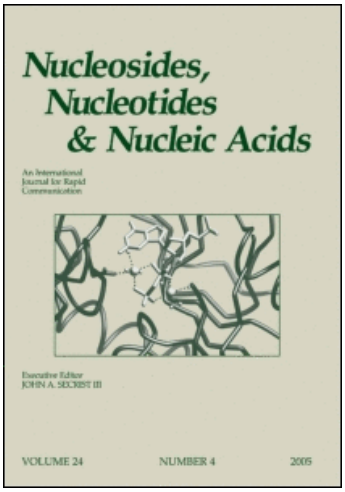

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Synthesis and Antiviral Activity of Carbocyclic Nucleosides Incorporating a Modified Cyclopentane Ring. Part 3: Adenosine and Uridine Analogues

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF CARBOCYCLIC NUCLEOSIDES INCORPORATING A MODIFIED CYCLOPENTANE RING. PART 3: ADENOSINE AND URIDINE ANALOGUES.

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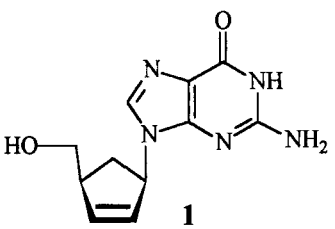
Abstract: Six new carbocyclic nucleosides were prepared by mounting a purine (compounds **4-6**), 8-azapurine (**7** and **8**) or uridine (**9**) base on the amino group of (1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentylmethanol (**10**). At subtoxic concentrations, compounds **5-9** showed at best marginal antiviral activity.

In the search for new antitumour and antiviral therapeutic agents, much recent attention has been focused on carbocyclic nucleosides.[1] The potent antiviral properties of carbovir (**1**)[2] and abacavir (**2**)[3] prompted us to search for congeners of these compounds with a modified cyclopentane moiety that might have similar or improved antiviral properties. In previous papers[4,5] we reported the synthesis of carbocyclic analogues of guanine, 8-azaguanine, adenosine, 8-azaadenosine and uridine nucleosides by construction of the base on the amino group of (1*R*,3*S*)-3-aminomethyl-1,2,2-trimethylcyclopentylmethanol (**3**).[6] For further insight into how the biological activities of carbocyclic nucleosides



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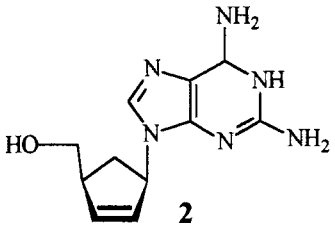

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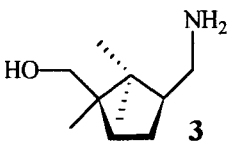

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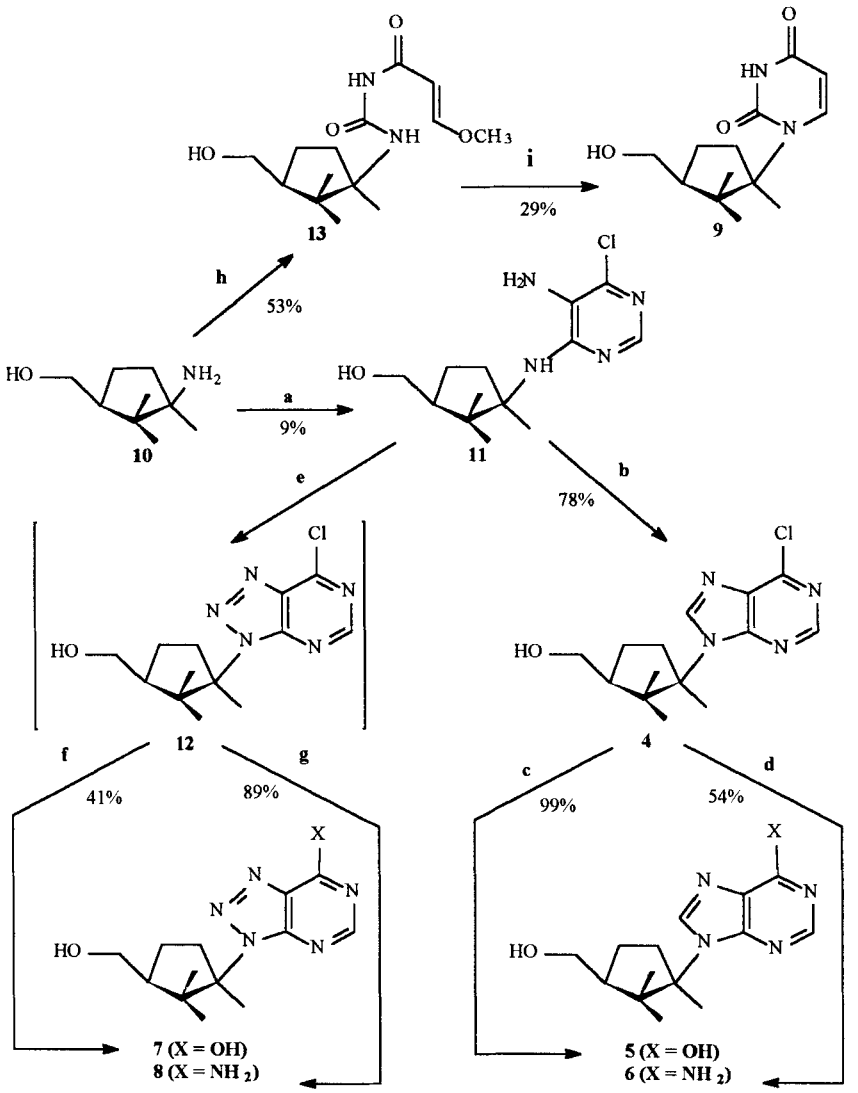

