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Synthesis and antiviral activity of monofluorinated cyclopropanoid nucleosides

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Diastereopure monofluorinated cyclopropanoid nucleosides were synthesized for biological studies. As key intermediates *cis*- and *trans*-(±)-[1-fluoro-2-(acetoxymethyl)cyclopropyl]methanol were prepared starting from diastereopure fluorinated cyclopropanecarboxylates. The latter were synthesized by copper(I)-catalyzed cyclopropanation of α-fluorostyrene with ethyl diazoacetate. After reduction and *O*-acetylation the diastereomeric (2-fluoro-2-phenylcyclopropyl)methyl acetates were obtained. Oxidative degradation using RuO_4 and reduction of the formed carboxyl group with borane gave the fluorinated alcohols, which were coupled with different nucleobases. After deprotection, the corresponding cyclopropanoid nucleosides of adenine, cytosine, guanine, thymine and uracil were obtained. Antiviral tests revealed for the *cis*-configured guanosine a low, but specific activity against HSV-1 and HSV-2. In addition low affinities of the adenine derivatives to adenosine receptors were detected.

Introduction

Carbocyclic nucleosides are pharmaceutically very important compounds, which are characterized by significant antiviral and cancerostatic activity.[1] Nonetheless, toxicity[2,3] and the development of resistance[4–6] are limiting factors for therapeutical applications. Therefore, the synthesis of new target compounds remains important. Additionally, more detailed information about structure–activity relationships would be useful for rational drug design.[7]

The modification of the sugar moiety was demonstrated to be a very efficient strategy for the synthesis of new nucleosides with high biological activity.[8–10] Frequently, fluorine substituents have been introduced,[11] and fluorinated compounds are very often characterized by an increased biological activity.[12] In nucleosides fluorine stabilizes the glycosidic bond towards hydrolysis by alteration of the conformation of the sugar moiety.[13] Replacement of the sugar moiety by a cyclopropane is an additional approach for the design of new nucleosides.[8] In this context several authors demonstrated that methylene-spaced derivatives having higher structural flexibility are the best inhibitors.[14] In Fig. 1 some general types of analogous cyclopropanoid nucleosides are presented. Especially, compounds of type A synthesized by Tsuji *et al.* are potent antiviral agents.[15] Similarly, Ashton *et al.* demonstrated that *trans*-configured adenosine and *cis*-guanosine derivatives of type B are characterized by anti-HSV-1 and -HSV-2 activity.[16] Remarkably, enantiopure (1*S*,2*R*)-derivatives of this type were inactive.[17] The strong relationship between the stereochemistry of the cyclopropyl group and biological activity was also demonstrated by Cheng *et al.* for type C adenosines. Only the isomers with *cis*-configuration demonstrated high anti-HIV activity.[18] Additional nucleosides of type C with high antiviral activity were prepared by Chen and Zemlicka.[19]

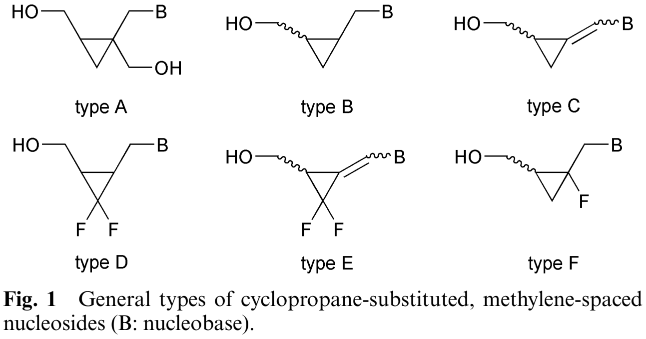

Fig. 1 General types of cyclopropane-substituted, methylene-spaced nucleosides (B: nucleobase).

Because of the strong influence of fluorine on biological activity, several authors have synthesized fluorinated cyclopropanoid nucleosides. Csuk and Eversmann described the synthesis of difluorinated analogues (type D)[20] of type B possessing no antiviral activity.[21] Difluorinated derivatives (type E) of type C were characterized by moderate, but decreased antiviral activity compared to that of the parent nonfluorinated compounds.[22] Some monofluorinated analogues of type B with *cis*-configuration (type F) were prepared by Lee *et al.*[23] However, no antiviral activity was found for these nucleosides.[23] Moreover, other cyclopropanoid nucleosides with two hydroxymethyl groups exhibiting low biological activity have been described.[16,18,24]

Because of the strong relationship between the configuration of the cyclopropyl substituent and biological activity we became interested in the synthesis of all *trans*- and *cis*-configured diastereomers of nucleosides of type F. Further information about the influence of a fluorine substituent on the biological activity was to be expected.

Results and discussion

Synthesis

Recently, different methods for the synthesis of monofluorinated cyclopropanes have been reviewed.[25] Especially, copper(I)-catalyzed cyclopropanation of vinyl fluorides with diazoacetates is a very useful method for the synthesis of *cis*/*trans* isomeric monofluorinated cyclopropanecarboxylates.[26] Vinyl fluorides are readily available from the corresponding alkenes applying a two-step sequence consisting of bromofluorination with $NBS/Et_3N·3HF$[27] followed by HBr elimination.[28] From thus-formed α-fluorostyrene (**1**) racemic esters **2a** and **2b** were prepared by reaction with ethyl diazoacetate in a 1:1 ratio.[26] After separation by column chromatography the diastereopure esters **2a** and **2b** were reduced with $LiAlH_4$ to

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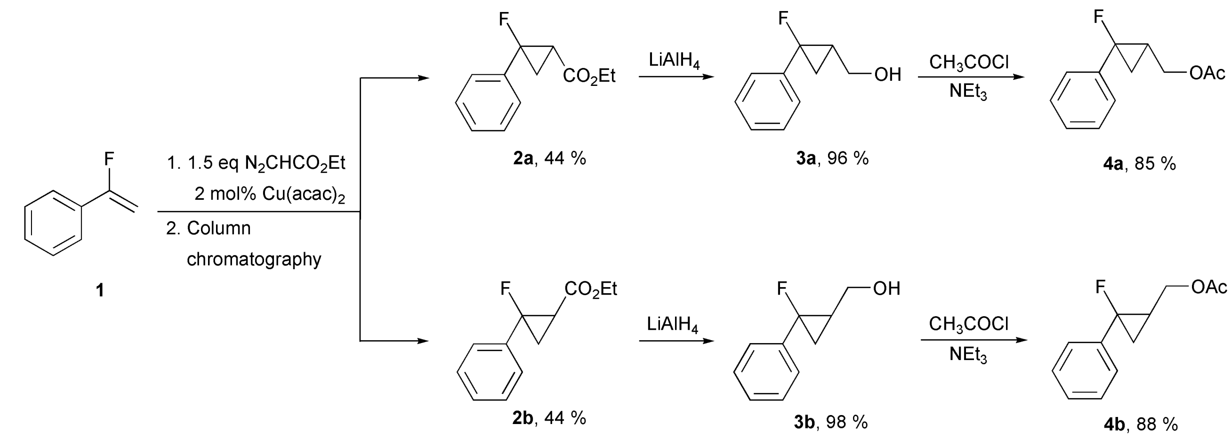


Scheme 1 Synthesis of *cis*- and *trans*-(2-fluoro-2-phenylcyclopropyl)methyl acetates (**4a** and **4b**) from α-fluorostyrene (**1**).

give the corresponding alcohols **3a** and **3b**. *O*-Acetylation led to *cis*- and *trans*-(2-fluoro-2-phenylcyclopropyl)methyl acetates (**4a** and **4b**),[29] which then serve as precursors for the cyclopropanoid nucleosides (Scheme 1). †

From the latter acetates primary alcohols **6a** and **6b** were prepared, which were used as alkylation reagents for nucleobases. First, the phenyl group of **4a** and **4b** was degraded into a carboxyl group. Aromatic groups can be oxidatively degraded by ruthenium tetraoxide[30] or ozone.[31] From the literature it is known that a cyclopropyl group[32] as well as the fluorine–carbon bond[33] are not affected by these reagents. Oxidative degradation of the acetates **4a** and **4b** was realized using a catalytic amount of $RuCl_3$ in combination with an excess of $NaIO_4$ in a biphasic system consisting of water and acetonitrile/tetrachloromethane.[34] Conversion was complete after six or seven days. The corresponding acids **5a** and **5b** were isolated in good yields of 79% and 84%, respectively. The products are characterized by a butyric acid like odor. In contrast, no conversion of **4b** was observed after treatment with ozone. The configuration of **5b** was evidenced by spectroscopic data and X-ray structural analysis (Fig. 2).[35]

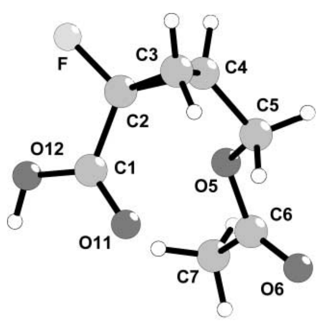


Fig. 2 X-ray structure of *cis*-(±)-2-acetoxymethyl-1-fluorocyclopropanecarboxylic acid (**5b**).

From **5a** and **5b**, the corresponding alcohols **6a** and **6b** were obtained by selective reduction of the carboxylic acid group with borane analogously to a literature procedure.[36] For complete conversion at least 2 mol equivalents of the borane reagent were necessary. These results might be explained by a deactivation of one borane molecule by coordination to a fluorine substituent. Similar results were published for nitrogen donors.[37] When **5a** and **5b** were treated with 3 equivalents of $BH_3{\cdot}SMe_2$, the alcohols **6a** and **6b** were isolated in 78% and 66% yields, respectively (Scheme 2).

