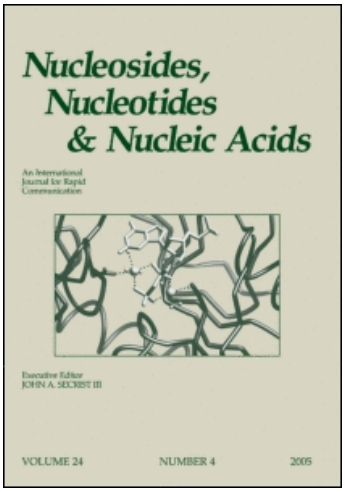

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Synthesis, Structural Studies, and Biological Evaluation of Some Purine Substituted 1-Aminocyclopropane-1-carboxylic Acids and 1-Amino-1-hydroxymethylcyclopropanes

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Synthesis, Structural Studies, and Biological Evaluation of Some Purine Substituted 1-Aminocyclopropane-1-carboxylic Acids and 1-Amino-1-hydroxymethylcyclopropanes

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ABSTRACT

The novel purine derivatives of 1-aminocyclopropane-1-carboxylic acid (**8** and **9**) and 1-amino-1-hydroxymethylcyclopropane (**12** and **13**) with methylene spacer between the base and the cyclopropane ring were prepared by multistep synthetic route involving alkylation of adenine and 6-(*N*-pyrrolyl)purine with 2-hydroxy-

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methyl-1-aminocyclopropane-1-carboxylic acid derivative **3** as a key reaction. All novel compounds were racemic. The *N*-9 substitution of the purine ring and the *Z*-configuration of the cyclopropane ring in **4**–**13** were deduced from their ^{1}H and ^{13}C NMR spectra by analyses of chemical shifts, H-H coupling constants and connectivities in two-dimensional homo- and heteronuclear correlation spectra. An unequivocal proof of the stereostructure of **1**, **4** and **5** was obtained by their X-ray structure analysis. The novel compounds were evaluated on cytostatic and antiviral activities in several cell lines. The 6-(*N*-pyrrolyl)purine derivative of 1,2-aminocyclopropane alcohol **12** exhibited a more pronounced inhibitory activity against the proliferation of cervical carcinoma (HeLa) and human fibroblast (WI-38) cells than other types of tumor cell lines. None of the compounds showed inhibitory activities against cytomegalovirus, varicella-zoster virus or other viruses.

INTRODUCTION

Searching for new antiviral agents with better activities than the known drugs acyclovir, ganciclovir and penciclovir[1] led to discovery of novel carboxylic nucleoside analogues containing two hydroxymethyl groups on the four membered ring.[2,3] Of these compounds, oxetanocins and the related carbocyclic analogue cyclobut-G[2] were shown to be highly potent inhibitors of broad spectrum of herpes viruses, including herpes simplex virus (HSV-1 and HSV-2), varicella-zoster virus (VZV) and human cytomegalovirus (HCMV). The cyclopropane nucleoside analogues have been of particular interest for medicinal chemists and virologists since their strained three-membered ring has been found to be involved in many important biological processes.[4] These nucleoside analogues could generally be divided in two types of molecules. The first ones consist of the base moieties directly linked to the cyclopropane moiety, which may be considered as ring-contracted analogues of oxetanocins. The second type of those molecules contains a spacer, which may be either a methylene or an unsaturated group, between the heterocyclic base and the cyclopropane ring[5]. The latter nucleoside analogues containing a methylenecyclopropane functional group instead of a ribofuranose moiety, exhibit potent antiviral effects against a broad range of viruses. Among these compounds, synadenol and synguanol are of particular importance due to their inhibitory activity on the replication of human and murine cytomegalovirus (HCMV and MCMV), Epstein-Barr virus (EBV) as well as human herpes virus type 6 (HHV-6).[6,7] The cyclopropane nucleoside analogues uith two hydroxymethyl groups mimicking the 3′- and 5′-hydroxyl groups of the 2′-deoxyribose moiety, have been shown to possess strong antiherpetic activities. Among those, 1′*S*, 2′*R* enantiomer of 9-[[*cis*-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine (HMCMG) showed extremely potent activity against HSV-1 with good selectivity[2]. The present study deals with the synthesis of novel purine derivatives of cyclopropyl amino acids (**8**, **9**) and amino alcohols (**12**, **13**) with functional groups geminally substituted on the cyclopropane ring, their structural studies and evaluation on antitumor and antiviral activities.

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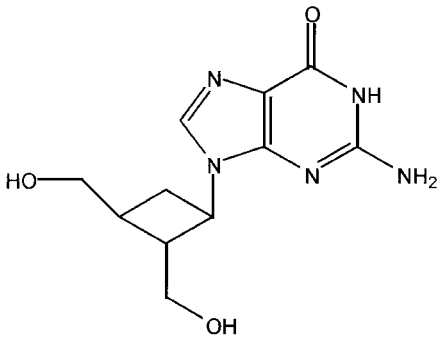
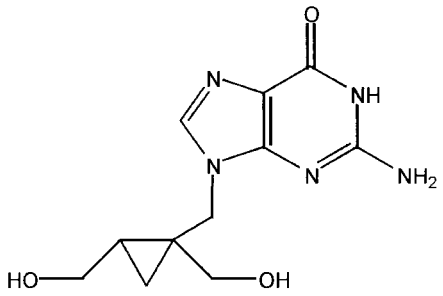
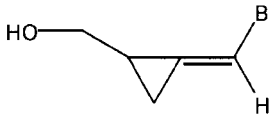


2-CYCLOBUT-G



HMCMG



SYNADENOL: B = Ade
SYNGUANOL: B = Gua

Structure 1.

RESULTS AND DISCUSSION

Synthesis

The synthetic strategy to the desired purine derivatives of 1-aminocyclopropane-1-carboxylic acids **8** and **9** and 1-amino-1-hydroxymethylcyclopropanes **12** and **13** was based on alkylation of adenine and 6-(*N*-pyrrolyl)purine with **3** containing protected amino and carboxylic group and as well as tosylated hydroxymethyl group (Sch. 1). Preparation of the bicyclic lactone **1** from the racemic epichlorohydrin was performed by the procedure given in the literature.[8] Transformation of the lactone **1** into alcohol **2** was performed as described in the literature.[9–11] The alcohol **2** was converted into the tosylate **3**, which was then coupled with 6-(*N*-pyrrolyl)purine[12,13] and adenine to afford the purine derivatives of cyclopropyl amino acid **4** and **5**.