a) 5-Amino-4,6-dichloropyrimidine, Et_3N, n-butanol, reflux, 72 h; b) $CH(OEt)_3$, 12N HCl, r.t., 72 h; c) 0.33 N NaOH, reflux, 6 h; d) 14M NH_4OH, reflux, 18 h; e) $NaNO_2$, AcOH or 1N HCl; f) H_2O, r.t., 18 h; g) 14M NH_4OH, reflux, 5 min.; h) methyl 3-methoxyacryloyl isocyanate, C_6H_6, r.t., 17 h; i) 2N H_2SO_4, reflux, 3.5 h.

Scheme 1

Table 1. Preparation of **9**

Entry	Reagent	t (h)	Yield (%)
1	14M NH_4OH	20	11
2	14M NH_4OH	60	5
3	2N H_2SO_4	3.5	29
4	4N HCl/dioxan	8	0.5
5	2N H_2SO_4/dioxan	3.5	15

depend on their structural characteristics, we have now synthesized and determined the antiviral activities of adenosine, 8-azaadenosine and uridine analogues **4-9**, in which the cyclopentane ring is linked directly to the base heterocyclic.

The synthesis of these analogues is depicted in Scheme 1. In all cases, the base was constructed on the amino group of (1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl methanol (**10**)[7] by condensation with 5-amino-4,6-dichloropyrimidine.[5,8,9] After a 48-hour reaction in refluxing *n*-BuOH, compound **11** was isolated by column chromatography, albeit with some difficulty and in only 9% yield (this low yield was expected, given that attack on the amino group of **10** is strongly hindered by the two methyl groups on C-2).[7] Treatment of compound **11** with triethyl orthoformate gave the 9-substituted-6-chloropurine **4**, which was hydrolysed with dilute sodium hydroxide to the inosine analogue **5** or aminated with NH_4OH to the adenine derivative **6**. To obtain the corresponding 8-aza analogues, the triazole ring was formed by diazotation of **11** with sodium nitrite in hydrochloric acid[8] or acetic acid[5] to afford the 6-chloro-8-azapurine derivative **12** which was not isolated but left overnight in the aqueous medium to form the 8-azainosine analogue **7** or converted to **8** by reaction with boiling aqueous ammonia.

The uridine analogue was obtained by a route based on the acryloylurea variant[5,10] of the Shaw synthesis ethoxypropenoyl isocyanate (prepared and used under rigorously anhydrof 2,4-(1*H*,3*H*)-pyrimidinediones. Briefly, 3-mous conditions)[11,12] was reacted with **10** to obtain the acryloylurea **13**, which attempts with various agents showed to be best cyclized to **9** by heating with 2N H_2SO_4 (Table 1).