For the coupling with nucleobases, the hydroxy group can be activated as mesylate or tosylate for nucleophilic substitution reactions under basic conditions.[38,39] Alternatively, direct alkylation of nucleobases can be achieved under Mitsunobu conditions.[40] For the synthesis of nucleosides of type F, the diastereopure alcohols **6a** and **6b** were coupled with different nucleobases under the latter conditions. Reaction with adenine gave **7a** and **7b**, which were isolated in moderate yields of 52% (**7a**) and 66% (**7b**). After deprotection with ammonia in methanol, the corresponding adenine derivatives **8a** and **8b** were obtained in excellent yields of 90% and 96%, respectively (Scheme 3). Ammonia in methanol proved to be a very suitable reagent because no side reactions were observed and ammonia could be removed easily under vacuum. The products were soluble in polar organic solvents such as methanol and dimethyl sulfoxide.

Analogous syntheses of uracil and thymine derivatives were achieved using N^3-benzoyluracil (**13**) and N^3-benzoylthymine (**14**).[41] After coupling under Mitsunobu conditions uracil derivatives **9a** and **9b** were isolated in moderate yields of 53% and 41%, respectively, while thymine derivatives **11a** and **11b** were obtained in good yields of 73% and 80%, respectively (Scheme 3). The acetate and benzoyl groups were removed by treatment with ammonia in methanol. The corresponding nucleosides were isolated in good yields (Scheme 3).

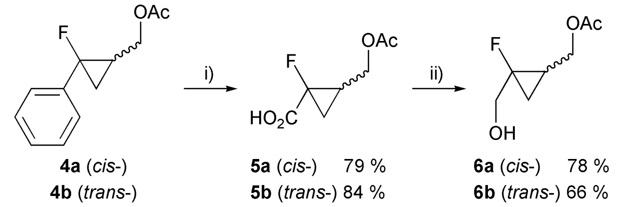
Unfortunately, analogous alkylation of cytosine with **6b** under Mitsunobu conditions failed. Alternatively, we synthesized the corresponding mesylates of **15a** and **15b**. Since mesylates **15a** and **15b** were expected to be unstable, they were reacted directly with cytosine and Cs_2CO_3 as a base at 70 °C analogously to a published procedure.[42] After deprotection with ammonia in methanol and purification by HPLC, the corresponding cytosine derivatives **16a** and **16b** were isolated in yields of 38% (**16a**) and 41% (**16b**) (Scheme 4).

For the synthesis of guanosine nucleosides, precursors such as 2-amino-6-(benzyloxy)purine[15] or 2-amino-6-chloropurine[16,17,21–23] have been frequently used. Again, conversion of alcohol **6b** with 2-amino-6-chloropurine under Mitsunobu conditions failed, while reaction of mesylates **15a** and **15b** with 2-amino-6-chloropurine and Cs_2CO_3 at 50 °C resulted in the formation of the guanosine precursors **17a** and **17b** in moderate yields of 56% and 53%, respectively. Hydrolysis with glacial acetic acid at 70 °C and subsequent treatment with ammonia in methanol led to the guanosine analogues **18a** and **18b** in low yields of 41% and 30%, respectively after chromatography (Scheme 4). The formation of at least one side product was observed, which could not be isolated.

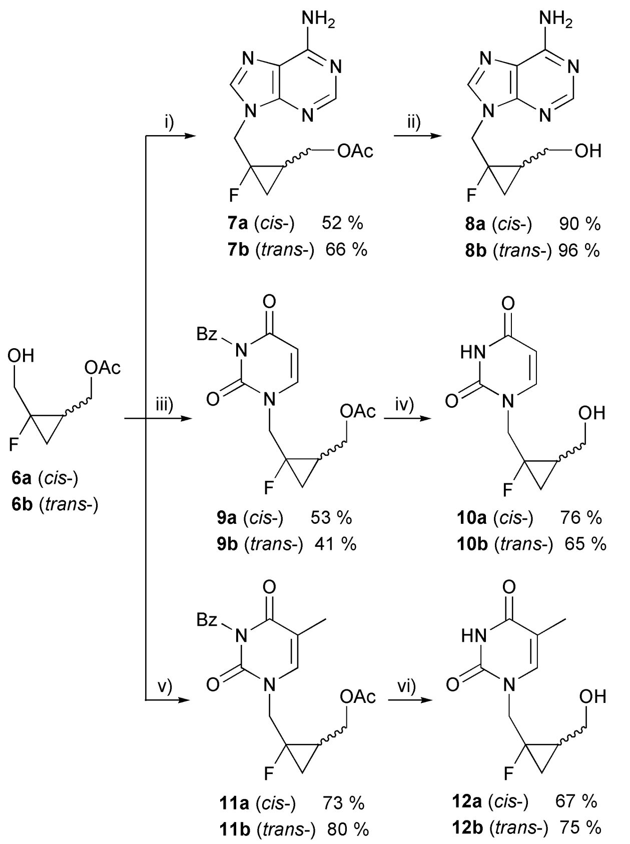
Biological activity

The diastereopure monofluorinated cyclopropanoid nucleosides were examined for antiviral activity against a wide variety of DNA and RNA viruses [herpes simplex virus type 1 (HSV-1, strain KOS) and type 2 (HSV-2, strain G), vaccinia virus,

† In general, the terms *cis* and *trans* refer to the relative configuration of the vicinal carbon substituents attached to the three-membered ring.



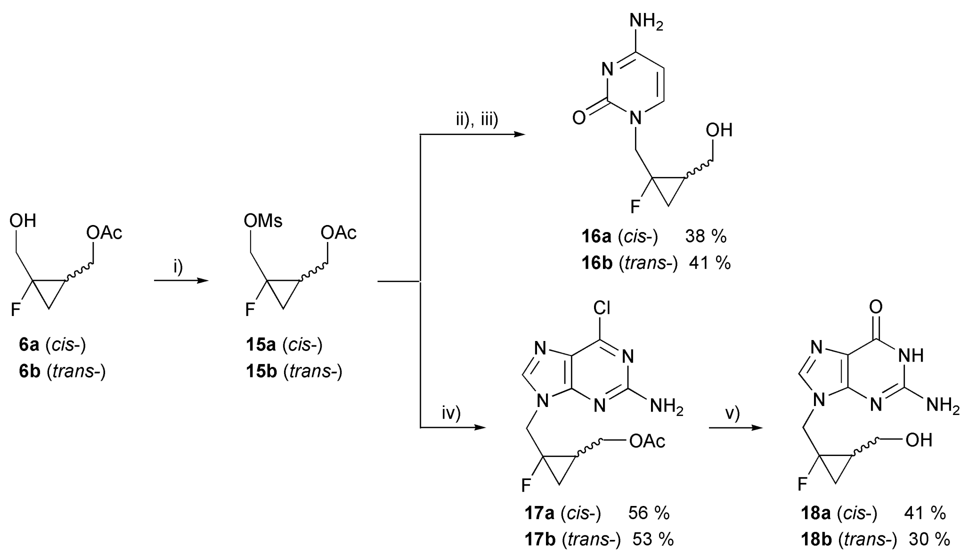
Scheme 2 *Reagents and conditions:* i, cat. $RuCl_3 \cdot H_2O$, 22 eq $NaIO_4$, CH_3CN, CCl_4, H_2O, rt, 6–7 d; ii, 3 eq $BH_3 \cdot SMe_2$, Et_2O, rt, 16 h.



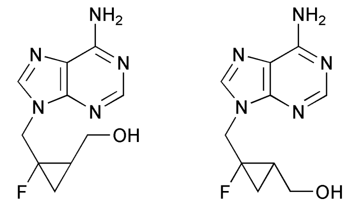
Scheme 3 *Reagents and conditions:* i, adenine, PPh_3, DEAD, 1,4-dioxane, rt, overnight; ii, NH_3, MeOH, rt; iii, N^3-Bz-uracil (**13**), PPh_3, DEAD, 1,4-dioxane, rt, overnight; iv, NH_3, MeOH, rt; v, N^3-Bz-thymine (**14**), PPh_3, DEAD, 1,4-dioxane, rt, overnight; vi, NH_3, MeOH, rt.

vesicular stomatitis virus, thymidine kinase-deficient (TK^- HSV-1 strain KOS), varicella-zoster virus (TK^- VZV strain Oka and TK^- strain 07/1), cytomegalovirus (strains AD-169 and Davis) in human embryonic lung (HEL) cells; Coxsackie B4 virus, respiratory syncytial virus in HeLa cells; parainfluenza type 3 virus, reovirus type 1, Sindbis virus and Punta Toro virus in Vero cells]. Antiviral activity and, in parallel cytotoxicity, were monitored at compound concentrations up to 400 $\mu g\ mL^{-1}$. Antiviral activity was expressed as the minimum effective concentration (EC_{50}) required to inhibit virus-induced cytopathicity by 50%. Cytotoxicity was expressed as the minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology. None of the compounds proved antivirally active or cytotoxic at concentrations up to 400 $\mu g\ mL^{-1}$, except for the *cis*-configured guanosine **18a**, which showed some low activity against HSV-1 (EC_{50}: 16 $\mu g\ mL^{-1}$) and HSV-2 (EC_{50}: 48 $\mu g\ mL^{-1}$). In contrast, Lee *et al.* reported no activity for this derivative.[23] Ashton *et al.*[16] found that the non-fluorinated analogue was active (at 6 $\mu g\ mL^{-1}$ against HSV-1 and at 12–25 $\mu g\ mL^{-1}$ against HSV-2). Also the corresponding *trans*-configured adenine derivative proved active.[16] When the compounds were evaluated for their cytostatic activity against HSV-1 TK gene transfected human osteosarcoma cells, no inhibitory activity was observed at 100 μM. In contrast, ganciclovir became exquisitely cytostatic, due to HSV-1 TK mediated activation in the transduced tumor cells. Our results demonstrate that incorporation of a fluorine substituent leads to decreased antiviral activity in these cases. Since the conformations of the three membered ring is very rigid, we believe that the fluorine group influences the spatial orientation of the nucleobase and the cyclopropyl substituent.