The ester group in **4** and **5** was cleaved by basic hydrolysis to afford the N-Boc protected derivatives of cyclopropane amino acids **6** and **7**. Treatment of **6** and **7** with trifluoroacetic acid provided, after ion-exchange chromatography, the novel 6-(*N*-pyrrolyl)purine **8** and adenine **9** derivatives of 1-aminocyclopropane-1-carboxylic acid. The ester group in **4** and **5** was reduced with lithium borohydride to afford the *N*-Boc protected 1,2-aminocyclopropane alcohols **10** and **11**. Subsequent treatment of **10** and **11** with trifluoracetic acid provided, after ion exchange resin neutralization, the 6-(*N*-pyrrolyl)purine **12** and adenine **13** derivatives of the 1,2-aminocyclopropane alcohols. The novel compounds **8**, **9**, **12** and **13** were racemic. Subsequently we have found that the synthesis of the enantiomerically pure

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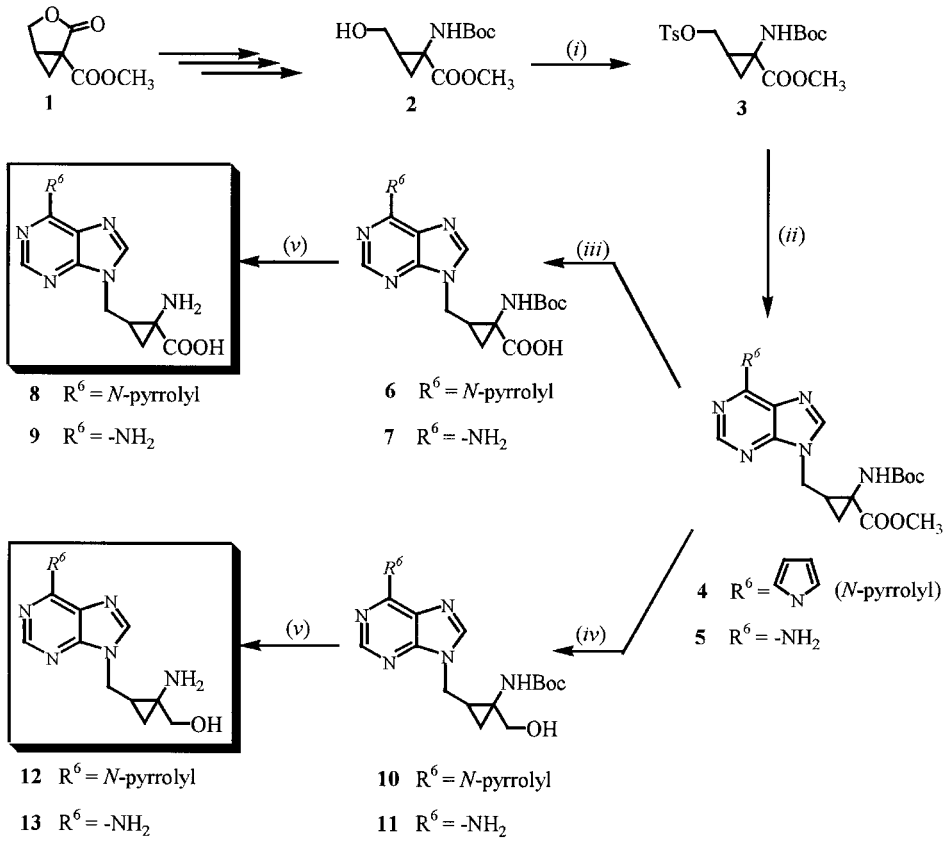

Scheme 1. (*i*) *p*-TsCl, DMAP, CH_2Cl_2; (*ii*) BH, K_2CO_3, DMF; (*iii*) OH^-, dioxane; (*iv*) $LiBH_4$, CH_2Cl_2; (*v*) CF_3COOH, DOWEX 50W-X8 (H^+).

adenine derivative **13** has been described previously by a different strategy using (-)-(*Z*)-2,3-methanohomoserine as a chiral precursor.[14]

^{1}H- and ^{13}C-NMR Spectra

In order to establish the stereostructure, especially the *Z*- or *E*-configuration of the novel compounds, their one- and two-dimensional ^{1}H and ^{13}C NMR spectra were analysed in detail. The ^{1}H and ^{13}C NMR data of **4**–**13** with spectral assignments are displayed in Tables 1 and 2. Assignments of the spectra were based upon a combination of chemical shifts, signal intensities, magnitude and multiplicity of H-H spin-spin coupling constants analyses and connectivities in COSY, HETCOR, DEPT and NOESY spectra. The ^{1}H NMR spectra of **4**–**13** showed the following general features: H-2 protons of the purine bases are more deshielded than H-8; this is consistent with *N*-9 substitution of the purine ring.[12,15] In the compounds **10**–**13**, the non-equivalence of methylene protons *N*-CH_AH_B and *O*-CH_AH_B was observed. *N*-methylene protons (3.96–4.48 ppm) are more deshielded than *O*-methylene ones

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Table 1. ^{1}H NMR chemical shifts (δ/ppm)[n] and H-H coupling constants (J/Hz) for the compounds **4**–**13** (cf. Sch. 1).