TABLE 2. Antiviral activity against cytomegaloviruses* and cytotoxicity** of compounds **5-9**

VIRUS (Strain)	CELL	5	6	7	8	9	GCV[a]	CDV[b]	BVDU[c]	ACV[d]
AD-169	HEL	>50	41	>50	>50	>50	1.55	0.13		
DAVIS	HEL	>50	>50	>50	>50	>50		0.70		
TK$^+$VZV (OKA)	HEL	>50	>50	>50	34	>50			0.001	0.15
TK$^+$VZV (YS)	HEL	>50	>50	>50	>50	>50			0.003	0.98
TK$^-$ VZV (07/1)	HEL	>50	>50	>50	>50	>50			>50	22
TK$^-$ VZV (YS/R)	HEL	>20	33	>50	28	>50			>50	14
Cytotoxicity	HEL	>50	>50	48	>50	>50	>50	50	>200	>200

*MIC_{50} or Minimun inhibitory concentration (μg/mL) required to reduce virus-plaque formation by 50%. Virus input was 100 plaque units (PFU).
**MCC or Minimum cytotoxic concentration (μg/mL) required to reduce cell growth by 50%.
[a]Ganciclovir, [b]cidofovir, [c]brivudin, [d]acyclovir.
Cell lines used: human embryonic lung (HEL).

The activities of compounds **5-9** against a variety of DNA and RNA viruses, and their cytotoxicities for the host cell lines, were assayed in parallel with those of standard drugs with known antiviral activities.

At compound concentrations up to 400 μg/mL: herpes simplex virus type 1 (strain KOS), herpes simplex virus type 2 (strain G), thymidine kinase-deficiente (TK^-) herpes simplex virus type 1 (strains B 2006 and VMW 1837), vaccinia virus and vesicular stometitis virus in human embryonic skin-muscles fibroblast (E_6SM); vesicular stomatitis virus, respiratory syncytial virus and Coxsackie B4 virus in HeLa cells; parainfluenza virus type 3, reovirus type 1, Sindbis virus, Coxsackie B4 virus, and Punta Toro virus in Vero Cells. At subtoxic concentrations the compounds generally showed no activity or only marginal activity against the viruses tested [i.e. HSV-1 (KOS, B2006, VMW1837), HSV-2, vaccinia virus and vesicular stomatitis virus].

Experimental

Silica gel (230 mesh) was purchased from Merck. 3-Methoxypropenoyl chloride was prepared from methyl 3-methoxypropenoate following a procedure similar to that used by Shaw to prepare the analogous 3-ethoxy derivative.[10,11] All other chemicals used

TABLE 3. Activity of compounds **5-9** against HIV-1 and HIV-2 in human T-lymphocyte (CEM) cells.

	EC_{50}*(μg/mL)		CC_{50}**(μg/mL)
Compound	**HIV-1**	**HIV-2**	**Cell viability**
5	> 100	> 100	83 ± 3
6	> 100	> 100	62.5 ± 5
7	> 100	> 100	69.5 ± 4
8	> 100	> 100	64.5 ± 8
9	> 100	> 100	28 ± 13

*50% Effective concentration, or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%.
**50% Cytotoxic concentration, or conentration required to reduce viability of the cells by 50%.

were of reagent grade and were obtained from Aldrich Chemical Co. Melting points were measured in a Reichert Kofler Thermopan apparatus and are uncorrected; Na-D line polarimetry was carried out at 25°C in a Perkin-Elmer 241 polarimeter; infrared spectra were recorded in a Perkin-Elmer FTIR 1640 spectrometer; ^{1}H NMR and ^{13}C NMR spectra were recorded in a Bruker AMX 300 spectrometer; and mass spectra were recorded on a Kratos MS-59 spectrometer.

(1*S*,3*R*)-[3-(5-Amino-6-chloropyrimidin-4-ylamino)-2,2,3-trimethylcyclopentyl]methanol (11). Freshly prepared **10** (2.40 g, 15.26 mmol), 5-amino-4,6-dichloropyrimidine (2.88 g, 17.56 mmol), triethylamine (15.20 mL) and n-butanol (76 mL) were refluxed under argon for 72 h. The volatile solvents were evaporated, the residue was dissolved in CH_2Cl_2, and the solid that precipitated (0.8 g) was filtered out and identified from its physical and spectroscopic charateristics as **10·HCl**.[7] Evaporation of solvent from the filtrate under low pressure afforded an oil (5.28 g) that was adsorbed on silica gel, packed on top of a silica gel column (174 g) and chromatographed with 1.5:1 EtOAc/hexane and MeOH as eluants. The EtOAc/hexane fractions containing the desired product (**11**) were concentrated to a foamy oil (0.48 g, 9%); the MeOH fraction afforded a further 1.48 g of **10·HCl**.