Furthermore, the affinities of **7a** and **7b** to adenosine receptors A_1 and A_{2A} were measured.[43] Selective ligands of these adenosine receptors are discussed as potential drugs for different therapeutic areas such as the cardiovascular and the central nervous system.[44,45] The methods used to assay the compounds are described in the literature.[45] Whereas both adenine diastereomers did not demonstrate any affinity against the A_1 receptors, low affinity in μM scale towards the A_{2A} receptor was found for **7a** and **7b**. For the *trans*-diastereomer **7b** a significantly higher affinity was found. This demonstrated the influence of the configuration of the cyclopropane moiety on binding (Fig. 3). In comparison, for adenosine K_i-values of 10 nM (A_1 receptor) and 30 nM (A_{2A} receptor) were described.[46]



Scheme 4 *Reagents and conditions:* i, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 1,4-dioxane, 0 °C, 6 h; ii, cytosine, Cs_2CO_3, 70 °C, DMF; iii, NH_3, MeOH, rt; iv, 2-amino-6-chloropurine, Cs_2CO_3, 50 °C, DMF; v, glacial acid, 70 °C, 24 h, then NH_3, MeOH, rt.



	7a	7b
K_i (A_1)	> 100 μM	> 100 μM
K_i (A_{2A})	41.4 ± 8.9 μM	25.3 ± 4.1 μM

Fig. 3 Binding affinity of **7a** and **7b** for A_1 and A_{2A} adenosine receptors.

Experimental

Materials and methods

According to a literature procedure,[29] the *cis* and *trans* isomers of (±)-(2-fluoro-2-phenylcyclopropyl)methyl acetate (**4a** and **4b**) were synthesized from the corresponding ethyl (±)-2-fluoro-2-phenylcylopropanecarboxylates which were obtained by transition metal-catalyzed cyclopropanation of α-fluorostyrene.[26] All reagents were obtained from commercial suppliers. Diethyl ether was dried over sodium, while *N*,*N*-dimethylformamide was dried over molecular sieves. If not stated otherwise, ^1H (300.13 MHz), ^{13}C (75.47 MHz), ^{19}F NMR (282.4 MHz): Bruker WM 300. For some marked cases ^1H (360 MHz) and ^{13}C NMR (90.57 MHz): Bruker AM 360. TMS was the internal standard for ^1H, $CDCl_3$ for ^{13}C and $CFCl_3$ for ^{19}F NMR spectroscopy. Mass spectra (70 eV): GC/MS coupling: Varian GC 3400/MAT 8230 and data system SS 300 of Finnigan MAT and Varian GC 3400/Varion Saturn IT (Ion Trap) and data system NIST. ESI: Quadrupol mass spectrometer Quattro LC-Z of Micromass. IR: Nicolet 5DXC-FT-IR. Melting points: DuPont Instruments 910 Differential Scanning Calorimeter with Thermal Analyst 2000, TA Instruments. Elemental analysis: Mikroanalytisches Laboratorium, Organisch-Chemisches Institut, Universität Münster. X-Ray crystal data sets were collected with Nonius CAD4. For column chromatography silica gel 60 from Merck was used. HPLC: System D-7000 from Merck and Hitachi with SP 250/10 Nucleosil 50-7D-700 from Macherey-Nagel as stationary phase.

The methodology used for measuring antiviral activity has been described previously.[47]

cis-(±)-2-Acetoxymethyl-1-fluorocyclopropanecarboxylic acid (5a)

$NaIO_4$ (18.6 g, 87 mmol) and $RuCl_3 \cdot H_2O$ (100 mg, 0.44 mmol) were added to a suspension consisting of CCl_4 (17 cm^3), CH_3CN (17 cm^3) and H_2O (27 cm^3). The mixture was stirred for 30 min at room temperature. Then *cis*-(±)-(2-fluoro-2-phenylcyclopropyl)methyl acetate (**4a**) (832 mg, 4 mmol), synthesized as previously described,[29] was added. The suspension was stirred intensively for 6–7 d at room temperature. After complete conversion the mixture was filtered and washed with ethyl acetate (100 cm^3). After separation of the phases the organic layer was discarded and the aqueous layer was acidified with HCl to pH 1 and extracted with ethyl acetate (4 × 150 cm^3). The combined organic layer was dried ($NaSO_4$) and concentrated. The obtained dark residue was adsorbed to SiO_2 and purified by column chromatography (cyclohexane/ethyl acetate, 2 : 1). **5a** (554 mg, 79%) was isolated as a colorless solid. Crystallization from ethyl acetate/pentane (1 : 1) gave crystals suitable for X-ray analysis; mp 70 °C (ethyl acetate/pentane); (Found: C, 47.8; H, 5.0. Calc. for $C_7H_9FO_4$: C, 47.7; H, 5.1%); ν_{max}(KBr)/cm^{-1} 1744s (C=O), 1714s (C=O), 1262s, 1243s (CF), 1197m, 1063m, 1036m; δ_H ($CDCl_3$) 1.44 (1 H, ddd, *J* 8.8, 8.6 and 6.7, CH_AH_B), 1.62 (1 H, ddd, *J* 17.2, 11.2 and 6.7, CH_AH_B), 2.00 (3 H, s, CH_3), 2.06 (1 H, ddddd, *J* 19.1, 11.2, 8.8, 8.8 and 6.4, CH_X), 4.01 (1 H, dd, *J* 11.9 and 8.8, CH_CH_DO), 4.34 (1 H, ddd, *J* 11.9, 6.4 and 2.4, CH_CH_DO), 9.51 (1 H, s, CO_2H); δ_C ($CDCl_3$) 19.2 (dt, *J* 10.2, CH_AH_B), 20.7 (q, CH_3), 26.6 (dd, *J* 12.7, CH_X), 61.3 (t, CH_CH_DO), 76.0 (ds, *J* 230.2, *C*-F), 171.2 (s, *C*(O)-CH_3), 173.8 (ds, *J* 24.2, CO_2H); δ_F ($CDCl_3$) −188.5 (ddd, *J*19.1, 17.2 and 8.6); *m*/*z* of the trimethylsilyl ester 206 (3%), 188 (68), 173 (18), 150 (14), 145 (6), 134 (7), 117 (95), 97 (20), 77 (100), 75 (71), 73 (100), 69 (12), 43 (100). The structure of **5a** was confirmed by X-ray structural analysis.

Crystal structure determination of compound 5a

Crystal data. $C_7H_9FO_4$, *M* 176.14, monoclinic, *a* = 10.120(1) Å, *b* = 7.299(1) Å, *c* = 10.965(1) Å, = 98.76(1)°, *U* = 800.49(15) Å^3, *T* = 223(2) K, space group $P2_1/n$ (No. 14), *Z* = 4, μ(Cu-K$_\alpha$) = 1.54178 Å, 1726 reflections measured, 1633 unique (R_{int} = 0.0628) which were used in all calculations. The final $wR(F^2)$ was 0.1582 (all data).[35]

trans-(±)-2-Acetoxymethyl-1-fluorocyclopropanecarboxylic acid (5b)

Analogous to the procedure described above, **5b** was prepared using **4b** (832 mg, 4 mmol). The product **5b** (590 mg, 84%) was isolated as a colorless oil. (Found: C 47.3, H 5.1. Calc. for $C_7H_9FO_4$: C, 47.7; H, 5.1%); ν_{max}(film)/cm^{-1} 1728br (C=O), 1256s (CF), 1168s, 1036s, 609s; δ_H ($CDCl_3$) 1.36 (1 H, ddd, *J* 19.0, 8.2 and 7.0, CH_AH_B), 1.67 (1 H, ddd, *J* 10.4, 9.1 and 7.0, CH_AH_B), 2.03–2.16 (4 H, m, CH_X and CH_3), 4.06 (1 H, ddd, *J* 11.9, 8.9 and 1.0, CH_CH_DO), 4.43 (1 H, ddd, *J* 11.9, 5.9 and 1.4, CH_CH_DO), 10.88 (1 H, s, CO_2H); δ_C ($CDCl_3$) 18.4 (dt, *J* 10.1, CH_AH_B), 20.7 (q, CH_3), 24.6 (dd, *J* 10.3, CH_X), 61.4 (dt, *J* 7.8, CH_CH_DO), 75.8 (ds, *J* 237.2, C-F), 171.2 (s, *C*(O)-CH_3), 174.8 (ds, *J* 26.3, CO_2H); δ_F ($CDCl_3$) −210.9 (dm, *J* 19.0); *m*/*z* of the trimethylsilyl ester 233 (1%), 188 (36), 173 (6), 150 (6), 134 (4), 117 (29), 97 (13), 75 (48), 73 (62), 69 (8), 43 (100).

cis-(±)-[1-Fluoro-2-(acetoxymethyl)cyclopropyl]methanol (6a)