	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
H-2	8.74 (s, 1H)	8.20 (s, 1H)	8.74 (s, 1H)	8.20 (s, 1H)	8.74 (s, 1H)	8.11 (s, 1H)	8.74 (s, 1H)	8.19 (s, 1H)	8.74 (s, 1H)	8.17 (s, 1H)
H-8	8.71 (s, 1H)	8.14 (s, 1H)	8.71 (s, 1H)	8.13 (s, 1H)	8.65 (s, 1H)	8.11 (s, 1H)	8.72 (s, 1H)	8.12 (s, 1H)	8.70 (s, 1H)	8.12 (s, 1H)
-CH_{CYCLOP}	2.35 (m[b], 1H)	2.18 (m[b], 1H)	2.30 (m[b], 1H)	2.12 (m[b], 1H)	1.97 (m[b], 1H)	1.79 (m[b], 1H)	1.59 (m[b], 1H)	1.52 (m[b], 1H)	0.85 (m[b], 1H)	0.86 (mb, 1H)
-$CH_{2\ CYCLOP}$	1.24 (dd, 1H) $^{2}J=5.2$, $^{3}J_{trans}=7.4$	1.17 (dd, 1H) $^{2}J=5.2$, $^{3}J_{trans}=7.3$	1.16 (dd, 1H)c	1.10 (dd, 1H)c	0.93 (dd, 1H) $^{2}J=4.4$, $^{3}J_{trans}=5.5$	0.83 (dd, 1H) $^{2}J=4.5$, $^{3}J_{trans}=5.1$	0.88 (dd, 1H) $^{2}J=5.3$, $^{3}J_{trans}=8.6$	0.85 (dd, 1H) $^{2}J=5.1$, $^{3}J_{trans}=8.9$	0.68 (dd, 1H) $^{2}J=4.5$, $^{3}J_{trans}=8.8$	0.62 (dd, 1H) $^{2}J=4.5$, $^{3}J_{trans}=8.8$
	1.43 (dd, 1H) $^{2}J=5.2$, $^{3}J_{cis}=9.4$	ca. 1.40 (dd, 1H)[d]	*ca.* 1.35 (dd, 1H)[d]	1.38 (dd, 1H)[d]	1.28 (dd, 1H) $^{2}J=4.4$, $^{3}J_{cis}=9.2$	1.19 (dd, 1H) $^{2}J=4.5$, $^{3}J_{cis}=10.2$	*ca.* 1.30 (dd, 1H)[d]	1.46 (dd, 1H)[d]	*ca.* 1.29 (dd, 1H)[e]	*ca.* 1.19 (dd, 1H)[e]
-CH_AH_BN	4.11 (dd, 1H) $^{2}J=14.4$, $^{3}J=8.7$	4.01 (dd, 1H) $^{2}J=14.5$, $^{3}J=8.3$	4.09 (dd, 1H) $^{2}J=14.5$, $^{3}J=9.2$	3.99 (dd, 1H) $^{2}J=14.5$, $^{3}J=9.2$	3.78 (dd, 1H)[i]	4.18 (dd, 1H) $^{2}J=14.5$, $^{3}J=7.8$	4.07 (dd, 1H) $^{2}J=14.2$, $^{3}J=8.4$	3.96 (dd, 1H) $^{2}J=14.3$, $^{3}J=8.1$	4.33 (dd, 1H) $^{2}J=13.9$, $^{3}J=8.0$	4.16 (dd, 1H) $^{2}J=13.9$, $^{3}J=7.7$
	4.55 (dd, 1H) $^{2}J=14.4$, $^{3}J=5.9$	4.35 (dd, 1H) $^{2}J=14.5$, $^{3}J=6.0$	4.55 (dd, 1H) $^{2}J=14.5$, $^{3}J=5.7$	4.35 (dd, 1H) $^{2}J=14.5$, $^{3}J=6.5$	4.47 (dd, 1H)c	4.34 (dd, 1H) $^{2}J=14.5$, $^{3}J=6.2$	4.39 (dd, 1H) $^{2}J=14.2$, $^{3}J=5.3$	4.25 (dd, 1H) $^{2}J=14.3$, $^{3}J=5.7$	4.48 (dd, 1H) $^{2}J=13.9$, $^{3}J=6.3$	4.30 (dd, 1H) $^{2}J=13.9$, $^{3}J=6.2$
N-H	7.82 (s, 1H)	7.95 (s, 1H)	7.69 (s, 1H)	7.81 (s, 1H)	[g]	[g]	7.41 (s, 1H)	7.53 (s, 1H)	1.23 (s, 2H)	1.23 (s, 2H)
-$C(CH_3)_3$	1.40 (s, 9H)	1.42 (s, 9H)	1.39 (s, 9H)	1.41 (s, 9H)	—	—	1.38 (s, 9H)	1.40 (s, 9H)	—	—
-OCH_3	3.60 (s, 3H)	3.58 (s, 3H)	—	—	—	—	—	—	—	—
−COOH	—	—	12.56 (bs, 1H)	12.48 (bs, 1H)	[h]	[h]	—	—	—	—
$-CH_2OH$	—	—	—	—	—	—	*ca.* 3.30 (1H)[f] *ca.* 3.49 (1H)[f]	*ca.* 3.30 (1H)[f] *ca.* 3.45 (1H)[f]	*ca.* 3.17 (1H)[f] *ca.* 3.57 (1H)[f]	*ca.* 3.19 (1H)[f] *ca.* 3.48 (1H)[f]
$-CH_2OH$	—	—	—	—	—	—	4.70 (t, 1H)	4.65 (bs, 1H)	4.72 (bs, 1H)	4.70 (bs, 1H)
H-2/2′$_{PYRROLE}$	8.30 (m[i], 2H)	—	8.30 (m[i], 2H)	—	8.30 (m[i], 2H)	—	8.30 (m[i], 2H)	—	8.31 (m[i], 2H)	—
H-3/3′$_{PYRROLE}$	6.45 (m[i], 2H)	—	6.45 (m[i], 2H)	—	6.44 (m[i], 2H)	—	6.44 (m[i], 2H)	—	6.44 (m[i], 2H)	—
-$NH_{2\ ADENINE}$	—	7.26 (s, 2H)	—	7.25 (s, 2H)	—	7.24 (s, 2H)	—	7.19 (s, 2H)	—	7.15 (s, 2H)

[a]-DMSO-d_6 solutions, chemical shifts referred to TMS. Multiplicity of coupling and number of protons are given in brackets: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet.
[b]-The ^{3}J couplings with -CH_AH_BN and -$CH_{2CYCLOP}$ are not seen.
[c]-The ^{2}J and ^{3}J couplings with -CH_{CYCLOP} are not resolved.
[d]-superimposed on $C(CH_3)_3$.
[e]-superimposed on -NH_2.
[f]-superimposed on the water signal.
[g]-NH_2 group not observed.
[h]-COOH group, not seen due to zwitterionic effect.
[i] -AA'XX' spinsystem.

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Table 2. ^{13}C NMR chemical shifts (δ/ppm)[a] for the compound **4**–**13** (cf. Sch. 1).

	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
C-2	151.63	152.30	151.60	152.21	151.68	152.32	151.59	152.17	151.61	152.21
C-4	146.36	149.42	146.47	149.35	146.40	149.37	146.44	149.44	146.38	149.39
C-5	121.20	118.68	121.32	118.63	121.25	118.73	121.35	118.46	121.34	118.52
C-6	153.24	155.98	153.37	155.91	153.22	156.01	153.35	155.94	153.33	155.89
C-8	145.86	140.93	145.82	140.86	145.78	140.77	145.84	140.83	145.68	140.57
CH_2N	42.53	41.95	42.87	42.08	42.41	41.93	43.37	42.81	43.16	42.31
$-CH_{2CYCLOP}$	20.33	20.29	20.14	19.91	19.38	18.54	14.50	14.32	15.16	14.86
$-CH_{CYCLOP}$	25.58	26.33	25.40	25.93	25.30	25.07	20.44	20.64	21.41	20.53
$-C_{CYCLOP}$	38.04	37.89	37.89	37.56	39.00	37.59	38.79	37.17	38.34	36.94
-NHCO	156.27	156.26	156.40	156.12	–	–	156.05	156.11	–	–
-COO	172.24	172.35	173.59	173.51	175.44	175.15	–	–	–	–
$-OCH_3$	52.25	52.21	–	–	–	–	–	–	–	–
$-CH_2OH$	–	–	–	–	–	–	66.40	64.15	68.66	66.64
$-\underline{C}(CH_3)_3$	78.64	78.55	78.47	78.18	–	–	78.10	78.02	–	–
$-C(\underline{C}H_3)_3$	28.05	28.09	28.22	28.07	–	–	28.23	28.16	–	–
$C\text{-}2/2'_{PYRROLE}$	120.07	–	120.19	–	120.11	–	120.19	–	120.16	–
$C\text{-}3/3'_{PYRROLE}$	112.43	–	112.55	–	112.48	–	112.47	–	112.45	–

[a]DMSO-d_6 solutions, chemical shifts referred to TMS.