Compound **11**. IR (film): 3413, 3341, 1652, 1608, 1386, 1282, 930 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.04 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.78-1.89 (m, 2H),

1.94-2.09 (m, 3H, one of them D_2O exchangeable, OH), 2.28-2.37 (m, 1H), 3.47 (br. s, 2H, D_2O exchangeable, NH_2), 3.68-3.78 (m, 2H, OCH_2), 5.62 (b s, 1H, D_2O exch., NH), 7.99 (s, 1H, pyrimidine H-2). ^{13}C NMR ($CDCl_3$) δ: 18.74 (CH_3), 19.31 (CH_3), 24.30 (C-5), 27.52 (CH_3), 34.37 (C-4), 47.28 (C-2), 49.23 (C-1), 64.05 (CH_2O), 66.44 (C-3), 123.01 (pyrimidine C-5), 142.47 (pyrimidine C-4), 149.32 (pyrimidine C-2), 155.14 (pyrimidine C-6).

(1*S*,3*R*)-[3-(6-Chloro-9*H*-purin-9-yl)-2,2,3-trimethylcyclopentyl]methanol (4). A mixture of **11** (0.41 g, 1.44 mmol), triethyl orthoformate (8 mL, 60.58 mmol) and 12N HCl (0.50 mL) was stirred for 72 h. The resulting suspension was concentrated to dryness *in vacuo*, the residue was treated with 0.5N HCl (30 mL) for 2 h at room temperature, and this mixture was adjusted to pH 7 with 0.5N NaOH. The solvents were evaporated, and the crude solid product (1.46 g) was chromatographed on silica gel (15 g), eluting with 1:0.05 $HCCl_3$/MeOH. Compound **4** (0.33 g, 78%) was isolated as a solid. M.p. 220-222°C. IR (KBr): 3442, 3300, 2956, 1616, 1556, 1521, 1414, 1217, 1095, 852, 784 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.42 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.43-1.55 (m, 1H), 1.82 (s, 3H, CH_3), 1.86-1.93 (m, 1H), 2.00-2.07 (m, 2H), 3.29-3.36 (m, 2H), 3.42-3.53 (m, 1H), 4.46 (t, 1H, D_2O exchangeable, J = 4.89 Hz, OH), 8.73 and 8.84 (s, 2H, purine H-2 and H-8). ^{13}C NMR (DMSO-d_6) δ: 19.22 (CH_3), 22.95 (CH_3), 23.85 (CH_3), 24.00 (C-5), 34.02 (C-4), 47.02 (C-2), 48.25 (C-1), 63.02 (CH_2O), 73.33 (C-3), 131.89 (purine C-5), 147.50 (purine C-2), 149.86 (purine C-6), 150.81 (purine C-8), 153.38 (purine C-4). EIMS *m/z* (%): 294 (M^+, 4), 207 (6), 197 (12), 195 (39), 167 (13), 157 (19), 155 (62), 122 (11), 109 (6), 107 (15), 95 (6), 91 (6), 85 (6),82 (7), 77 (7), 69 (16), 67 (14), 58 (100), 57 (17), 55 (19), 53 (10). Anal. Calcd. for $C_{14}H_{19}ClN_4O$: C, 54.04, H, 6.50, N, 19.01. Found: C, 54.37, H, 6.72, N, 18.94.

(1*R*,·3*S*)-9-[3-(hydroxymethyl)-1,2,2-trimethylcyclopentyl]-9*H*-purin-6-one (5). A mixture of **4** (0.13 g, 0.44 mmol) and 0.33 N NaOH (10 mL) was refluxed for 6 h. The solvent was evaporated, and the pale yellow solid obtained (0.30 g) was chromatographed on silica gel (9 g), eluting with 1:0.1 $CHCl_3$/MeOH. Compound **5** (0.12 g, 99%) was isolated as a white solid. Recrystallization from MeOH afforded an analytical sample with m.p. 282-283.5°C. $[\alpha]_D^{25}$ + 48.00 (*c* 0.15, DMSO). IR (KBr): 3052, 2879, 1700, 1654, 1593, 1412, 1363, 1218, 1021 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.42 (s, 3H, CH_3), 1.17 (s,