Under argon **5a** (528 mg, 3 mmol) was dissolved in anh. Et_2O (25 cm^3). A 1 M $BH_3 \cdot SMe_2$ solution in CH_2Cl_2 (9 cm^3, 9 mmol) was added. The obtained reaction mixture was stirred for 16 h at room temperature. A white precipitate was formed. After addition of H_2O (25 cm^3) the resulting suspension was vigorously stirred for 3 h. Then sat. $NaHCO_3$ (5 cm^3) was added and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 50 cm^3), dried ($NaSO_4$) and concentrated. After column chromatography (pentane/Et_2O, 1 : 1) **6a** (377 mg, 78%) was isolated as a colorless oil. (Found: C, 51.8; H 7.2. Calc. for $C_7H_{11}FO_3$: C, 51.8; H 6.8%); ν_{max}(film)/cm^{-1} 3444br (OH), 1739s (C=O), 1667m, 1375m (C–O), 1240s (CF), 1191m, 1039s; δ_H ($CDCl_3$) 0.68 (1 H, ddd, *J* 9.5, 9.5 and 7.2, CH_AH_B), 1.32 (1 H, dddd, *J* 18.8, 11.0, 7.2 and 0.9, CH_AH_B), 1.71–1.89 (1 H, m, CH_X), 2.09 (3 H, s, CH_3), 2.29 (1 H, s, O*H*), 3.78 (1 H, ddd, *J* 28.6, 13.5 and 0.8, CH_EH_FOH), 3.88 (1 H, dd, *J* 12.2 and 8.8, CH_CH_DOAc), 4.12 (1 H, ddd, *J* 18.5, 13.5 and 0.9, CH_EH_FOH), 4.24 (1 H, ddd, *J* 12.2, 6.9 and 2.6, CH_CH_DOAc); δ_C ($CDCl_3$) 14.0 (dt, *J* 11.4, CH_AH_B), 20.8 (q, CH_3), 20.9 (dd, *J* 12.7, CH_X), 63.2 (dt, *J* 22.9, CH_EH_FOH), 63.4 (t, CH_CH_DOAc), 81.7 (ds, *J* 220.0, C-F), 171.0 (s, *C*(O)-CH_3); δ_F ($CDCl_3$) −181.5 (dddm, *J* 28.6, 19.1 and 9.5); *m*/*z* 145 (82%), 131 (3), 119 (2), 102 (34), 86 (43), 82 (22), 72 (71), 69 (38), 61 (22), 59 (24), 55 (27), 53 (25), 43 (100).

trans-(±)-[1-Fluoro-2-(acetoxymethyl)cyclopropyl]methanol (6b)

Analogous to the procedure described above, **6b** was synthesized using **5b** (528 mg, 3 mmol). The product **6b** (319 mg, 66%) was isolated as a colorless oil. (Found: C, 51.6; H, 6.8. Calc. for $C_7H_{11}FO_3$: C, 51.8; H 6.8%); ν_{max}(film)/cm^{-1} 3425br (OH), 1732s (C=O), 1656m, 1376s (C–O), 1250s (CF), 1092m, 1041s; δ_H ($CDCl_3$) 0.96–1.04 (2 H, m, CH_AH_B), 1.33–1.45 (1 H, m, CH_X), 2.08 (3 H, s, CH_3), 2.53 (1 H, s, O*H*), 3.78 (1 H, m, CH_EH_FOH), 3.85 (1 H, m, CH_EH_FOH), 4.07 (ddd, *J* 11.7, 7.9 and 1.3, 1 H, CH_CH_DOAc), 4.32 (1 H, ddd, *J* 11.7, 6.9 and 1.5, CH_CH_DOAc); δ_C ($CDCl_3$) 13.4 (dt, *J* 11.4, CH_AH_B), 19.3 (dd, *J* 11.4, CH_X), 20.9 (q, CH_3), 62.5 (dt, *J* 8.9, CH_CH_DOAc), 65.6 (dt, *J* 22.9, CH_EH_FOH), 81.9 (ds, *J* 222.5, *C*-F), 171.2 (s, *C*(O)-CH_3); δ_F ($CDCl_3$) −203.6 (m); *m*/*z* 145 (9%), 119 (1), 102 (5), 86 (11), 82 (4), 73 (17), 69 (12), 61 (5), 59 (7), 55 (7), 53 (9), 43 (100).

General procedure for Mitsunobu reactions

Under argon the alcohols **6a** or **6b** (162 mg, 1.0 mmol), PPh_3 (525 mg, 2.0 mmol) and the corresponding nucleobase (2.0 mmol) were suspended in anh. 1,4-dioxane (10 cm^3). A solution of diethyl azodicarboxylate (DEAD) (351 mg, 2.0 mmol) in anh. 1,4-dioxane (15 cm^3) was added within 3–4 h. After stirring overnight at room temperature all volatiles were removed under vacuum. The residue was absorbed to SiO_2 and purified by column chromatography.

9-{[*cis*-1′-Fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]methyl}-adenine (7a). According to the general procedure for the Mitsunobu reaction, **6a** (122 mg, 0.75 mmol) was reacted with adenine (203 mg, 1.5 mmol). After column chromatography (ethyl acetate/methanol, 10 : 1) **7a** (68 mg, 52%) was isolated as an amorphous, white powder; mp 183 °C; (Found: C, 51.1; H, 4.6; N, 24.3. Calc. for $C_{12}H_{14}FN_5O_2$: C, 51.6; H, 5.0; N, 25.1%); δ_H (MeOH-d_4) 1.02–1.12 (1 H, m, CH_AH_B), 1.30–1.43 (1 H, m, CH_AH_B), 1.79–2.01 (1 H, m, CH_X), 1.88 (3 H, s, CH_3), 3.84 (1 H, dd, *J* 12.0 and 9.9, CH_CH_DOAc), 4.38 (1 H, ddd, *J* 12.0, 6.2 and 2.7, CH_CH_DOAc), 4.60–4.88 (2 H, m, CH_EH_F-N), 8.18–8.21 (2 H, m, Ar); δ_C (MeOH-d_4) 15.1 (dt, *J* 10.2, CH_AH_B), 20.5 (q, CH_3), 22.7 (dd, *J* 12.7, CH_X), 45.9 (dt, *J* 22.9, CH_EH_F-N), 64.2 (t, CH_CH_DOAc), 81.7 (ds, *J* 218.7, C-F), 119.6 (s), 142.6 (d), 151.0 (s), 153.9 (d), 157.3 (s, Ar), 172.2 (s, *C*=O); δ_F (MeOH-d_4) −174.8 (m); *m*/*z* 279 (2%), 259 (9), 236 (6), 220 (45), 216 (45), 200 (85), 183 (4), 173 (3), 148 (17), 135 (100), 119 (5), 108 (38), 85 (18), 65 (6), 54 (5), 43 (55); *m*/*z* (ESI) 280.1210 (M + H^+, $C_{12}H_{14}FO_2$ requires 280.1241); 302.1065 (M + Na^+, $NaC_{12}H_{13}FO_2$ requires 302.1029).

9-{[*trans*-1′-Fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]methyl}-adenine (7b). According to the procedure described above, **7b** was prepared from **6b** (98 mg, 0.60 mmol). After column chromatography (ethyl acetate, ethyl acetate/methanol, 20 : 1) **7b** (110 mg, 66%) was isolated as a white, amorphous powder; mp 161 °C; (Found: C, 51.2; H, 5.2; N, 24.7. Calc. for $C_{12}H_{14}FN_5O_2$: C, 51.6; H, 5.1; N, 25.1%); δ_H (MeOH-d_4, 360 MHz, 50 °C) 1.09 (1 H, ddd, 20.4, 7.4 and 7.4, CH_AH_B), 1.32 (1 H, ddd, *J* 10.2, 10.2 and 7.4, CH_AH_B), 1.70–1.79 (1 H, m, CH_X), 1.82 (3 H, s, CH_3), 3.84 (1 H, ddd, *J* 11.5, 9.4 and 1.2, CH_CH_D-OAc), 4.38 (1 H, ddd, *J* 11.5, 5.9 and 1.4, CH_CH_DOAc), 4.49 (1 H, dd, 25.3 and 15.4, CH_EH_FN), 4.75 (1 H, dd, 18.3 and 15.4, CH_EH_FN), 8.16 (1 H, d, *J* 1.1, Ar), 8.22 (1 H, s, Ar); δ_C (MeOH-d_4, 90.57 MHz, 50 °C) 15.2 (dt, *J* 11.1, CH_AH_B), 20.7 (q, CH_3), 22.0 (dd, *J* 9.6, CH_X), 49.2 (dt, *J* 20.7, CH_EH_FN), 63.6 (dt, *J* 9.1, CH_CH_DOAc), 81.9 (ds, *J* 222.8, C-F), 120.2 (s), 143.0 (d), 151.4 (s), 154.2 (d), 157.7 (s, Ar), 172.7 (s, *C*=O); δ_F (MeOH-d_4) −198.4 (m); *m*/*z* 279 (17%), 236 (8), 220 (100), 200 (22), 173 (3), 152 (2), 135 (100), 119 (3), 108 (30), 85 (17), 81 (7), 59 (4), 43 (50); *m*/*z* (ESI) 280.1210 (M + H^+, $C_{12}H_{14}FO_2$ requires 280.1257); 302.1029 (M + Na^+, $NaC_{12}H_{13}FO_2$ requires 302.1088).

3-Benzoyl-1-{[*cis*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]-methyl}uracil (9a). According to the general procedure for the Mitsunobu reaction, *cis* alcohol **6a** (90 mg, 0.556 mmol) was reacted with N^3-benzoyluracil (**13**) (240 mg, 1.112 mmol), which was synthesized as described in the literature.[41] The reaction mixture was purified twice by column chromatography (ethyl acetate/cyclohexane, 1 : 1 and ethyl acetate/cyclohexane, 3 : 2). After HPLC (ethyl acetate/cyclohexane 3 : 1) **9a** (106 mg, 53%) was isolated as a viscous oil. (Found: C, 59.7; H, 4.6; N, 7.7. Calc. for $C_{18}H_{17}FN_2O_5$: C, 60.0; H, 4.8; N, 7.8%); ν_{max}(KBr)/cm^{-1} 1750s (aliph. C=O), 1707m (arom. C=O), 1663s (arom. C=O), 1386s (C–O), 1242s (CF); δ_H ($CDCl_3$) 0.91 (1 H, ddd, *J* 10.3, 10.3 and 7.4, CH_AH_B), 1.38 (1 H, dddd, *J* 18.8, 10.3, 7.4 and 1.3, CH_AH_B), 1.78–1.99 (1 H, m, CH_X), 2.05 (3 H, s, CH_3), 3.54–3.75 (1 H, m, CH_CH_DOAc), 4.08–4.41 (3 H, m, CH_CH_DOAc and CH_EH_FN), 5.85 (1 H, d, *J* 8.1, Ar), 7.45–7.50 (3 H, m, Ar), 7.62–7.68 (2 H, m, Ar), 7.91–7.94 (2 H, m, Ar); δ_C ($CDCl_3$) 14.7 (dt, *J* 11.4, CH_AH_B), 20.7 (q, CH_3), 21.8 (dd, *J* 12.7, CH_X), 49.2 (dt, *J* 20.3, CH_EH_FN), 62.7 (t, CH_CH_DOAc), 80.7 (ds, *J* 218.7, *C*-F), 102.4 (d), 129.1 (d), 130.4 (d), 131.4 (s), 135.1 (d), 144.2 (dd, *J* 2.5, Ar), 150.1 (s, C_{Ar}=O), 162.2 (s, C_{Ar}=O), 168.4 (s, *C*=O), 170.5 (s, *C*(O)-CH_3); δ_F ($CDCl_3$) −175.6 (m); *m*/*z* 361 (1%), 332 (1), 317 (2), 301 (15), 273 (9), 255 (2), 217 (5), 197 (6), 189 (2), 145 (7), 122 (2), 105 (100), 85 (7), 77 (92), 51 (18), 43 (56).