(3.17–3.57 ppm). NOESY spectra of **4** and **5** show the cross-peak arising from spatial interactions of protons *N*-H and H-3_{trans} with the *N*-methylene ones (Fig. 1.) This is compatible with the *Z*-configuration of **4** and **5**. The C-2 carbon in ^{13}C NMR spectra of **4**–**13** is more deshielded than C-8 (C-2: 151.6–152.3 ppm and C-8: 140.8–145.9 ppm); this is also in accordance with the *N*-9 substitution of the purine ring. The C-8 atom of the adenine derivatives **5**, **7**, **9**, **11** and **13** is shifted upfield (140.57–140.93 ppm) compared to the 6-(*N*-pyrrolyl)purine derivatives **4**, **6**, **8**, **10** and **12** (145.68–145.86 ppm). The C-4 and C-6 atoms of **5**, **7**, **9**, **11** and **13** are more deshielded (C-4: 149.35–149.44 ppm and C-6: 155.89–156.01 ppm) than the corresponding atoms of **4**, **6**, **8**, **10** and **12** (C-4; 146.36–146.47 ppm and C-6; 153.22–153.37 ppm). Signals of C-5 atoms of **4**, **6**, **8**, **10** and **12** are shifted downfield (121.20–121.35 ppm) compared to the C-5 signals of **5**, **7**, **9**, **11** and **13** (118.46–118.73 ppm). The assignment of C-5 signals upfield is in agreement with the explanation that this carbon atom has the highest π-electronic density in the purine base,[16] but also is in accordance with the chemical shifts of the corresponding C-atoms in structurally related compounds.[17,18] Comparison with the spectra of *N*-9 substituted purine acyclic nucleoside analogues[12,15] is consistent with this assignment. Summing up, both ^{1}H and ^{13}C NMR spectral data corroborate with the structure of the novel compounds.

X-Ray Crystal Structural Study

Stereostructure of the bicyclic lactone **1** (Fig. 2) was determined by its X-ray crystal structure analysis. The molecular structure with the atom numbering scheme is displayed in Fig. 2.

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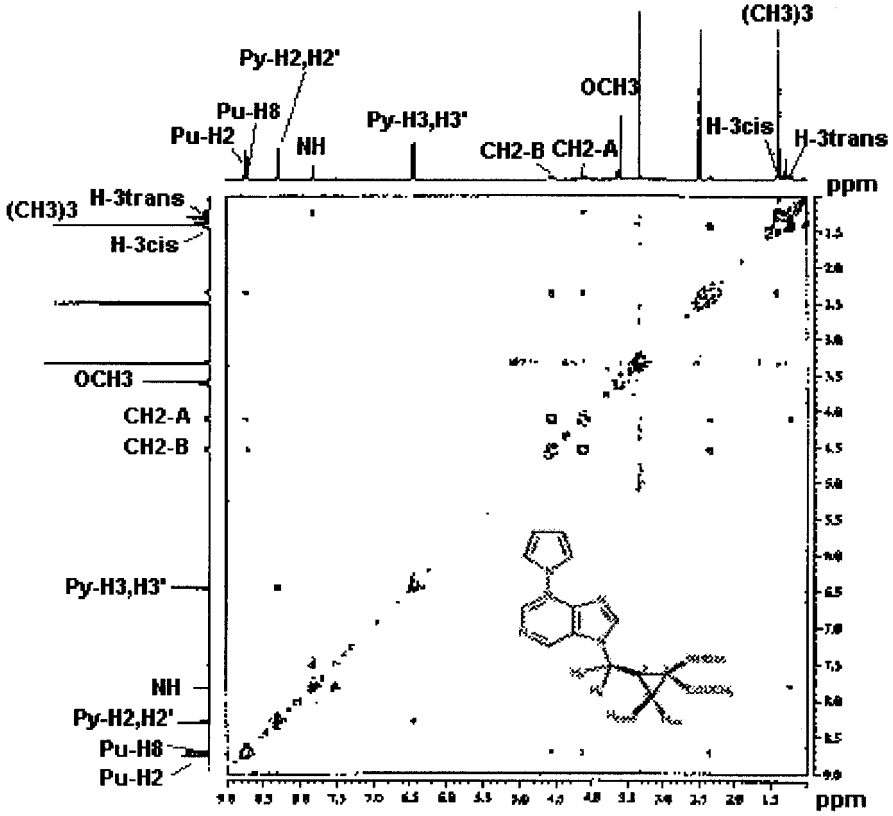

Figure 1. NOESY spectrum of the compound **4**.

The skeleton of the molecule **1** consists of the cyclopropane and the five-membered lactone rings fused via the common carbon atoms C6 and C8. The conformation of the molecule is described by the dihedral angle of the cyclopropane ring and the least square (l.s.) plane of the lactone ring C6-C5-O1-C4-C8 amounting to 73.7(1)°. The five-membered ring exists, due to deviation of the atom C5 from the least square plane of the atoms O1, C4, C6 and C8 [0.177(2) Å] in the envelope conformation. The common carbon atom C8 of the lactone and cyclopropane rings is bonded to the atom C3 of the methylcarboxylate group. The bond angle around the atom C8 (C4-C8-C3) amounting 120.4(1)° is significantly greater than the value of the tetrahedral angle. This angle widening may be explained by the strain effect of the three- and the five-membered ring. The torsion angle C2-O4-C3-C8 amounts to 175.6(1)°; this means that atoms C2 of the methyl group and C8 of the ring skeleton are disposed in the *antiperiplanar* fashion.

The perspective views of the molecule of the compound **4** and the ethanol solvate of the compound **5** with the atom numbering are displayed in Figs. 3 and 4.

The oxygen atom O3 of the methylcarboxylate group in the compound **5** was observed to be disordered and it is represented in Fig. 4 in the position of higher occupancy factor (74%) as O3a. Oxygen atoms O3a and the corresponding one with

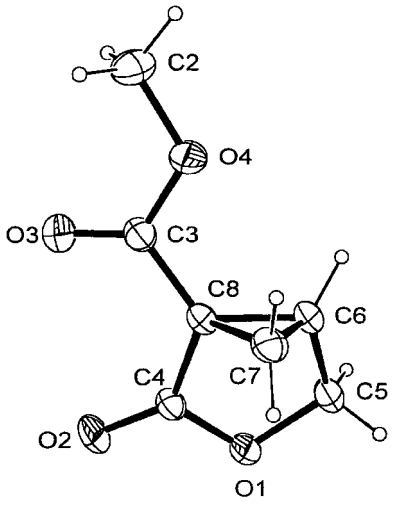

Figure 2. The molecular structure and labelling of the compound **1**. Displacement ellipsoids are drawn at the 30% probability level.

lower occupancy factor designated as O3b are out of the plane of the sp^2 hybridized atom C9 (C8-C9-O4); deviation from the planarity of these atoms amounts to −0.12(3) and 0.56(6) Å.