3H, CH_3), 1.43-1.51 (m, 1H), 1.74 (s, 3H, CH_3), 1.72-1.79 (m, 1H), 1.89-2.04 (m, 2H), 3.27-3.34 (m, 2H), 3.36-3.55 (m, 1H, the residual H_2O signal overlaps this signal; addition of D_2O simplifies both this signal and the signal at 3.27-3.34 to multiplet and ABX system, J_{AB} = 10.41 Hz, J_{AX} = 7.58 Hz, J_{BX} = 5.78 Hz, H-3' + OCH_2), 4.44 (t, 1H, D_2O exchangeable, J = 4.90 Hz, OH), 7.95 and 8.20 (2s, 2H, purine H-2 and H-8), 12.23 (br. s, 1H, D_2O exchangeable, purine H-1). ^{13}C NMR (DMSO-d_6) δ: 19.15 (CH_3), 23.34 (CH_3), 23.97 (CH_3), 24.08 (C-4), 34.30 (C-5), 46.78 (C-2), 48.42 (C-3), 63.09 (CH_2O), 72.43 (C-1), 125.59 (purine C-5), 140.42 (purine C-2), 143.94 (purine C-8), 149.72 (purine C-4), 157.22 (purine C-6). EIMS *m/z* (%): 276 (M^+, 6), 177 (10), 137 (100), 136 (29), 125 (6), 123 (12), 121 (6), 109 (8), 107 (7), 95 (7), 82 (9), 81 (13), 69 (6), 67 (9), 65 (6). Anal. Calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85, H, 7.29, N, 20.27. Found: C, 61.03, H, 7.41, N, 20.06

(1*S*,3*R*)-[3-(6-Amino-9*H*-purin-9-yl)-2,2,3-trimethylcyclopentyl]methanol (6). A solution of **4** (0.14 g, 0.47 mmol) in 14M NH_4OH (16 mL) was refluxed for 18 h. The solvent were evaporated, and the pale yellow solid obtained (0.15 g) was chromatographed on silica gel (4.50 g), eluting with 1:0.1 $CHCl_3$/MeOH. Crude **5** (0.07 g, 54%) was isolated as a white solid. Recrystallization of the crude product from H_2O afforded pure **6**. M.p. 185-187°C. $[\alpha]_D^{25}$ + 54.80 (*c* 0.97, MeOH). IR (KBr): 3321, 1658, 1599, 1564, 1481, 1315, 1232 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.40 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.42-1.52 (m, 1H), 1.71-1.78, (m, 1H), 1.76 (s, 3H, CH_3), 1.87-2.07 (m, 2H), 3.26-3.42 (m, 2H), 3.45-3.52 (m, 1H), 4.42 (t, 1H, J = 4.87 Hz, D_2O exchangeable, OH), 7.07 (s, 2H, D_2O exchangeable, NH_2), 8.07 and 8.24 (2s, 2H, purine H-2 and H-8). ^{13}C NMR (DMSO-d_6) δ: 19.22 (CH_3), 23.30 (CH_3), 24.07 (CH_3), 24.20 (C-5), 34.06 (C-4), 46.86 (C-2), 48.47 (C-1), 63.15 (CH_2O), 71.95 (C-3), 120.07 (purine C-5), 140.85 (purine C-8), 151.12 (purine C-4), 151.71 (purine C-2), 156.57 (purine C-6). EIMS *m/z* (%): 275 (M^+, 12), 244 (17), 176 (26), 148 (11), 137 (8), 136 (100), 135 (56), 108 (16), 81 (9), 67 (8), 55 (8). Anal. Calcd. for $C_{14}H_{21}N_5O$: C, 61.07, H, 7.69, N, 25.43. Found: C, 61.35, H, 7.83, N, 25.32

(1*R*,3*S*)-3-(3-Hydroxymethyl-1,2,2-trimethylcyclopentyl)-3,6-dihydro[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one (7). A solution of **11** (0.15 g, 0.53 mmol) in AcOH (1.00 mL) and H_2O (1.50 mL) cooled in an ice bath was treated with $NaNO_2$ (0.05 g, 0.71

