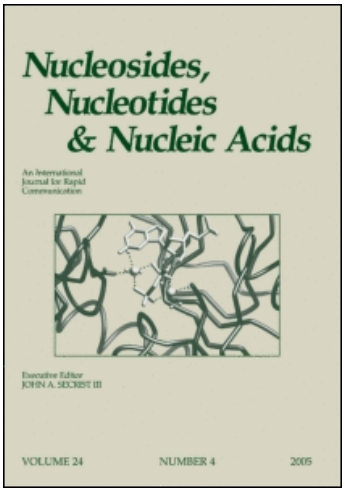

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SYNTHESIS, ANTIVIRAL AND CYTOSTATIC ACTIVITIES, OF CARBOCYCLIC NUCLEOSIDES INCORPORATING A MODIFIED CYCLOPENTANE RING. IV. ADENOSINE AND URIDINE ANALOGUES

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SYNTHESIS, ANTIVIRAL AND CYTOSTATIC ACTIVITIES, OF CARBOCYCLIC NUCLEOSIDES INCORPORATING A MODIFIED CYCLOPENTANE RING. IV. ADENOSINE AND URIDINE ANALOGUES

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ABSTRACT

Eight new carbocyclic nucleosides were prepared by mounting a purine (compounds **8–10**), 8-azapurine (**12** and **13**) or pyrimidine (**15**, **16** and **17b**) on the amino group of (1*S*,3*R*)-3-aminomethyl-2,2,3-trimethyl-cyclopentylmethanol (**6**). All the compounds were evaluated as antiviral and antitumor agents in a variety of assay systems. Only compound **8** showed any cytostatic activity against the tumor cell lines examined.

INTRODUCTION

The development of nontoxic selective inhibitors of kinases and polymerases for control of viral diseases has been the focus of intense research[1]. Despite significant progress, there is still a need for new viral replication inhibitors, especially for the treatment of infection by human immunodeficiency virus (HIV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human cytomegalovirus (CMV) and hepatitis B virus (HBV). Nucleoside analogues that are good substrates for cellular kinases but are resistant to

other host enzymes, such as phosphorylases, are essential for the development of useful therapeutic agents.

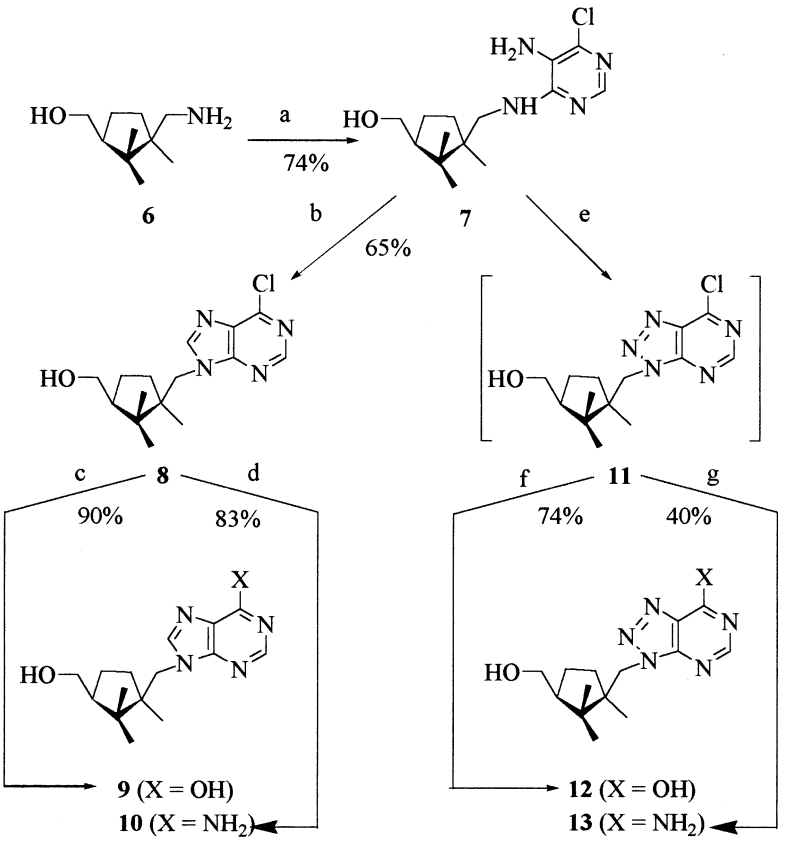
The anomeric centre of natural nucleosides is essential for their conformational behaviour, and hence for their biological properties. One way of eliminating this centre is to replace the endocyclic oxygen of the nucleoside sugar moiety with a methylene unit. The resulting carbocyclic nucleoside analogues have biological properties and structure-activity relationships that differ radically from those of the starting furanose nucleosides[2]: in particular, they are highly resistant to phosphorylases[3] and have shown significant antiviral and antitumoral activity[4], including the inhibition of HIV replication by carbovir (**1**)[5]and abacavir (**2**)[6].