3-Benzoyl-1-{[*trans*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]methyl}uracil (9b). According to the procedure described above, **9b** was prepared from **6b** (105 mg, 0.648 mmol). After column chromatography (ethyl acetate/cyclohexane, 1 : 1) and HPLC (ethyl acetate/methanol, 1 : 1) **9b** (95 mg, 41%) was isolated as a viscous oil. (Found: C, 59.7; H, 4.8; N, 7.5. Calc. for $C_{18}H_{17}FN_2O_5$: C, 60.0; H, 4.8; N, 7.8%); ν_{max}(KBr)/cm^{-1} 1749s (aliph. C=O), 1707s (arom. C=O), 1666s (arom. C=O), 1386s (C–O), 1245s (CF); δ_H ($CDCl_3$) 0.94–1.24 (2 H, m, CH_AH_B), 1.43–1.55 (1 H, m, CH_X), 1.98 (3 H, s, CH_3), 3.88 (1 H, ddd, *J* 11.7, 9.1 and 1.3, CH_CH_DOAc), 4.01–4.10 (2 H, m, CH_EH_FN), 4.31 (1 H, ddd, *J* 11.7, 5.8 and 1.5, CH_CH_DOAc), 5.75 (1 H, d, *J* 7.9, Ar), 7.35 (1 H, dd, *J* 7.9 and 1.1, Ar), 7.26 (2 H, m, Ar), 7.55–7.61 (1 H, m, Ar), 7.84–7.88 (2 H, m, Ar); δ_C ($CDCl_3$) 14.4 (dt, *J* 11.4, CH_AH_B), 20.4 (dd, *J* 10.2, CH_X), 20.8 (q, CH_3), 52.1 (dt, *J* 20.3, CH_EH_FN), 61.9 (dt, *J* 8.9, CH_CH_DOAc), 80.4 (ds, *J* 222.5, *C*-F), 102.2 (d), 129.1 (d), 130.3 (d), 131.4 (s), 135.1 (d), 144.2 (d), 150.2 (s, C_{Ar}=O), 162.2 (s, C_{Ar}=O), 168.4 (s, *C*=O), 170.7 (s, *C*(O)-CH_3); δ_F ($CDCl_3$) −198.7 (m); *m*/*z* 360 (3%), 328 (3), 317 (6), 301 (100), 290 (9), 287 (4), 255 (2), 217 (8), 206 (13), 197 (15), 189 (10), 145 (28), 122 (6), 105 (100), 95 (30), 77 (100), 51 (43), 43 (100).

3-Benzoyl-1-{[*cis*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]methyl}thymine (11a). According to the general procedure for the Mitsunobu reaction, *cis* alcohol **6a** (84 mg, 0.519 mmol) was reacted with N^3-benzoylthymine (**14**) (239 mg, 1.038 mmol), which was synthesized as described.[41] After column chromatography (ethyl acetate/cyclohexane, 3 : 2) a mixture of **11a** and ethyl *N*′-(2-ethoxyacetyl)hydrazine carboxylate (30%) was isolated. The latter compound was removed by crystallization from ethyl acetate at −20 °C. After further purification of the mother liquor by column chromatography (ethyl acetate/cyclohexane, 3 : 2), **11a** (142 mg, 73%) was isolated as a white solid. For elemental analysis the product was recrystallized from CH_2Cl_2/pentane (1 : 2) at −20 °C; mp 87 °C (from CH_2Cl_2/pentane); (Found: C, 60.4; H, 4.9; N, 7.5. Calc. for $C_{19}H_{19}FN_2O_5$: C, 61.0; H, 5.1; N 7.5%); ν_{max}(KBr)/cm^{-1} 1749s (aliph. C=O), 1699m (arom. C=O), 1656s (arom. C=O), 1251m (CF), 1231m; δ_H ($CDCl_3$) 0.92 (1 H, ddm, *J* 10.3 and 7.5, CH_AH_B), 1.25–1.43 (1 H, ddm, *J* 10.3 and 1.5, CH_AH_B), 1.76–1.93 (1 H, m, CH_X), 1.98 (3 H, s, CH_3), 2.05 (3 H, s, C(O)-CH_3), 3.73 (1 H, dd, *J* 12.2 and 9.4, CH_CH_DOAc), 4.11–4.25 (2 H, dm, *J* 1.5, CH_EH_FN), 4.30–4.40 (1 H, dm, *J* 12.2, CH_CH_DOAc), 7.30 (1 H, t, *J* 1.2, Ar), 7.46–7.52 (2 H, m, Ar), 7.64 (1 H, tt, *J* 7.4 and 1.3, Ar), 7.89–7.94 (2 H, m, Ar); δ_C ($CDCl_3$) 12.4 (q, CH_3), 14.7 (dt, *J* 11.0, CH_AH_B), 20.7 (q, C(O)-CH_3), 21.9 (dd, *J* 12.7, CH_X), 49.0 (dt, *J* 20.3, CH_EH_FN), 62.7 (t, CH_CH_DOAc), 80.9 (ds,

J 218.7, C-F), 111.0 (s), 129.1 (d), 130.3 (d), 131.6 (s), 135.0 (d), 140.1 (dd, J 2.5, Ar), 150.1 (s, C_{Ar}=O), 162.9 (s, C_{Ar}=O), 168.7 (s, C=O), 170.5 (s, C(O)-CH$_3$); δ_F (CDCl$_3$) −175.2 (m); *m*/*z* 374 (5%), 346 (2), 315 (42), 304 (12), 287 (20), 231 (9), 211 (6), 202 (3), 145 (14), 122 (2), 105 (65), 85 (12), 77 (100), 70(4), 65 (4), 59 (4), 51 (22), 43 (72).

3-Benzoyl-1-{[*trans*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]methyl}thymine (11b). According to the procedure described above, **11b** was synthesized from **6b** (106 mg, 0.654 mmol). After column chromatography (ethyl acetate/cyclohexane, 1 : 1) **11b** (195 mg, 80%) was isolated as a viscous oil. For elemental analysis the product was further purified by HPLC (ethyl acetate/methanol, 1 : 1). (Found: C, 60.6; H, 5.3; N, 7.2. Calc. for $C_{19}H_{19}FN_2O_5$: C, 61.0; H, 5.1; N, 7.5%); ν_{max}(KBr)/cm^{-1} 1750s (aliph. C=O), 1701m (arom. C=O), 1656s (arom. C=O), 1245s (CF), 1227s; δ_H (CDCl$_3$) 1.00–1.36 (2 H, m, C$H_A$$H_B$), 1.50–1.65 (1 H, m, C$H_X$), 1.98 (3 H, d, J 1.2, CH_3), 2.05 (3 H, s, C(O)-CH_3), 3.97 (1 H, ddd, J 11.7, 9.1 and 1.2, CH_CH$_D$OAc), 4.06–4.15 (2 H, m, C$H_E$$H_F$N), 4.38 (1 H, ddd, J 11.7, 6.0 and 1.4, CH$_C$$H_D$OAc), 7.26 (1 H, s, Ar), 7.48 (2 H, dd, J 7.9 and 7.8, Ar), 7.64 (1 H, tt, J 7.9 and 1.4, Ar), 7.92 (2 H, dd, J 7.8 and 1.4, Ar); δ_C (CDCl$_3$) 12.4 (q, CH$_3$), 14.5 (dt, J 11.4, CH$_A$H$_B$), 20.4 (dd, J 10.2, CH$_X$), 20.8 (q, C(O)-CH$_3$), 51.9 (dt, J 20.3, CH$_E$H$_F$N), 62.0 (dt, J 8.9, CH$_C$H$_D$OAc), 80.7 (ds, J 223.8, C-F), 110.8 (s), 129.1 (d), 130.4 (d), 131.6 (s), 135.0 (d), 140.1 (d, Ar), 150.2 (s, C_{Ar}=O), 163.0 (s, C_{Ar}=O), 168.7 (s, C=O), 170.7 (s, C(O)-CH$_3$); δ_F (CDCl$_3$) −198.4 (m); *m*/*z* 374 (2%), 345 (1), 315 (4), 304 (1), 287 (4), 242 (2), 233 (2), 211 (2), 145 (4), 122 (2), 105 (100), 85 (4), 77 (31), 51 (8), 43 (9).

General procedure for deprotection with ammonia in methanol

The protected nucleoside (1 mmol) was dissolved in a sat. solution of ammonia in methanol (25 cm^3). The solution was stirred at room temperature until complete conversion (TLC). All volatiles were removed under reduced pressure. The residue was absorbed to SiO$_2$ and purified by column chromatography. Pure samples for elemental analysis and biological studies were obtained by HPLC.