mmol) in H_2O (1.2 mL). After 10 min the ice bath was removed and the suspension was left stirring 18 h at room temperature. The solvents were evaporated, and the solid gum obtained (0.62 g) was chromatographed on silica gel (16 g), eluting with 1:0.5 EtOAc/hexane. Crude **7** (0.06 g, 41%) was isolated as a white yellow solid. Recrystallization of the crude product from EtOH afforded pure **7**. M.p. 268-271°C. $[\alpha]_D^{25}$ + 54.50 (*c* 0.11, MeOH). IR (KBr): 3398, 3065, 2878, 1703, 1595, 1544, 1364, 1276, 1010 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.37 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.50-1.53 (m, 1H), 1.76 (s, 3H, CH_3), 1.89-2.06 (m, 3H), 3.29-3.36 (m, 1H), 3.47-3.60 (m, 2 H), 4.44 (t, 1H, D_2O exchangeable, J = 4.90 Hz, OH), 8.18 (s, 1H, H-5), 12.66 (br. s, 1H, D_2O exchangeable, triazolopyrimidine H-6). ^{13}C NMR (DMSO-d_6) δ: 18.49 (CH_3), 23.27 (2 × CH_3), 23.88 (C-4), 33.29 (C-5), 47.09 (C-2), 48.23 (C-3), 62.58 (CH_2O), 75.50 (C-1), 130.26 (triazolopyrimidine C-7a), 148.28 (triazolopyrimidine C-5), 149.51 (triazolopyrimidine C-3a), 157.79 (triazolopyrimidine C-7). EIMS *m/z* (%): 262 (M^+-CH_3, 17), 248 (16), 218 (13), 190 (13), 176 (15), 164 (27), 162 (17), 151 (28), 150 (100), 136 (15), 123 (27), 122 (13), 121 (16), 110 (20), 109 (23), 108 (20), 107 (30), 105 (13), 96 (19), 95 (26), 93 (15), 91 (23), 82 (13), 81 (24), 80 (18), 79 (32), 77 (33), 69 (16), 68 (23), 67 (49), 66 (15), 65 (23), 57 (15), 55 (39), 54 (24), 53 (41), 51 (13). Anal. Calcd. for $C_{13}H_{19}N_5O_2$: C, 56.30, H, 6.91, N, 25.25. Found: C, 56.51, H, 6.99, N, 25.42

(1*S*,3*R*)-[3-(7-Amino-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-2,2,3-trimethyl-cyclopentyl]methanol (8). A suspension of **11** (0.15 g, 0.53 mmol) in 1N HCl (6 mL) was stirred for 15 min with $NaNO_2$ (0.05 g, 0.71 mmol) in H_2O (6 mL) at 0°C. 14M NH_4OH (3.00 mL) was added, and the resulting suspension was refluxed for 5 min. The precipitate was filtered out, washed with H_2O and air-dried in a fume hood to yield a solid (0.11 g) which was purified on silica gel (6 g) with 7:3 EtOAc/hexane as eluant. Crude **8** (0.13 g, 89%) was isolated as a yellow solid; an analytical sample was obtained by recrystallization from EtOH. M.p. 208-209°C. $[\alpha]_D^{25}$ + 71.10 (*c* 0.10, MeOH). IR (KBr): 3278, 1684, 1654, 1610, 1566, 1328 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.34 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.49-1.58 (m, 1H), 1.79 (s, 3H, CH_3), 1.86-2.10 (m, 3H), 3.30-3.43 (m, 1H), 3.47-3.54 (m, 1H), 3.67-3.75 (m, 1H), 4.42 (t, 1H, J = 4.86 Hz, D_2O exchangeable, OH), 7.98 (br. s, 1H, D_2O exchangeable, NHH), 8.23 (br. s, 2H, one of them D_2O exchangeable, NHH + triazolopyrimidine H-5). ^{13}C NMR (DMSO-d_6) δ: 18.94

(CH_3), 23.64 (CH_3), 23.76 (CH_3), 24.36 (C-5), 33.44 (C-4), 47.51 (C-2), 48.65 (C-1), 63.02 (CH_2O), 75.36 (C-3), 124.72 (triazolopyrimidine C-7a), 150.25 (triazolopyrimidine C-3a), 156.16 (triazolopyrimidine C-5), 156.80 (triazolopyrimidine C-7). EIMS *m/z* (%): 276 (M^+, 2), 261 (M^+- CH_3, 7), 217 (12), 175 (12), 163 (41), 161 (9), 151 (9), 150 (25), 149 (100), 148 (10), 137 (40), 135 (8), 122 (10), 111 (13), 110 (11), 109 (21), 108 (11), 107 (12), 95 (22), 91 (9), 81 (11), 79 (13), 69 (9), 67 (33), 66 (16), 55 (16), 53 (13). Anal. Calcd. for $C_{13}H_{20}N_6O$: C, 56.50, H, 7.29, N, 30.41. Found: C, 56.71, H, 7.39, N, 30.56.