The anomeric centre of natural nucleosides is also eliminated if a methylene unit is introduced between the sugar ring and the base, giving rise to homo-*N*-nucleosides (**3**). Guanine- and adenine-based members of this class have been found to possess selective activity against type 1 and type 2 herpes simplex viruses[7].

Both the above structural modifications – inclusion of a methylene between sugar and base, and substitution of a methylene for endocyclic oxygen of the sugar – are present in a number of trimethylcyclopentane derivates **4** that we have found to possess moderate antiviral or cytostatic activities[8,9]. To explore further the dependence of biological activity on structural characteristics in derivatives of this kind, we have now synthesized trimethylcyclopentane derivatives of type **5** and screened them for antiviral and cytostatic activity. In these compounds the distance between the hydroxymethyl oxygen and the pseudoglycosidic nitrogen is the same as in compounds **4**, but the absolute configuration of the pseudosugar moiety is different (also, the non-geminal methyl group now lies on the α face instead of the β face, but this not thought to be relevant).

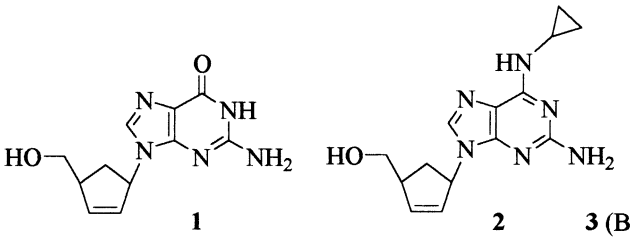
RESULTS AND DISCUSSION

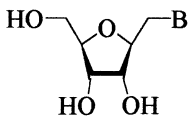
The carbocyclic homo-N-nucleosides here described were prepared by construction of adenine, 8-azaadenine or uracil on the amino group of amino alcohol **6**[10] using the classical approach to carbonucleosides[11–13]. The first step in the preparation of the adenosine and 8-azaadenosine analogues (Sch. 1) was condensation of **6** with 5-amino-4,6-dichloropyrimidine, which afforded diamine **7**. Cyclization of this diamine with triethyl orthoformate gave the 9-substituted-6-chloropurine **8**, which was hydrolysed with dilute sodium hydroxide to the inosine analogue **9** or converted to adenosine analogue **10** by heating in concentrated aqueous ammonia. To obtain the corresponding 8-aza analogues, the triazole ring was formed by diazotation of **7** with sodium nitrite in acetic acid, which afforded the highly reactive 6-chloro-8-azapurine cyclization product **11** (not isolated).



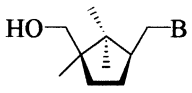
a)5-Amino-4,6-dichloropyrimidine, Et_3N, n-butanol, reflux, 72 h; b) $CH(OEt)_3$, 12N HCl, r.t., 17 h; c) 0.33N NaOH, reflux, 6.5 h; d) 14M NH_4OH, reflux, 16 h; e) $NaNO_2$, AcOH H_2O, rt; f) stirring, rt, 72 h.; g) 14M NH_4OH, reflux, 4 h.

