 178.1236.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **23**.

4.2.16. (*S*)-3-Pyrrolidinol (30b). The title compound was prepared from (*S*)-*N*-benzyl-3-hydroxypyrrolidine (**30a**) (26.6 g, 150 mmol) according to the procedure described for compound **24**. Yield, 11.8 g (90%, yellowish oil) of **30b**.

EI$^+$: for C_4H_9NO M^+ calcd 87.0684, found 87.0684.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **24**.

4.2.17. (*S*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (31). The title compound was prepared from (*S*)-3-pyrrolidinol (**30b**) (13.1 g, 150 mmol) according to the procedure described for compound **25**. Yield, 26.0 g (92%, white solid) of **31**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 188.1287.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **25**.

4.2.18. (*S*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (32). The title compound was prepared from (*S*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**31**) (24 g, 128.2 mmol) according to the procedure described for compound **26a**. Yield, 29.2 g (85%, yellowish solid) of **32**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1068.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **26a**.

4.2.19. (*R*)-*N*-*tert*-Butyloxycarbonyl-3-pyrrolidinol (33). A mixture of (*S*)-*N*-*tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**31**) (8 g, 30 mmol) and sodium acetate (24.6 g, 300 mmol) in DMF (300 mL) was heated at 110 °C for 3 d. Dark brown solution was concentrated in vacuo, and the crude (*R*)-*N*-*tert*-butyloxycarbonyl-3-acetyloxypyrrolidine was purified on silica gel column (elution with a linear gradient of ethyl acetate in toluene). The obtained product was treated with saturated methanolic ammonia (300 mL) at 0 °C overnight, the solution was evaporated to dryness, the residue was co-evaporated with ethanol (2×30 mL), and the compound **33** was purified by silica gel chromatography (elution with a linear gradient of ethyl acetate in toluene). Yield, 4.2 g (76%, white solid) of **33**.

HRMS: for $C_9H_{18}NO_3$ $(M+H)^+$ calcd 188.1287, found 189.1284.

^{1}H NMR and ^{13}C NMR spectra identical with those of compound **25**.

4.2.20. (*R*)-*N*-*tert*-Butyloxycarbonyl-3-mesyloxypyrrolidine (34). The title compound was prepared from (*R*)-*N*-*tert*-butyloxycarbonyl-3-pyrrolidinol (**33**) (4 g, 21.8 mmol) according to the procedure described for compound **26a**. Yield, 5.2 g (90%, yellowish solid) of **34**.

HRMS: for $C_{10}H_{20}NO_5S$ $(M+H)^+$ calcd 266.1062, found 266.1067.

^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **26a**.

4.2.21. (*S*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (35). The title compound was prepared from (*R*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**34**) (5.1 g, 19.3 mmol) according to the procedure described for compound **27a**. Yield, 4 g (68%, white solid) of **35**.

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1726.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **27a**.

4.2.22. (*S*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (36). The title compound was prepared from (*S*)-9-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**35**) (4 g, 13 mmol) according to the procedure described for compound **28a**. Yield, 1.9 g (71%, white solid) of **36**.

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1196.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **28a**.

4.2.23. (*R*)-9-(*N-tert*-Butoxycarbonyl-3-pyrrolidinyl)adenine (37). The title compound was prepared from (*S*)-*N-tert*-butyloxycarbonyl-3-mesyloxypyrrolidine (**32**) (7.0 g, 26.6 mmol) according to the procedure described for compound **27a**. Yield, 5.5 g (68%, white solid) of **37**.

HRMS: for $C_{14}H_{21}N_6O_2$ $(M+H)^+$ calcd 305.1726, found 305.1725. ^1H NMR and ^{13}C NMR spectra were identical with those of compound **27a**.

4.2.24. (*R*)-9-(3-Pyrrolidinyl)adenine dihydrochloride (38). The title compound was prepared from (*R*)-9-(*N-tert*-butoxycarbonyl-3-pyrrolidinyl)adenine (**37**) (5.5 g, 18 mmol) according to the procedure described for compound **28a**. Yield, 2.4 g (65%, white solid) of **38**.

HRMS: for $C_9H_{13}N_6$ $(M+H)^+$ calcd 205.1202, found 205.1206.

^1H NMR and ^{13}C NMR spectra were identical with those of compound **28a**.