9-{[*cis*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-adenine (8a). According to the general procedure for deprotection with ammonia in methanol **7a** (46 mg, 0.165 mmol) was treated with sat. ammonia in methanol (10 cm^3). After column chromatography (ethyl acetate/methanol, 10 : 1) and HPLC (ethyl acetate/methanol, 5 : 1) **8a** (35 mg, 90%) was isolated as a white, amorphous powder; mp 188 °C; (Found: C, 50.5; H, 5.1. Calc. for $C_{10}H_{12}FN_5O$: C, 50.6; H, 5.1%); ν_{max}(KBr)/cm^{-1} 3456s (NH$_2$), 3318m (NH$_2$), 3163br (OH), 1654s, 1605m, 1251m (CF), 1145m, 1073m, 1050m, 1036m, 1004m; δ_H (MeOH-d$_4$) 0.94 (1 H, ddm, J 9.5 and 7.1, CH_AH$_B$), 1.22 (1 H, dddm, J 19.1, 7.1 and 1.2, CH$_A$$H_B$), 1.68–1.87 (1 H, m, C$H_X$), 3.35 (1 H, s, O$H$), 3.48 (1 H, ddd, J 12.1, 8.6 and 1.2, CH_CH$_D$OH), 3.87 (1 H, ddd, J 12.1, 5.7 and 2.7, CH$_C$$H_D$OH), 4.61–4.85 (2 H, m, C$H_E$$H_F$N), 4.77 (2 H, s, N$H_2$), 8.20–8.24 (2 H, m, Ar); δ_C (MeOH-d$_4$) 14.5 (dt, J 10.2, CH$_A$H$_B$), 26.5 (dd, J 12.7, CH$_X$), 46.3 (dt, J 20.3, CH$_E$H$_F$N), 61.6 (t, CH$_C$H$_D$OH), 81.7 (ds, J 218.7, C-F), 120.1 (s), 143.4 (d), 151.2 (s), 154.1 (d), 157.7 (s, Ar); δ_F (MeOH-d$_4$) −175.3 (ddm, J 19.1 and 9.5); *m*/*z* (ESI) 260 (M + Na$^+$, 58%), 238 (M + H$^+$, 100%), 237 (4), 217 (8), 195 (5), 181 (12), 169 (17), 151 (8), 136 (29), 102 (7); *m*/*z* (ESI) 238.1091 (M + H$^+$. $C_{10}H_{13}FN_5O$ requires 238.1104), 260.0946 (M + Na$^+$. $C_{10}H_{12}$-FN_5ONa requires 260.0923).

9-{[*trans*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-adenine (8b). According to the procedure described above, **8b** was synthesized from **7b** (110 mg, 0.394 mmol). After column chromatography (ethyl acetate/methanol, 10 : 1) **8b** (90 mg, 96%) was isolated as a white, amorphous powder. Pure samples for biological examinations were obtained by HPLC (ethyl acetate/methanol 2 : 1); mp 189 °C; (Found: C, 50.1; H, 4.8; N, 28.9. Calc. for $C_{10}H_{12}FN_5O$: C, 50.6; H, 5.1; N, 29.5%); ν_{max}(KBr)/cm^{-1} 3287br (NH$_2$, OH), 1699s, 1616s, 1386m, 1297m, 1257w (CF), 1051m, 1022m; δ_H (DMSO-d$_6$) 0.86 (1 H, ddd, J 20.3, 7.2 and 6.7, CH$_A$$H_B$), 1.19 (1 H, ddd, J 9.8, 9.8 and 6.7, CH_AH$_B$), 1.50–1.61 (1 H, m, CH_X), 3.28–3.62 (2 H, m, C$H_C$$H_D$OH), 4.53 (2 H, d, J 23.7, C$H_E$$H_F$N), 4.67 (1 H, s, O$H$), 7.19 (2 H, s, N$H_2$), 8.16 (1 H, s, Ar), 8.21 (1 H, s, Ar); δ_C (DMSO-d$_6$) 13.6 (dt, J 10.2, CH$_A$H$_B$), 24.0 (dd, J 10.2, CH$_X$), 47.5 (dt, J 21.6, CH$_E$H$_F$N), 58.8 (dt, J 7.6, CH$_C$H$_D$OH), 81.0 (ds, J 222.5, C-F), 118.2 (s), 140.8 (d), 149.9 (s), 152.7 (d), 156.1 (s, Ar); δ_F (DMSO-d$_6$) −198.3 (m); *m*/*z* (ESI) 238 (M + H$^+$, 27%), 220 (7), 200 (4), 136 (100), 85 (7), 55 (7). Structural analysis was confirmed by ^{1}H,^{1}H COSY and ^{1}H,^{13}C HETCOR experiments.

1-{[*cis*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-uracil (10a). According to the general procedure for deprotection with ammonia in methanol, **10a** was synthesized from **9a** (77 mg, 0.214 mmol). After column chromatography (ethyl acetate) **10a** (35 mg, 76%) was isolated as a white solid. For elemental analysis the product was purified by HPLC (ethyl acetate); mp 130 °C; (Found: C, 50.2; H, 5.0; N, 12.9. Calc. for $C_9H_{11}FN_2O_3$: C, 50.5; H, 5.2; N, 13.1%); ν_{max}(KBr)/cm^{-1} 3464br (OH), 1698s (arom. C=O), 1339m (C–O), 1250w (CF), 1171m, 1040m; δ_H (MeOH-d$_4$) 0.85 (1 H, ddd, J 10.4, 7.3 and 7.3, CH_AH$_B$), 1.16–1.29 (1 H, m, CH$_A$$H_B$), 1.63–1.82 (1 H, m, C$H_X$), 3.37 (1 H, dd, J 11.8 and 8.5, CH_CH$_D$OH), 3.79 (1 H, ddd, J 11.8, 5.9 and 2.5, CH$_C$$H_D$OH), 4.26 (1 H, s, C$H_EH_F$N), 4.34 (1 H, s, CH$_E$$H_F$N), 4.74 (2 H, s, N$H$ and OH), 5.68 (1 H, d, J 7.8, Ar), 7.66 (1 H, dd, J 7.8 and 1.3, Ar); δ_C (MeOH-d$_4$) 14.8 (dt, J 14.8, CH$_A$H$_B$), 26.3 (dd, J 10.3, CH$_X$), 50.0 (dt, J 20.3, CH$_E$H$_F$N), 61.9 (t, CH$_C$H$_D$OH), 82.1 (ds, J 214.8, C-F), 102.6 (d), 147.6 (d, Ar), 153.3 (s, C_{Ar}=O), 166.8 (s, C_{Ar}=O); δ_F (MeOH-d$_4$) −175.3 (m); *m*/*z* (ESI, daughters of 215) 215 (M + H$^+$, 38%), 197 (17), 185 (4), 154 (5), 113 (100), 85 (34), 83 (7), 55 (16).

1-{[*trans*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-uracil (10b). According to the procedure described above, **10b** was synthesized from **9b** (85 mg, 0.236 mmol). After column chromatography (ethyl acetate) **10b** (33 mg, 65%) was isolated as a white solid. For elemental analysis the product was purified by HPLC (ethyl acetate); mp 133 °C; (Found: C, 50.6; H, 4.9; N, 12.8. Calc. for $C_9H_{11}FN_2O_3$: C, 50.5; H, 5.2; N, 13.1%); ν_{max}(KBr)/cm^{-1} 3370br (OH), 3193m, 3180m, 1690s (arom. C=O), 1386m, 1342m (C–O), 1265w (CF), 1186m, 1082m, 1046m, 1031m; δ_H (MeOH-d$_4$) 0.91 (1 H, ddd, J 20.3, 7.2 and 7.2, CH$_A$$H_B$), 1.07–1.20 (1 H, ddm, J 9.0 and 7.2, CH_AH$_B$), 1.43–1.55 (1 H, m, CH_X), 3.45–3.54 (1 H, m, CH_CH$_D$OH), 3.78 (1 H, ddd, J 11.6, 5.9 and 1.6, CH$_C$$H_D$OH), 4.11–4.21 (2 H, m, C$H_E$$H_F$N), 4.75 (2 H, s, N$H$ and OH), 5.66 (1 H, d, J 7.9, Ar), 7.63 (1 H, dd, J 7.9 and 0.9, Ar); δ_C (MeOH-d$_4$) 14.4 (dt, J 9.4, CH$_A$H$_B$), 25.2 (dd, J 11.3, CH$_X$), 53.1 (dt, J 20.2, CH$_E$H$_F$N), 61.0 (dt, J 8.1, CH$_C$H$_D$OH), 82.4 (ds, J 223.5, C-F), 102.5 (d), 147.5 (d), 153.3 (s, C_{Ar}=O), 166.9 (s, C_{Ar}=O). δ_F (MeOH-d$_4$) −200.2 (m); *m*/*z* 214 (1%), 198 (11), 197 (100), 183 (18), 177 (2), 171 (6), 156 (7), 151 (28), 140 (10), 126 (10), 113 (2), 106 (2), 98 (9), 85 (24), 82 (21), 69 (11), 59 (6), 54 (3).