Torsion angles C11-C6-C8-N1 in **4** and **5** are −3.2(3)° and 5.7(4)°; that is the both compounds possess *Z*-configuration of the cyclopropane ring. The bond

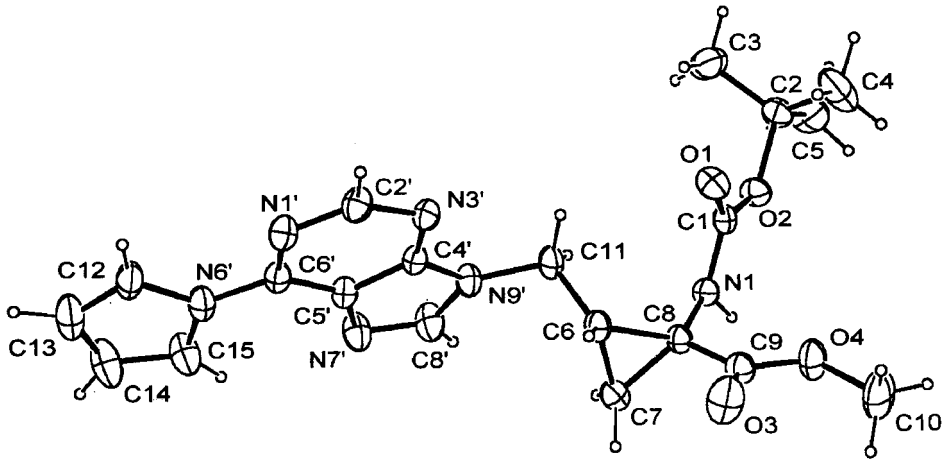

Figure 3. The molecular structure and labelling of the compound **4**. Displacement ellipsoids are drawn at the 30% probability level.

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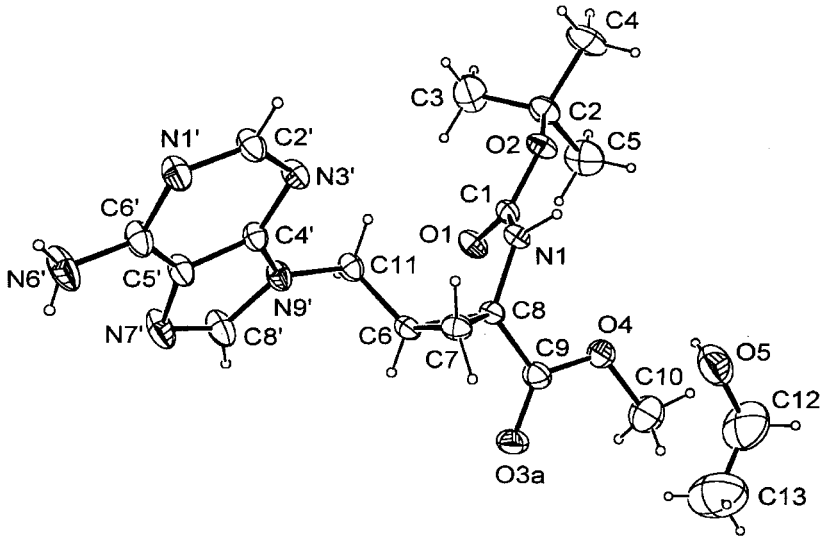

Figure 4. The molecular structure and labelling of the compound **5**. Displacement ellipsoids are drawn at the 30% probability level. Disordered atom O3 is represented in the position of higher occupancy factor.

distances and angles in both structures are in a good agreement, except for the bond distances N3′-C4′, C4′-C5′ and C6-C11 amounting to 1.329(3), 1.397(3) and 1.499(3) Å in **4** and 1.344(3), 1.370(4) and 1.479(4) Å in **5**. The shortest bond in the cyclopropane ring is C6-C7 [1.482(3) and 1.477(5) Å in **4** and **5**]. The bond lengths C6–C8 and C7–C8 in both structures vary in the range of 1.504(4) to 1.511(3) Å. Endocyclic bond angles in the cyclopropane ring of **4** and **5** are as expected close to 60°, but the angle at C8 is slightly smaller than the angles at C6 and C7. Concomitantly, the exocyclic bond angle N1-C8-C9 is in the both structures significantly greater [117.4(2)° and 117.5(3)° in **4** and **5**] than the tetrahedral angle. The torsion angles relating the cyclopropane ring and connected nitrogen atom N1 (C6-C7-C8-N1 and C7-C6–C8-N1) and the corresponding carbon atom C9 (C6-C7-;C8-C9 and C7-C6-C8-C9) are in both structures in the range of ± 104.0(2)° to 108.7(3)°, which closely agrees with those for the *skew* conformation. The carbon atom C8 of the cyclopropane ring as well as the carbon atom C2 of the *tert*-butyl group and the carbonyl oxygen atom O1 are disposed in the *synperiplanar* fashion. The values of the torsion angles C8-N1-C1-O1 and C2-O2-C1-O1 are −9.6(3) and −1.9(3)° in **4** and 10.0(4) and −6.0(5)° in **5**. The torsion angles C8–N1–C1–O2 and N1-C1-O2-C2 are −172.0(2) and −176.5(2)° in **4** and −172.5(2) and −176.5(3)° in **5**. The dihedral angle between the cyclopropane ring and the plane of the atoms N1-C8-C9 is 89.1(3)° in **4** and 89.0(4)° in **5**, i.e. those planes are almost perpendicular to each other. The dihedral angle between the plane of the cyclopropane ring and the l.s. plane of the purine ring in **4** is less than that

found in **5** [26.9(2)°; 45.6(3)°]. The dihedral angle between 6-*N*-pyrrolyl and purine rings in **4** is found to be 9.4(2)°; that is they are not coplanar.

BIOLOGICAL ASSAYS

Cytostatic Activity

Compounds **4**–**10**, **12**, **13** and 6-(*N*-pyrrolyl)purine were evaluated for their cytostatic activity against several malignant tumor cell lines: murine leukemia (L1210/0), murine mammary carcinoma cells (FM3A/0), human T-lymphocyte (Molt4/C8 and CEM), cervical carcinoma (HeLa), breast carcinoma (MCF7), laryngeal carcinoma (Hep-2), human fibroblast cells (WI-38), pancreatic carcinoma (MIAPaCa-2), colon carcinoma (CaCo-2), as well as melanoma (HBL).

Of all the compounds evaluated, compounds **4** and **12** containing 6-(*N*-pyrrolyl)-purine ring showed rather marked cytotoxic activities in comparison with the adenine derivatives. Compound **4** inhibited the growth of human T-lymphocyte cells CEM/0 ($IC_{50} = 64\,\mu M$). and Molt4/C8 cell lines ($IC_{50} = 98\,\mu M$) as well as murine leukemia cell line L1210/0 ($IC_{50} = 188\,\mu M$). The 6-(*N*-pyrrolyl)purine derivative of 1-amino-1-hydroxymethylcyclopropane **12** showed the most significant cytotoxic activities against the cervical carcinoma cell line HeLa ($IC_{50} = 38\,\mu M$) and the human fibroblast cell line WI-38 ($IC_{50} = 46\,\mu M$). 6-(*N*-pyrrolyl)purine itself showed the most significant antitumor activities against the cervical carcinoma cell line HeLa ($IC_{50} = 45\,\mu M$), breast carcinoma MCF7 ($IC_{50} = 34\,\mu M$), laryngeal carcinoma Hep-2 ($IC_{50} = 50\,\mu M$), and colon carcinoma CaCo-2 ($IC_{50} = 58\,\mu M$).