Scheme 1.





3 (B = adenin-9-yl or guanin-9-yl)



4 (B = adenine, guanine or uridyl type base)

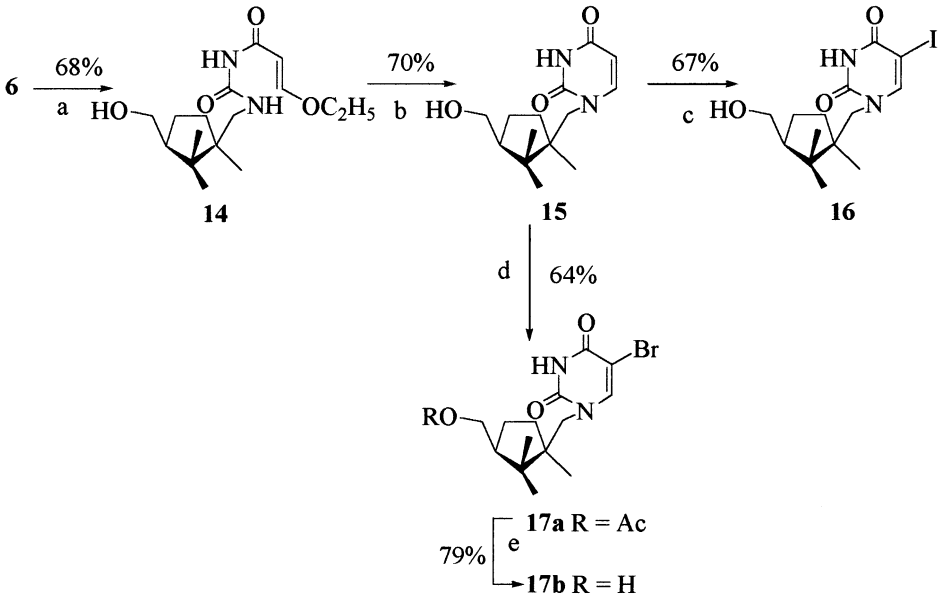
5 (B = adenine or uracil type base)

This was converted to 8-azainosine analogue **12** by simply stirring the crude reaction mixture at room temperature for 72 h, and to the 8-azaadenine analogue **13** by treatment with concentrated aqueous ammonia followed by 4 h refluxing.

The uridine analogue **15** was obtained by a route based on the acryloylurea variant[14] of the Shaw synthesis of 2,4-(1*H*,3*H*)-pyrimidinediones (Sch. 2). Briefly, 3-ethoxypropenoyl isocyanate (prepared and used under rigorously anhydrous conditions)[15] was reacted with **6** to obtain the acryloylurea **14**, which was then cyclized by refluxing in a basic medium, affording **15** in 70% yield. The 5-iodouracil derivative **16** was prepared by the method of Prusoff[16], by treatment of the uracil **15** with iodine in dioxan in the presence of nitric acid. The 5-bromouracil derivative **17b** was prepared by procedures similar to those used by Visser[17] for the preparation of 5-bromo-2′-deoxyuridine (BrdUrd), by bromination of **15** in acetic anhydride and deacylation of **17a**.

The new carbocyclic nucleosides **8–10**, **12**, **13**, **15**, **16** and **17b** were evaluated for their antiviral activity in a wide variety of assay systems, as follows.

At compound concentrations up to 400 μg/mL: type 1 herpes simplex virus (strain KOS), type 2 herpes simplex virus (strain G), vaccinia virus and



a) 3-Ethoxypropenoyl isocyanate, C_6H_6, r.t., 17 h; b) 14M NH_4OH, reflux, 28 h.; c) I_2, dioxan, HNO_3, reflux, 3 h; d) Ac_2O, Br_2, r.t., 3 h; e) 20% NH_4OH , MeOH, reflux, 72 h.