1-{[*cis*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-thymine (12a). According to the general procedure for deprotection with ammonia in methanol, **12a** was synthesized from **11a** (105 mg, 0.281 mmol). After column chromatography (ethyl acetate/cyclohexane, 2 : 1 and ethyl acetate) **12a** (43 mg, 67%) was isolated as a white solid. For elemental analysis the product was purified by HPLC (ethyl acetate/cyclohexane, 4 : 1); mp 150 °C; (Found: C, 52.5; H, 5.8; N 12.1. Calc. for $C_{10}H_{13}FN_2O_3$: C, 52.6; H, 5.7; N, 12.3%); ν_{max}(KBr)/cm^{-1}

3419br (OH), 1703s (arom. C=O), 1672s (arom. C=O), 1385m (C–O), 1350m, 1260m (CF), 1051m; δ_H ($CDCl_3$, MeOH-d_4 5 : 1, 400 MHz) 0.82 (1 H, ddd, *J* 10.2, 7.4 and 7.4, CH_AH_B), 1.25 (1 H, ddd, *J* 19.0, 10.2 and 7.4, CH_AH_B), 1.69–1.83 (1 H, m, CH_X), 1.93 (s, 3 H, CH_3), 3.36 (1 H, dd, *J* 12.2 and 8.8, CH_CH_D-OH), 3.85 (1 H, ddd, *J* 12.2, 5.7 and 2.8, CH_CH_DOH), 4.16–4.35 (4 H, m, CH_EH_FN, N*H* and O*H*), 7.35 (1 H, s, Ar); δ_C ($CDCl_3$, MeOH-d_4, 5 : 1, 100.63 MHz) 11.6 (q, CH_3), 13.1 (dt, *J* 11.6, CH_AH_B), 24.6 (dd, *J* 11.2, CH_X), 48.2 (dt, *J* 20.1, CH_EH_FN), 60.2 (t, CH_CH_DOH), 80.4 (ds, *J* 218.0, *C*-F), 110.4 (s), 141.1 (dd, *J* 2.4), 151.5 (s, C_{Ar}=O), 164.8 (s, C_{Ar}=O); δ_F ($CDCl_3$, MeOH-d_4, 5 : 1, 188 MHz) −175.7 (m); *m*/*z* 228 (14%), 211 (100), 208 (22), 197 (13), 184 (3), 169 (6), 164 (21), 154 (9), 141 (4), 139 (6), 126 (35), 109 (7), 96 (28), 85 (48), 72 (6), 59 (12), 55 (36), 53 (7), 41 (15), 39 (10). Structural analysis was confirmed by ^{1}H,^{1}H COSY and ^{1}H,^{13}C HETCOR experiments.

1-{[*trans*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-thymine (12b). According to the procedure described above, **12b** was synthesized from **11b** (163 mg, 0.436 mmol). After column chromatography (ethyl acetate) **12b** (75 mg, 75%) was isolated as a white solid; mp 162 °C; (Found: C, 52.5; H, 5.6; N, 12.3. Calc. for $C_{10}H_{13}FN_2O_3$: C, 52.6; H, 5.7; N, 12.3%); ν_{max}(KBr)/cm^{-1} 3470m (OH), 1693s (arom. C=O), 1674s (arom. C=O), 1241w (CF), 1206m, 1031m; δ_H (DMSO-d_6) 0.81 (1 H, ddd, *J* 20.5, 7.2 and 6.8, CH_AH_B), 1.05 (1 H, ddd, *J* 10.0, 9.8 and 6.8, CH_AH_B), 1.33–1.45 (1 H, m, CH_X), 1.77 (3 H, s, CH_3), 3.32 (1 H, s, O*H*), 3.54–3.62 (1 H, m, CH_CH_DOH), 4.05 (2 H, d, *J* 22.2, CH_EH_FN), 4.63–4.66 (1 H, m, CH_CH_DOH), 7.53 (1 H, s, Ar), 11.24 (1 H, s, N*H*); δ_C (DMSO-d_6) 12.0 (q, CH_3), 13.2 (dt, *J* 10.2, CH_AH_B), 23.7 (dd, *J* 10.2, CH_X), 50.7 (dt, *J* 20.3, CH_EH_FN), 58.8 (dt, *J* 7.6, CH_CH_DOH), 81.0 (ds, *J* 223.8, *C*-F), 108.6 (s), 141.3 (d, Ar), 151.3 (s, C_{Ar}=O), 164.3 (s, C_{Ar}=O); δ_F (DMSO-d_6) −198.8 (m); *m*/*z* 228 (16%), 211 (100), 208 (28), 184 (3), 167 (4), 164 (33), 155 (20), 141 (16), 139 (14), 126 (39), 112 (18), 96 (38), 85 (70), 77 (10), 72 (15), 59 (34), 55 (82), 53 (23), 41 (36), 39 (32). Structural analysis was confirmed by ^{1}H,^{1}H COSY and ^{1}H,^{13}C HETCOR experiments.

General procedure for the synthesis of mesylates of (±)-[1-Fluoro-2-(acetoxymethyl)cyclopropyl]methanols (15a and 15b)

To an ice-cooled solution of the alcohol **6a** or **6b** (162 mg, 1.0 mmol) in anh. CH_2Cl_2 (4 cm^3) triethylamine (606 mg, 6 mmol) and mesyl chloride (344 mg, 3 mmol) were added. The reaction mixture was stirred for 6 h at 0 °C. Sat. NH_4Cl (12 cm^3) was added and the aqueous phase was extracted with Et_2O (3 × 20 cm^3). The combined organic layers were washed with sat. $NaHCO_3$ (10 cm^3), sat. NaCl (10 cm^3) and dried over $NaSO_4$. All volatiles were removed under reduced pressure. The obtained mesylates were used without further purification.

1-{[*cis*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-cytosine (16a). As described above, the mesylate **15a** was prepared from **6a** (132 mg, 0.815 mmol). This mesylate was reacted with cytosine (136 mg, 1.22 mmol) and Cs_2CO_3 (797 mg, 2.45 mmol) in anh. DMF at 70 °C for 17 h. Under vacuum all volatiles were removed. According to the general procedure the residue was treated with sat. ammonia in methanol. After column chromatography (ethyl acetate/methanol, 5 : 1) and HPLC (ethyl acetate/methanol, 3 : 1) **16a** (66 mg, 38%) was isolated as a white solid. For elemental analysis **16a** was recrystallized from methanol/Et_2O (1 : 3); mp 185 °C (from methanol/Et_2O); (Found: C, 50.4; H, 5.3; N, 19.5. Calc. for $C_9H_{12}FN_3O_2$: C, 50.7; H, 5.7; N, 19.7%); δ_H (MeOH-d_4) 0.81–0.90 (1 H, m, CH_AH_B), 1.18 (1 H, ddd, *J* 19.4, 11.2 and 6.8, CH_AH_B), 1.60–1.80 (1 H, m, CH_X), 3.32–3.42 (1 H, m, CH_CH_D-OH), 3.78 (1 H, ddd, *J* 11.9, 6.2 and 2.8, CH_CH_DOH), 4.26–4.39 (2 H, m, CH_EH_FN), 4.76 (3 H, s, O*H* and NH_2), 5.87 (1 H, dd, *J* 7.1 and 1.8, Ar), 7.65 (1 H, d, *J* 7.1, Ar); δ_C (MeOH-d_4) 14.5 (dt, *J* 12.8, CH_AH_B), 26.6 (dd, *J* 12.7, CH_X), 51.0 (dt, *J* 21.4, CH_EH_FN), 62.1 (t, CH_CH_DOH), 82.3 (ds, *J* 218.5, *C*-F), 96.1 (d), 148.1 (d, Ar), 159.5 (s, C_{Ar}=O), 168.3 (s, C_{Ar}=O); δ_F (MeOH-d_4) −175.0 (m); *m*/*z* (ESI, daughter ions of 214) 214 (M + H$^+$, 73%), 196 (15), 176 (6), 112 (100), 85 (11), 83 (5), 55 (6).

1-{[*trans*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-cytosine (16b). According to the procedure described above, **16b** was synthesized from **6b** (132 mg, 0.815 mmol). After column chromatography (ethyl acetate/methanol, 5 : 1) and HPLC (ethyl acetate/methanol, 3 : 1) **16b** (71 mg, 41%) was isolated as a white solid; mp 190 °C; (Found: C, 50.5; H, 5.4; N, 19.5; Calc. for $C_9H_{12}FN_3O_2$: C, 50.7; H, 5.7; N, 19.7%); δ_H (methanol-d_4, 400 MHz) 0.88 (1 H, ddd, *J* 20.0, 7.1 and 7.0, CH_AH_B), 1.15 (1 H, ddd, *J* 10.2, 9.9 and 7.0, CH_AH_B), 1.29 (1 H, s, O*H*), 1.44–1.53 (1 H, m, CH_X), 3.31 (2 H, s, NH_2), 3.51 (1 H, dd, *J* 11.6 and 9.6, CH_CH_DOH), 3.76 (1 H, ddd, *J* 11.6, 6.1 and 1.3, CH_CH_D-OH_D), 4.15–4.23 (2 H, m, CH_EH_FN), 5.86 (1 H, d, *J* 7.1, Ar), 7.63 (1 H, d, *J* 7.1, Ar); δ_C (methanol-d_4, 100.63 MHz) 14.7 (dt, *J* 11.2, CH_AH_B), 25.2 (dd, *J* 10.8, CH_X), 54.1 (dt, *J* 21.3, CH_EH_FN), 61.1 (dt, *J* 9.6, CH_CH_DOH), 82.6 (ds, *J* 221.6, *C*-F), 96.0 (d), 147.8 (d, Ar), 159.5 (s, C_{Ar}=O), 168.3 (s, C_{Ar}=O); δ_F (methanol-d_4, 188 MHz) −199.6 (m); *m*/*z* (ESI) 214 (M + H$^+$, 28%), 196 (20), 176 (5), 111 (100), 85 (11), 83 (4), 55 (7). Structural analysis was confirmed by ^{1}H,^{1}H COSY and ^{1}H,^{13}C HETCOR experiments.