Antiviral Activity

Compounds **4**–**10**, **12**, **13** and 6-(*N*-pyrrolyl)purine were also evaluated against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus and herpes simplex virus-1 TK^- KOS ACV^r in E_6SM cultures, vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus in HeLa cell cultures, parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures, varicella-zoster virus (VZV) and cytomegalovirus (CMV) in human embryonic lung (HEL) cells and against human immunodeficiency virus (HIV-1 and HIV-2) in human lymphocyte (CEM) cells. None of the compounds showed appreciable activity against any of these viruses, except for some very slight activity of 6-(*N*-pyrrolyl)purine against varicella-zoster virus (VZV) in human embryonic lung (HEL) cells TK- VZV YS/R strain ($IC_{50} = 38\,\mu M$).

CONCLUSIONS

New types of 1-aminocyclopropane-1-carboxylic acids **8** and **9** and 1-amino-1-hydroxymethyl cyclopropanes **12** and **13** containing purine bases connected

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via a methylene spacer were synthesized and evaluated for their antitumor and antiviral activities. The synthesis shown in Sch. 1 was performed using racemic epichlorohydrine as starting compound; hence racemic products were obtained. This synthetic approach could be modified by using optically active epichlorohydrine for asymmetric synthesis of the purine derivatives of cyclopropane amino acids and amino alcohols. The *N*-9 substitution of the purine ring and the *Z*-configuration of the cyclopropane ring in **4**–**13** were elucidated from their ^{1}H and ^{13}C NMR spectra by analyses of chemical shifts and connectivities in one- and two-dimensional COSY, HETCOR, DEPT and NOESY spectra. The stereostructure of **1**, **4** and **5** was confirmed by their X-ray crystal structure analysis. Of all the compounds, the 6-(*N*-pyrrolyl)purine derivative of 1,2-aminocyclopropane alcohol **12** showed the most pronounced antitumor activities against the cervical carcinoma cell line HeLa ($IC_{50} = 38\,\mu M$) and the human fibroblast cell line WI-38 ($IC_{50} = 46\,\mu M$).

EXPERIMENTAL

General

Melting points were determined on a Kofler micro hot-stage apparatus (Reichert, Wien) and are uncorrected. Precoated Merck silica gel 60F-254 plates were used for thin-layer chromatography (TLC), and the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (0.05–0.2 mm, Merck); glass column was slurry-packed under gravity. The electron impact mass spectra were recorded with an EXTREL FT MS 2001 instrument with ionizing energy of 70 eV. The IR spectra were recorded on a Nicolet-Magna IR 760 spectrometer and UV spectra on a Hewlett-Packard 8452 spectrometer. Elemental analyses were performed by the Central Analytical Service, Ruder Bošković Institute, Zagreb. High field one- and two-dimensional ^{1}H- and ^{13}C-NMR spectra of **6**–**13** were recorded on a Varian Gemini 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75.46 MHz, University of Zagreb) and those of **4** and **5** on a Bruker Avance ARX 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100.61 MHz, University of Regensburg). ^{1}H and ^{13}C chemical shifts are reported in δ/ppm relative to internal TMS.

Single Crystal X-Ray Analysis

The single crystals of **1**, **4** and **5** suitable for X-ray structure analysis were obtained at room temperature by partial evaporation of a very dilute solutions of diethyl ether, methanol and ethanol, respectively. The intensities were collected at room temperature on a Philips PW1100 diffractometer updated by Stoe and Cie[19] using Mo-K_α radiation. The crystal structures were solved by direct methods. All non-hydrogen atoms were refined anisotropically by full-matrix least-square calculations. Coordinates of hydrogen atoms were included in structure factor calculations using SHELXS86[20] and SHELXL97[21] programmes. The molecular and crystal structure drawings were prepared by ORTEP-III[22] and PLUTON93[23]

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Table 3. The crystal data, data collection, and refinement for the compounds **1**, **4** and **5**.

Compound	**1**	**4**	**5**
Formula	$C_7H_8O_4$	$C_{20}H_{24}N_6O_4$	$C_{18}H_{28}N_6O_5$
Formula weight	156.13	412.45	408.46
Temperature [K]	293(2)	293(2)	293(2)
Radiation [Å]	Mo-K_α(0.71073)	Mo-K_α(0.71073)	Mo-K_α(0.71073)
Crystal size [mm]	$0.68 \times 0.48 \times 0.37$	$0.57 \times 0.48 \times 0.17$	$0.75 \times 0.23 \times 0.20$
Crystal colour	colourless	colourless	colourless
Crystal system	triclinic	monoclinic	triclinic
Space group	$P\ \bar{1}$	$C\ 2/c$	$P\ \bar{1}$
a [Å]	6.390(1)	26.520(5)	8.157(1)
b [Å]	7.000(1)	9.334(3)	9.953(1)
c [Å]	8.527(2)	23.394(6)	14.963(1)
α [°]	108.48(1)	90.00	89.13(1)
β [°]	100.99(2)	132.63(2)	82.35(1)
γ [°]	93.37(1)	90.00	66.93(1)
V [Å^3]	352.2(1)	4260.6(19)	1106.8(2)
Z	2	8	2
$D_{calc.}$ [gcm^{-3}]	1.472	1.286	1.226
μ [mm^{-1}]	0.122	0.092	0.091
$F(000)$	164	1744	436
Scan-mode	ω	ω	ω
θ range for data collection [°]	3.27 to 29.00	2.85 to 28.99	2.74 to 28.01
Index ranges	$-8 \le h \le 8$	$-36 \le h \le 26$	$-10 \le h \le 10$
	$-9 \le k \le 9$	$0 \le k \le 12$	$-13 \le k \le 13$
	$-2 \le l \le 11$	$0 \le l \le 27$	$-4 \le l \le 19$
Collected reflections	2352	5732	6999
Independent reflections/($R_{int.}$)	1848/0.0644	5427/0.0415	5295/0.0378
Reflection number $I \ge 2\sigma(I)$	1465	2323	2022
Refinement method	Full-matrix least-squares on F^2		
Data/restraints/parameters	1465/0/103	2323/0/275	2022/0/314
Weighting parameters a, b^*	0.1284, 0.0246	0.1000, 0	0.1069, 0
Goodness-of-fit on F^2	1.032	0.930	0.962
$R[I \ge 2\sigma(I)]$	0.0606	0.0562	0.0686
wR	0.1617	0.1341	0.1566
Max./min. elect. dens. [eÅ^{-3}]	0.523/−0.339	0.184/−0.172	0.362/−0.271
$(\Delta/\sigma)_{max.}$	0.001	0.001	0.004

*$w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$.

programmes. Crystal data, data collection and refinement for the lactone **1** and the compounds **4** and **5** are summarized in Table 3. Additional crystallographic data excluding structure factors for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications No. CCDC-192696, No. CCDC-192697 and CCDC-192698. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [Fax: +44-(0)1223-336033 or E-mail: deposit @ccdc.cam.ac.uk].