(1*R*,3*S*)-*N*-(3-Hydroxymethyl-1,2,2-trimethylcyclopentyl-*N'*-(3-methoxyacryloyl)urea (13). Silver cyanate (48 g), previously dried over P_2O_5 at 100°C under vacuum, was added in the dark to dry benzene (321 mL) under an argon atmosphere. The suspension was heated under reflux with vigorous stirring for 0.5 h, after which a solution of 3-methoxypropenoyl chloride (19.28 g, 160 mmol) in dry benzene (60 mL) was added dropwise. The resulting suspension was vigorously stirred at reflux for a further 0.5 h and at room temperature for 3 h, and was then allowed to settle. A portion of the supernatant (32 mL, theoretically containing 13.05 mmol of 3-methoxyacryloyl isocyanate) was transferred to a dry dropping funnel and added dropwise to a solution of **10** (2.05 g, 13.05 mmol) in dry dimethylformamide (61 mL) to −15°C. The mixture was allowed to warm to room temperature over 1 h, then stirred overnight at room temperature and concentrated under reduced pressure (oil pump) at a temperature below 40°C. Removal of the solvent by repeated co-evaporation with EtOH afforded a solid (3.51 g) which was chromatographed on a silica gel column (100 g) with 9.5:0.5 $CHCl_3$/MeOH as eluant. Compound **13** (1.96 g, 53 %) was isolated as a white solid. An analytical sample was obtained by recrystallization from 4:1 cyclohexane/EtOAc. M.p. 131-132°C. $[\alpha]_D^{25}$ + 30.60 (*c*, 0.51, MeOH). IR (KBr): 3242, 3104, 2975, 1703, 1679, 1622, 1558, 1505, 1253, 1196, 1161 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.78 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.70-176 (m, 1H), 1.79-1.94 (m, 4H), 3.24-3.31 (m, 1H, C<u>H</u>HO), 3.44-3.51 (m, 1H, CH<u>H</u>O), 3.66 (s, 3H, CH_3O), 4.33 (t, 1H, D_2O exchangeable, J = 4.94 Hz, OH), 5.51 (d, 1H, J = 12.29 Hz, CHCO), 7.58 (d, 1H, J = 12.29 Hz, C<u>H</u>OCH_3), 8.80 (s, 1H, D_2O exchangeable, CON<u>H</u>CH_2), 9.86 (s, 1H, D_2O exchangeable, CON<u>H</u>CO). ^{13}C NMR (DMSO-d_6) δ: 18.38 (CH_3), 21.51 (CH_3), 23.49 (CH_3), 24.95 (C-4), 35.89 (C-5),

45.48 (C-2), 47.99 (C-3), 58.35 (CH_3O), 63.36 (CH_2O), 64.30 (C-1), 98.28 ($HC=CHCH_3$), 153.08 (HNCONH), 163.16 ($HC=CHCH_3$), 168.38 (HNCOCH). EIMS *m/z* (%): 197 (13), 184 (3), 171 (9), 156 (9), 145 (30), 140 (7), 102 (19), 86 (6), 85 (100), 82 (10), 71 (6), 70 (19), 69 (10), 57 (7), 55 (6). Anal. Calcd. for $C_{14}H_{24}N_2O_4$: C, 59.14, H, 8.51, N, 9.85. Found: C, 59.48, H, 8.42, N, 9.98.