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References and notes

1. De Clercq, E. *Int. J. Antimicrob. Agents* **2001**, *18*, 309–328.
2. Kaspersen, F. M.; Bieräugel, H.; Pandit, U. K. *Heterocycles* **1974**, *2*, 15–19.
3. Kaspersen, F. M.; Pandit, U. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1617–1622.
4. Ng, K.-M. E.; Orgel, L. E. *J. Med. Chem.* **1989**, *32*, 1754–1757.
5. Kaspersen, F. M.; Pandit, U. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1798–1802.
6. Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787–2797.
7. Vaněk, V.; Buděšínský, M.; Kavenová, I.; Rinnová, M.; Rosenberg, I. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 1065–1067.
8. Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1991**, *32*, 3863–3866.
9. Harnden, M. R.; Jarvest, R. L.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2259–2263.
10. Westwood, N. B.; Walker, R. T. *Tetrahedron* **1998**, *54*, 13391–13404.
11. Oohashi, T.; Nishiyama, S.; Yamamura, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1187–1188.
12. Temple, C., Jr.; Kussner, C. L.; Montgomery, J. A. *J. Med. Chem.* **1972**, *15*, 441–442.
13. Nishitani, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I.; Miyoshi, M. *J. Org. Chem.* **1982**, *47*, 1706–1712.
14. Altmann, K.-H. *Tetrahedron Lett.* **1993**, *34*, 7721–7724.
15. Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G. *Tetrahedron Lett.* **1994**, *35*, 4019–4022.
16. Varaprasad, Ch. V.; Averett, D.; Ramasamy, K. S. *Tetrahedron* **1999**, *55*, 13345–13368.
17. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168–180.
18. Costenaro, E. R.; Fontoura, L. A. M.; Oliveira, D. F.; Correia, C. R. D. *Tetrahedron Lett.* **2001**, *42*, 1599–1602.
19. Du, J.; Chu, C. K. *Nucleosides Nucleotides* **1998**, *17*, 1–13.
20. Leggio, A.; Liguori, A.; Procopio, A.; Siciliano, G.; Sindona, G. *Tetrahedron Lett.* **1996**, *37*, 1277–1280.
21. Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron Lett.* **2002**, *43*, 4013–4014.
22. Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883–5892.
23. Schrärer, O. D.; Ortholand, J. Y.; Ganesan, A.; Ezaz-Nikpay, K.; Verdine, G. L. *J. Am. Chem. Soc.* **1995**, *117*, 6623–6624.
24. Schrärer, O. D.; Nash, H. M.; Jiricny, J.; Laval, J.; Verdine, G. L. *J. Biol. Chem.* **1998**, *273*, 8592–8597.
25. Prokhorenko, I. A.; Korshun, V. A.; Petrov, A. A.; Gontarev, S. V.; Berlin, Y. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2081–2084.
26. Hébert, N.; Davis, P. W.; De Baets, E. L.; Acevedo, O. L. *Tetrahedron Lett.* **1994**, *35*, 9509–9512.
27. Altmann, K. H.; Hüsken, D.; Cuenoud, B.; García-Echeverría, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 929–933.
28. Hickman, D. T.; King, P. M.; Cooper, M. A.; Slater, J. M.; Micklefield, J. *Chem. Commun.* **2000**, 2251–2252.
29. Jordan, S.; Schwemler, Ch.; Kosch, W.; Kretschmer, A.; Schwenner, E.; Stropp, U.; Mielke, B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 687–690.
30. Li, Y.; Jin, T.; Liu, K. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1705–1721.

31. Hickman, D. T.; King, P. M.; Slater, J. M.; Cooper, M. A.; Micklefield, J. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1169–1172.
32. Zhang, Z.; Chaltin, P.; Van Aerschot, A.; Lacey, J.; Rozenski, J.; Busson, R.; Herdewijn, P. *Bioorg. Med. Chem.* **2002**, *10*, 3401–3413.
33. Kumar, V.; Pallan, P. S.; Meena; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 1269–1272.
34. Jordan, S.; Schwemler, Ch.; Kosch, W.; Kretschmer, A.; Stropp, U.; Schwenner, E.; Mielke, B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 687–690.
35. Sternfeld, F.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Heal, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J. *J. Med. Chem.* **1999**, *42*, 677–690.
36. Clark, D. *Tetrahedron* **2000**, *56*, 6181–6184.
37. Lee, J.; Davis, C. B.; Rivero, R. A.; Reitz, A. B.; Shank, R. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1063–1066.
38. Skaddan, M. B.; Kilbourn, M. R.; Snyder, S. E.; Sherman, P. S.; Desmond, T. J.; Frey, K. A. *J. Med. Chem.* **2000**, *43*, 4552–4562.
39. Ahn, K. H.; Lee, S. J.; Lee, C. H.-H.; Hong, Ch. Y.; Park, T. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1379–1384.
40. Huang, Y.; Luedtke, R. R.; Freeman, R. A.; Wu, L.; Mach, R. H. *J. Med. Chem.* **2001**, *44*, 1815–1826.
41. Kraus, J. L.; Bouygues, M.; Courcambeck, J.; Chermann, J. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2023–2026.
42. Lerner, Ch.; Siegrist, R.; Schweizer, E.; Diederich, F. *Helv. Chim. Acta* **2003**, *86*, 1045–1062.
43. Temple, C.; Kussner, C. L.; Montgomery, J. A. *J. Med. Chem.* **1975**, *18*, 1255–1258.
44. D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *J. Org. Chem.* **2003**, *68*, 4439–4445.
45. Kočalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 805–808.
46. Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949–4952.
47. Nemia, M. M. B.; Lee, J.; Joullia, M. M. *Synth. Commun.* **1983**, *13*, 1117–1124.
48. Tomori, H.; Shibatani, K.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1996**, 207–216.
49. Bhat, K.; Flanagan, D. M.; Joullie, M. M. *Synth. Commun.* **1985**, *15*, 587–598.
50. Murahashi, S.; Ohtake, H.; Imada, Y. *Tetrahedron Lett.* **1998**, *39*, 2765–2766.
51. Seijas, J. A.; Vazquez-Tato, M. P.; Martinez, M. M.; Nunez-Corredoira, G. *J. Chem. Res., Synop.* **1999**, *7*, 420–421.
52. Lukeš, R.; Pergal, M. *Collect. Czech. Chem. Commun.* **1962**, *27*, 1387–1389.
53. Nagel, U.; Nedden, H. G. *Chem. Ber. Recl.* **1997**, *130*, 385–398.
54. Tamazawa, K.; Arima, H.; Kojima, T.; Isomura, Y.; Okada, M.; Fujita, S.; Furuya, T.; Takenaka, T.; Inagaki, O.; Terai, M. *J. Med. Chem.* **1986**, *29*, 2504–2511.
55. Werner, T. *J. Chem. Soc.* **1889**, *55*, 631.
56. Prasad, A. S. B.; Kanth, J. V. B.; Periassamy, M. *Tetrahedron* **1992**, *48*, 4623–4628.