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Biological Tests

Antitumor Activity Assays

Antitumor activities against L1210/0 (murine leukemia), FM3A/0 (murine mammary carcinoma), Molt4/C8 (human T-lymphoblast), and CEM/0 (human T-lymphoblast) cell lines was measured essentially as originally described for the mouse leukemia/L1210 cell lines.[24] Human tumor cell lines (CaCo-2, colon carcinoma; Hep-2, laryngeal carcinoma; MCF-7, breast carcinoma; HeLa, cervical carcinoma; MIA PaCa-2, pancreatic carcinoma) and normal human fibroblasts (WI-38) were tested for sensitivity in vitro. All cell lines were grown in DMEM medium (supplemented with 10% heat inactivated fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin) at 37°C in a humidified atmosphere with 5% CO_2. For the purpose of the experiment the cells were plated in quadruplicates in 96-microwell flat bottom plates at the concentrations of 2×10^4 cells/mL (all tumor cells lines except for WI-38) and 3×10^4 cells/mL (WI-38). The next day (24 h later) compounds were added to the cells at different concentrations of (5×10^{-4} M, 10^{-4} M and 10^{-5} M). Compounds were dissolved in DMSO at a concentration of 10^{-1} M and diluted with DMEM medium into working concentrations. The concentration of DMSO was less than 1% and it didn't affect the growth. Control cells (without any compound) were growing under the same conditions.

Cell viability was measured immediately before (day 0) and 72 h after addition of compounds, using the MTT assay, which defects dehydrogenase activity in viable cells. For this purpose the medium was discarded and MTT was added to each well at a concentration of 20 μg/40 μL. After 4 h of incubation at 37°C the precipitates formed were dissolved in 160 μL of DMSO. The absorbance was measured on an ELISA reader at 570 nm, and the percentage of growth was calculated. Each number was the mean from four parallel samples in three individual experiments.

Antiviral Activity Assays

Antiviral activity against thymidine kinase-positive (TK^+) and -negative (TK^-) strains of varicella-zoster virus (VZV), cytomegalovirus (CMV) and other viruses were determined as described previously.[25,26]

(*Z*)-Methyl 1-{N-[(*tert*-butoxy)carbonyl]amino}-2-(tosylmethyl)cyclopropanecarboxylate (3). *p*-TsCl (0.68 g; 3.61 mmol) was added to a solution of **2** (0.44 g; 1.80 mmol) and 4-(*N,N*-dimethylamino)pyridine (0.88 g; 7.22 mmol) in dichloromethane (16.2 mL) at 0°C, and the mixture was stirred at 0–5°C for 1.5 h. After that, the dichloromethane was evaporated, and the residue was purified by column chromatography (PE/EtOAc (1:1)) to give **3** as a colourless oil (0.62 g; 86.3%).

IR (cm^{-1}) 3360, 2977, 1730; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.20 (dd, 1H, superimposed with *t*-Boc), 1.45 (s, 9H), 1.74 (dd, $J = 5.49$, 14.56 Hz, 1H), 2.11 (m, 1H), 2.47 (s, 3H), 3.70 (s, 3H), 4.03 (dd, $J = 10.16$, 20.05 Hz, 1H), 4.22 (dd, $J = 8.24$, 12.63 Hz, 1H), 5.18 (s, 1H), 7.37 (d, $J = 7.96$ Hz, 2H), 7.80 (d, $J = 8.24$ Hz, 2H);

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^{13}C-NMR ($CDCl_3$, 300 MHz) 20.87, 21.50, 25.53, 28.03, 38.33, 52.53, 69.41, 80.30, 127.69, 128.78, 129.82, 132.71, 156.21, 171.60.

(*Z*)-Methyl 1-{N-[(*tert*-butoxy)carbonyl]amino}-2-[6-(*N*-pyrrolyl)purine-9-yl]cyclopropanecarboxylate (4). To a stirred mixture of 6- (*N*-pyrrolyl)purine (0.278 g; 1.50 mmol) and K_2CO_3 (0.248 g; 1.80 mmol) in DMF (20 mL) compound **3** was added (0.485 g; 1.22 mmol). The mixture was heated at 85°C for 10 h and then concentrated to dryness. Purification of the residue by column chromatography [EtOAc/PE (3:1)] afforded the compound **4** (0.295 g; 58.7%) as a white solid.

M. p. = 200–202.5°C; IR (KBr, cm^{-1}) 3225, 3146, 3098, 1731, 1696, 1598, 1584; FAB-MS m/z 412.2 (M^+); Anal. calcd for $C_{20}H_{24}N_6O_4$: C, 58.27; H, 5.82; N, 20.38. Found: C, 58.34; H, 5.79; N, 20.36.

(*Z*)-Methyl 1-{N-[(*tert*-butoxy)carbonyl]amino}-2-(6-aminopurine-9-yl)cyclopropanecarboxylate (5). To a stirred mixture of adenine (0.226 g; 1.67 mmol) and K_2CO_3 (0.276 g; 2.00 mmol) in DMF (20 mL) compound **3** was added (0.543 g; 1.36 mmol). The mixture was heated at 85°C for 10 h and then concentrated to dryness. Purification of the residue by column chromatography [CH_2Cl_2/MeOH (20:1)] afforded the compound **5** (0.317 g; 64.4%) as a white solid.

M. p. = 121–123°C; IR (KBr, cm^{-1}) 3322, 3183, 2978, 1732, 1706, 1655, 1600; EI-MS m/z 363 (M + H); Anal. calcd for $C_{16}H_{22}N_6O_4$: C, 53.06; H, 6.07; N, 23.19. Found: C, 53.09; H, 6.04; N, 23.23.

(*Z*)-1-{N-[(*tert*-butoxy)carbonyl]amino}-2-(6-(*N*-pyrrolyl)purine-9-yl)cyclopropane-1-carboxylic acid (6). An aqueous solution (0.67 M) of NaOH (3.5 mL) was added to a solution of **4** (0.20 g; 0.49 mmol) in dioxane (3 mL). After the mixture was stirred for 24 h at room temperature, water (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and pH value of the aqueous layer was adjusted to 3.0 with the 2.0 M aqueous solution of citric acid. Aqueous layer was than extracted with EtOAc (4 × 10 mL), combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated to give a glassy white solid of the compound **6** (0.15 g; 79.3%).

M. p. = 201–203°C; IR (KBr, cm^{-1}) 3429, 3207, 2929, 1731, 1703; UV (1M NaOH) λ_{max} 290 (log ε 3.63); FAB-MS *m/z* 399 (M^+); Anal. calcd for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09; O, 16.06. Found; C, 57.31; H, 5.60; N, 21.07; O, 16.02.