2-Amino-9-{[*cis*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]-methyl}-6-chloropurine (17a). As described above, the mesylate **15a** was prepared from the corresponding alcohol **6a** (100 mg, 0.617 mmol). This mesylate was reacted with 2-amino-6-chloropurine (131 mg, 0.77 mmol) and Cs_2CO_3 (251 mg, 0.77 mmol) in anh. DMF at 50 °C for 16 h. Under vacuum all volatiles were removed. According to the general procedure, the residue was treated with ammonia in methanol. After column chromatography (ethyl acetate/cyclohexane, 3 : 1) **17a** (108 mg, 56%) was isolated as a crystalline solid. For elemental analysis **17a** was recrystallized from methanol at −20 °C; mp 130 °C (from methanol); (Found: C, 45.8; H, 4.1; N, 22.2. Calc. for $C_{12}H_{13}ClFN_5O_2$: C, 45.9;H, 4.2; N, 22.3%); ν_{max}(KBr)/cm^{-1} 3504m (NH_2), 3290m (NH_2), 1731s (aliph. C=O), 1628s, 1247s (CF), 1169m, 919m; δ_H (MeOH-d_4) 1.05 (1 H, ddd, *J* 9.7, 7.5 and 7.3, CH_AH_B), 1.38 (1 H, ddd, *J* 18.8, 11.2 and 7.3, CH_AH_B), 1.77–1.96 (1 H, m, CH_X), 1.90 (3 H, s, CH_3), 3.84 (1 H, dd, *J* 12.2 and 9.8, CH_CH_DOAc), 4.38 (1 H, ddd, *J* 12.2, 6.0 and 2.7, CH_CH_DOAc), 4.58–4.71 (2 H, m, CH_EH_FN), 4.76 (2 H, s, NH_2), 8.13 (1 H, s, Ar); δ_C (MeOH-d_4) 15.3 (dt, *J* 12.3, CH_AH_B), 20.8 (q, CH_3), 22.8 (dd, *J* 12.5, CH_X), 46.1 (dt, *J* 19.2, CH_EH_FN), 64.6 (t, CH_CH_DOAc), 81.8 (ds, *J* 218.7, *C*-F), 124.8 (s), 144.8 (d), 151.9 (s), 155.7 (s), 162.0 (s, Ar), 172.6 (s, *C*=O); δ_F (MeOH-d_4) −175.0 (m); *m*/*z* 315/313 (3/10%), 256/254 (11/37), 251 (21), 236/234 (11/24), 218 (10), 198 (12), 182 (11), 172 (31), 170 (100), 158 (6), 146 (15), 141 (9), 134 (62), 128 (4), 119 (7), 114 (8), 107 (5), 92 (8), 85 (35), 82 (12), 69 (7), 65 (12), 60 (14), 53 (11), 43 (53).

2-Amino-9-{[*trans*-1′-fluoro-2′-(acetoxymethyl)cycloprop-1′-yl]-methyl}-6-chloropurine (17b). According to the procedure described above, **17b** was synthesized from **6b** (100 mg, 0.617 mmol). After column chromatography (ethyl acetate/cyclohexane, 3 : 1) **17b** (103 mg, 53%) was isolated as a crystalline solid. For elemental analysis **17b** was recrystallized from methanol at −20 °C; mp 167 °C (from methanol); (Found: C, 45.9; H, 4.0; N, 22.2. Calc. for $C_{12}H_{13}ClFN_5O_2$: C, 45.9; H, 4.2; N, 22.3%); ν_{max}(KBr)/cm^{-1} 3395m (NH_2), 3312m (NH_2), 1724s (aliph. C=O), 1630s, 1613s, 1566s, 1245m (CF), 1167m, 1038m (arom. CCl), 911m; δ_H (methanol-d_4) 1.10 (1 H, ddd, *J* 20.3, 7.2 and 7.2, CH_AH_B), 1.32 (1 H, ddd, *J* 10.3, 10.3 and 7.2, CH_AH_B), 1.71–1.83 (1 H, m, CH_X), 1.85 (3 H, s, CH_3), 3.81 (1 H, dd, *J* 11.8, 9.4 and 1.4, C$H_C$$H_D$OAc), 4.30–4.45 (2 H, m, CH_C*H_D*OAc and C*H_E*H_FN), 4.68 (1 H, dd, *J* 18.0 and 15.4, CH_E*H_F*N), 4.76 (2 H, s, N*H_2*), 8.12 (1 H, d, *J* 0.6, Ar); δ_C (methanol-d_4) 15.0 (dt, *J* 10.3, *C*H_AH_B), 20.8 (q, *C*H_3), 22.0 (dd, *J* 10.1, *C*H_X), 49.1 (dt, *J* 24.5, *C*H_EH_FN), 64.6 (dt, *J* 7.6, *C*H_CH_DOAc), 81.7 (ds, *J* 220.4, *C*-F), 125.0 (s), 144.8 (d), 151.9 (s), 155.8 (s), 161.9 (s, Ar), 172.7 (s, *C*=O); δ_F (methanol-d_4, 188 MHz) −198.9 (m); *m*/*z* 315/313 (9/24%), 272/270 (1/3), 256/254 (13/37), 236/234 (2/5), 218 (2), 213(4), 198 (6), 183 (6), 169 (52), 146 (8), 141 (3), 134 (35), 119 (3), 114 (2), 107 (3), 92 (4), 85 (31), 82 (3), 65 (7), 59 (6), 54 (4), 43 (100).

9-{[*cis*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-guanine (18a). A solution of **17a** (100 mg, 0.617 mmol) in glacial acid (15 cm^3) was stirred for 24 h at 70 °C. All volatiles were removed under vacuum. The obtained residue was dissolved in a sat. solution of ammonia in methanol (20 cm^3) and stirred overnight at room temperature. All volatiles were removed under vacuum. After column chromatography (ethyl acetate/methanol, 2 : 1) and HPLC (ethyl acetate/methanol, 2 : 1) **18a** (26 mg, 41%) was isolated as a white, amorphous solid. The product was insoluble in most organic solvents except DMSO. δ_H (D_2O, DMSO-d_6 10 : 1) 0.94 (1 H, ddd, *J* 9.9, 7.4 and 7.4, C*H_A*H_B), 1.20–1.34 (1 H, m, CH_A*H_B*), 1.70–1.87 (1 H, m, C*H_X*), 3.46 (1 H, dd, *J* 11.9 and 8.3, C*H_C*H_DOH), 3.75 (1 H, ddd, *J* 11.9, 6.6 and 2.5, CH_C*H_D*OH), 4.40 (1 H, dd, *J* 26.6 and 15.8, C*H_E*H_FN), 4.48 (3 H, s, O*H* and N*H_2*), 4.65 (1 H, ddd, *J* 19.4, 15.8 and 1.0, CH_E*H_F*N), 7.90 (1 H, s, Ar); δ_C (D_2O, DMSO-d_6 10 : 1, 90.57 MHz) 15.0 (dt, *J* 15.0, *C*H_AH_B), 25.9 (dd, *J* 11.0, *C*H_X), 45.8 (dt, *J* 20.7, *C*H_EH_FN), 61.3 (t, *C*H_C-H_DOH), 82.0 (ds, *J* 217.6, *C*-F), 116.9 (s), 140.7 (d), 153.2 (s), 155.1 (s), 159.4 (s, Ar); δ_F (D_2O, DMSO-d_6 10 : 1) −174.9 (m); *m*/*z* (ESI) 276 (M + Na^+, 100%), 254 (M + H^+, 81%), 191 (37), 169 (7), 152 (20), 142 (15), 125 (14), 107 (94), 85 (61), 72 (25), 60 (21); *m*/*z* (ESI) 254.1052 (M + H^+. $C_{10}H_{13}FN_5O_2$ requires 254.1053), 276.0863 (M + Na^+. $NaC_{10}H_{12}FN_5O_2$requires 276.0873).

9-{[*trans*-1′-Fluoro-2′-(hydroxymethyl)cycloprop-1′-yl]methyl}-guanine (18b). According to the procedure described above, **18b** was synthesized from **17b** (57 mg, 0.182 mmol). After column chromatography (ethyl acetate/methanol, 2 : 1) and HPLC (ethyl acetate/methanol, 2 : 1) **18b** (14 mg, 30%) was isolated as a white, amorphous solid. The product was insoluble in most organic solvents except DMSO. δ_H (MeOH-d_4, DMSO-d_6 10 : 1) 0.90 (1 H, ddd, *J* 20.2, 7.0 and 7.0, CH_A*H_B*), 1.17 (1 H, ddd, *J* 10.0, 10.0 and 7.0, C*H_A*H_B), 1.47–1.59 (1 H, m, C*H_X*), 3.45 (1 H, ddd, *J* 11.4, 8.2 and 1.0, C*H_C*H_DOH), 3.70 (1 H, ddd, *J* 11.4, 6.0 and 1.7, CH_C*H_D*OH), 4.31 (3 H, s, O*H* and N*H_2*), 4.33–4.42 (2 H, m, C*H_E**H_F*N), 7.81 (1 H, s, Ar); δ_C (MeOH-d_4, DMSO-d_6 10 : 1, 90.57 MHz) 14.9 (dt, *J* 11.0, *C*H_AH_B), 25.5 (dd, *J* 10.7, *C*H_X), 49.0 (dt, *J* 21.9, *C*H_EH_FN), 60.7 (dt, *J* 10.2, *C*H_CH_DOH), 82.4 (ds, *J* 223.5, *C*-F), 117.7 (s), 139.6 (d), 153.5 (s), 155.5 (s), 159.2 (s, Ar); δ_F (MeOH-d_4, DMSO-d_6 10 : 1) −199.1 (m); *m*/*z* (ESI) 276 (M + Na^+, 62%), 254 (M + H^+, 100), 152 (28), 142 (7), 107 (8), 102 (12), 85 (35), 73 (10), 60 (23); *m*/*z* (ESI) 254.1057 (M + H^+ $C_{10}H_{13}FN_5O_2$ requires 254.1053), 276.0876 (M + Na^+ $NaC_{10}H_{12}FN_5O_2$ requires 276.0873).

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