(1*R*,3*S*)-1-(3-Hydroxymethyl-1,2,2-trimethylcyclopentyl)-1*H*-pyrimidine-2,4-dione (9). A suspension of **13** (0.8 g, 2.82 mmol) in 2N H_2SO_4 (38 mL) was heated under reflux for 3.5 h, allowed to cool, brought to pH 7 with 2N NaOH, and concentrated to dryness. The residue was extracted with EtOH, and vacuum concentration of the resulting ethanolic solution afforded a residue (0.89 g) that was purified on silica gel (25 g) with 9.5:0.5 $CHCl_3$/MeOH as eluant. Compound **9** (0.21 g, 29%) was isolated as a white solid. M.p 171-174°CIR (KBr): 3366, 2972, 1716, 1662, 1458, 1374, 1294 cm^{-1}. ^1H NMR (Cl_3CD) δ: 0.81 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.25-1.29 (m, 1H), 1.51-1.59 (m, 1H), 1.63 (s, 3H, CH_3), 1.76 (br. s, 1H, D_2O exchangeable, OH), 1.92-2.04 (m, 3H), 2.60-2.64 (m, 1H), 3.54 and 3.77 (AB part of ABX system, 2H, J_{AB} = 10.25 Hz, J_{AX} = 7.92 Hz, J_{BX} = 5.07 Hz, OCH_2), 5.62 (dd, 1H, J = 8.42, 2.50 Hz, H-5), 7.47 (d, 1H, J = 8.42 Hz, 6-H), 8.81 (br. s, 1H, D_2O exchangeable, NH). ^{13}C NMR (Cl_3CD) δ: 19.67 (CH_3), 22.80 (CH_3), 24.22 (C-4), 25.55 (CH_3), 37.26 (C-5), 47.52 (C-2), 49.84 (C-3), 64.80 (CH_2O), 75.71 (C-1), 101.26 (pyrimidine C-5), 143.60 (pyrimidine C-6), 151.49 (pyrimidine C-2), 163.24 (pyrimidine C-4). EIMS *m/z* (%): 252 (M^+, 1), 153 (18), 152 (22), 123 (22), 122 (64), 113 (15), 110 (50), 109 (49), 107 (79), 96 (15), 95 (55), 94 (26), 93 (26), 91 (45), 82 (25), 81 (70), 80 (28), 79 (65), 77 (55), 70 (25), 69 (68), 68 (64), 67 (100), 65 (27), 57 (27), 55 (64), 54 (29), 53 (53), 50 (20). Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.89, H, 7.99, N, 11.10. Found: C, 62.03, H, 8.03, N, 11.23

Biological activity assays. Antiviral activity and cytotoxicity assays were carried out following established procedures.[13]

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REFERENCES

1. For recent reviews of the literature on the synthesis of CANs (carbocyclic nucleosides), see: a) Agrofoglio, L.;Suhas, E.; Farese, A.; Condom, R.; Challand, S.R.; Earl, R.A.; Guedj, R. *Tetrahedron*, **1994**, *50*, 10611-10670; b) Borthwick, A.D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623; c) Huryn, D.M.; Okaba, M. *Chem. Rev.* **1992**, *50*, 1745-1768.
2. Coates, J. A. V.; Ingall, H. J.; Pearson, B. A.; Penn, C. R.; Storer, R.; Williamson, C.; Cameron, J. M. *Antiviral. Res.* **1991**, *15*, 161-168.
3. Daluge, S.M.; Good, S.S.; Faletto, M.B.; Miller, W.H.; St. Clair, M.H.; Boone, L.R.; Tisdale, M.; Parry, N.R.; Reardon, J.E.; Dornsife, R.E.; Averett, D.R.; Krenitsky, T.A. *Antimicrob. Agents. Chemother.* **1997**, *41*, 1082-1093.
4. Blanco J.M.; Caamaño, O.; Fernández, F.; Gómez, G.; Nieto, M.I.; Balzarini, J.; Padalko, E.; De Clercq E. *Nucleosides & Nucleotides* **1997**, *16*, 159-171.
5. Nieto M.I.; Blanco J.M.; Caamaño O.; Fernández. F.; García-Mera, X.; Balzarini J.; Padalko E.; Neyts J.; De Clercq E. *Nucleosides & Nucleotides* **1998**, *17*, 1255-1266.
6. Caamaño, O.; Fernández, F.; Gómez, G.; Nieto, M.I. *Tetrahedron* **1994**, *50*, 2175-2182.
7. Nieto, M.I.; Blanco, J.M.; Caamaño, O.; Fernández, F.; Gómez, G. *Tetrahedron* **1998**, *54*, 7819-7830.
8. Patil, S.D.; Koga, M.; Schneller, S.W. *J. Med. Chem.* **1992**, *35*, 2191-2195.
9. Vince, R.; Daluge, S. *J. Org. Chem.* **1980**, *45*, 531-533.
10. Shealy, Y. F., O'Dell, C.A. *J. Heterocyclic Chem.* **1976** *13*, 1041-1047.
11. Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958** 157-161.
12. Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958** 153-156.
13. De Clercq, E. in "*In vitro* and *ex vivo* test systems to rationalize drug design and delivery", Crommelin, D.; Couvreur, P.; Duchêne, D.; Editions de Santé: Paris, France, 1994, pp 108-125.

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