(*Z*)-1-{N-[(*tert*-butoxy)carbonyl]amino}-2-(6-aminopurine-9-yl)cyclopropane-1-carboxyclic acid (7). An aqueous solution (1.0 M) of LiOH (1.0 mL) was added to a solution of 5 (0.10 g; 0.28 mmol) in dioxane (2 mL). After the mixture was stirred for 24 h at room temperature, water (5 mL) was added. The reaction mixture was extracted with CH_2CL_2 (3 x 10 mL) and the pH value of the aqueous layer was adjusted to 2.0 with 1.0 M aqueous solution of hydrochloric acid. After acidification, a white solid of the compound 7 (0.06 g; 62.5%) was collected by filtration.

M. p. = 225–227°C; IR (KBr, cm^{-1}) 3338, 3244, 2979, 2928, 1784, 1704; UV (1M NaOH) λ_{max} 261 (log ε 3.77); FAB-MS *m/z* 349 (M^+); Anal. calcd for $C_{15}H_{20}N_6O_4$: C, 51.72; H, 5.79; N, 24.12; O, 18.37. Found: C, 51.71; H, 5.83; N, 24.11; O 18.35.

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(*Z*)-1-Amino-2-(6-(*N*-pyrrolyl)purine-9-yl)cyclopropane-1-carboxylic acid (8). Trifluoroacetic acid (2.0 mL) was added dropwise to a cooled solution of **6** (0.10 g; 0.25 mmol) in dry CH_2Cl_2 (3 mL) and the reaction mixture was stirred at 0–5°C for 2.5 h. Solvent was than evaporated and water (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), loaded onto a Dowex 50W-X8 column (H^+-form) and eluted with 2M NH_4OH. The collected fractions containing free amino acid were lyophilized to give a white solid of the compound **8** (64 mg; 85.4%).

M. p. = 144°C (dec.); IR (KBr, cm^{-1}) 3431, 3147, 3099, 2922, 1596; UV (H_2O) λ_{max} 288 nm (log ε 3.84); EI-MS m/z 299 (M^+); Anal. calcd for $C_{14}H_{14}N_6O_2$: C, 56.37; H, 4.73; N, 28.17; O, 10.73. Found: C, 56.32; H, 4.76; N, 28.21; O, 10.71.

(*Z*)-1-Amino-2-(6-aminopurine-9-yl) cyclopropane-1-carboxylic acid (9). Trifluoroacetic acid (2.0 mL) was added dropwise to a cooled solution of 7 (0.10 g; 0.29 mmol) in dry CH_2Cl_2 (3 mL) and the reaction mixture was stirred at 0–5°C for 2.5 h. The solvent was than evaporated and water (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), loaded onto a Dowex 50W-X8 column (H^+-form) and eluted with 2M NH_4OH. The collected fractions containing free amino acid were lyophilized to give a white solid of the compound **9** (62 mg; 87.3%).

M. p. = 183°C (dec.); IR (KBr, cm^{-1}) 3423, 3208, 2922, 1647, 1605; UV (H_2O) λ_{max} 261 nm (log ε 3.86); EI-MS m/z 249 (M^+); Anal. calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.86; O, 12.89. Found: C, 48.34; H, 4.85; N, 33.89; O, 12.92.

(*Z*)-1-{N-[(*tert*-butoxy)carbonyl]amino}-1-hydroxymethyl-2-[6-(*N*-pyrrolyl)purin-9-yl]cyclopropane (10). A 2 M solution of $LiBH_4$ in THF (1.5 mL) was slowly added to a solution of ester **4** (113 mg; 0.27 mmol) in anhydrous THF (5 mL) at −78°C. The mixture was allowed to reach r. t. and then stirred 20 h. The excess hydride was destroyed by slow addition of methanol, and the solvents were removed at reduced pressure. The residue was dissolved in water and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried and the solvent was evaporated. The residue was purified by column chromatography [EtOAc/PE (3:1)] to give compound **10** as a colourless oil (85 mg; 81.7%) which solidified upon standing.

M. p. = 85°C; IR (KBr, cm^{-1}) 3349, 3247, 2931, 1699, 1596; FAB-MS m/z 385 (M + H).

(*Z*)-1-{N-[(*tert*-butoxy)carbonyl]amino}-1-hydroxymethyl-2-(6-aminopurine-9-yl)-cyclopropane (11). A 2 M solution of $LiBH_4$ in THF (3 mL) was slowly added to a solution of ester **5** (79 mg; 0.22 mmol) in anhydrous THF (5 mL) at −78°C. The mixture was allowed to reach r. t. and then stirred 20 h. The excess hydride was destroyed by slow addition of methanol, and solvents were removed at reduced pressure. The residue was dissolved in water and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried and the solvent was evaporated. The residue was purified by column chromatography [CH_2Cl_2/MeOH (3:1)] to give compound **11** as a colourless oil (52 mg; 70.3%) which solidified upon standing.

M. p. = 96°C; IR (KBr, cm^{-1}) 3332, 2932, 2873, 1694, 1651, 1601; FAB-MS m/z 334 (M^+).

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(*Z*)-1-Amino-1-hydroxymethyl-2-[6-(*N*-pyrrolyl)purin-9-yl]cyclopropane (12). A suspension of the *N*-Boc-protected nucleoside **10** (40 mg; 0.10 mmol) in dichloromethane (3 mL) was stirred with trifluoroacetic acid (1.5 mL) at 0°C. The reaction was completed within 1 h (TLC). The volatile components were removed under vacuum, and the residue was chromatographed on an ion-exchange resin (Dowex 50W-X8, H^+ form). A total of 22 mg (78.6%) of white solid was isolated from the chromatography (2 M NH_4OH).

M. p. = 108–110°C; IR (KBr, cm^{-1}) 3349, 2928, 1599, 1579; UV (methanol) λ_{max} 287 (log ε 4.01); FAB-MS m/z 285 (M + H); Anal. calcd for $C_{14}H_{16}N_6O$: C, 51.30; H, 5.98; N, 35.88. Found: C, 51.24; H, 5.93; N, 35.95.

(*Z*)-1-Amino-1-hydroxymethyl-2-[6-aminopurin-9-yl]cyclopropane (13). A suspension of the *N*-Boc-protected nucleoside **11** (70 mg; 0.21 mmol) in dichloromethane (3 mL) was stirred with trifluoroacetic acid (1.5 mL) at 0°C. The reaction was completed within 1 h (TLC). The volatile components were removed under vacuum, and the residue was chromatographed on an ion-exchange resin (Dowex 50W-X8, H^+ form). A total of 40 mg (81.6%) of a white solid was isolated from the chromatography (2M NH_4OH).

M. p. = 158–160°C; IR (KBr, cm^{-1}) 3407, 2923, 2853, 1660, 1651, 1600; UV (methanol) λ_{max} 259 (log ε 3.94); FAB-MS m/z 235 (M + H); Anal. calcd for $C_{10}H_{14}N_6O$: C, 51.30; H, 5.98; N, 35.88, Found: C, 51.35; H, 6.02; N, 35.82.

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