Scheme 2.

vesicular stomatitis virus in human embryonic skin-muscle fibroblasts (E_6SM); vesicular stomatitis virus, respiratory syncytial virus and Coxsackie B4 virus in human epithelial (HeLa) cells; and type 3 parainfluenza virus, type 1 reovirus, sindbis virus, Coxsackie B4 and Punta Toro virus in African green monkey (Vero) kidney cells. Brivudine, and ribavirin, acyclovir and ganciclovir and/or (S)-9-(2,3-dihydroxypropyl)adenine were used in parallel tests as reference drugs.

At compound concentrations up to 100 μg/mL: human immunodeficiency virus (HIV) (types 1 and 2) in CEM/0 T-lymphocytes (cytoxicity against host cells was also evaluated).

At compound concentrations up to 50 μg/mL: cytomegalovirus (CMV, strains AD-169 and DAVIS) and varicella-zoster virus (VZV, strains OKA, YS, 07/1 and YS/R) in human embryonic lung (HEL) cells. Cidofovir and ganciclovir, or brivudine and acyclovir, were used in parallel tests as reference drugs.

At subtoxic concentrations the new compounds generally showed no activity or only marginal activity against the viruses tested. In tests of cytostatic activity against tumour cell lines the most active compound was **8**, which was moderately effective in inhibiting the proliferation of human T-lymphocytes [CEM (14 ± 3 μg/mL) and MOLT 4/C8 (9 ± 1 μg/mL)] and murine leukemia cells [L1210 (13 ± 7 μg/mL)].

In conclusion, comparison of the above results with those obtained previously for the corresponding isomeric compounds **4**[9] suggests that quasi-inversion of absolute configuration of the pseudosugar moiety eliminates antiviral activity, and that among these carbocyclic homo-*N*-nucleosides cytostatic activity is possessed by 6-chloropurines (regardless of carbocycle structure) but no other members of this class.

EXPERIMENTAL SECTION

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Melting points were measured on a Reichert Kofler thermopan 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 1640 FTIR spectrophotometer, ^1H and ^{13}C NMR spectra in a 300 MHz Bruker AMX 300 spectrometer, and mass spectra on a Kratos MS-59 spectrometer.

(+)-(1*S*,3*R*)-3-[(5-Amino-6-chloropyrimidin-4-yl)aminomethyl]-2,2,3-trimethylcyclopentylmethanol (7). A solution of aminoalcohol **6** (0.73 g, 4.27 mmol) and 5-amino-4,6-dichloropyrimidine (0.87 g, 5.33 mmol) in dry *n*-BuOH (40 mL) and dry Et_3N (4.36 mL) was refluxed under argon for

72 h. Evaporation of the solvents under vacuum left 2.47 g of a residue that was purified by column chromatography on silica gel with 15:1 CH_2Cl_2/MeOH and then pure MeOH as eluents, affording **7** as a yellowish solid (0.94 g, 74%) that was recrystallized twice from AcOEt containing active carbon as decolorant. Mp. 195–196°C. $[\alpha]_D^{25}$+31.3 (*c* 0.49; MeOH). IR (KBr) ν (cm^{-1}): 3344, 2960, 1579, 1458, 1433, 1362, 1296, 1087, 1057, 1024, 998, 893, 772. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.63 (s, 1H, pyrimidine 2-H); 6.28 (t, 1H, $J = 5.79$ Hz, D_2O exchang., NH); 5.12 (s, 2H, D_2O exchang., NH_2); 4.25 (t, 1H, $J = 4.90$ Hz, D_2O exchang., OH); 3.51–3.42 (m, 2H); 3.28–3.24 (m, 2H); 1.97–1.94 (m, 1H); 1.76–1.67 (m, 2H); 1.37–1.29 (m, 2H); 0.92 (s, 3H, CH_3); 0.88 (s, 3H, CH_3), 0.77 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 152.96 (pyrimidine C6); 145.80 (pyrimidine C2); 137.18 (pyrimidine C4); 123.75 (pyrimidine C5); 63.22 (OCH_2); 49.83; (C1); 48.14 (C2); 46.82 (NCH_2); 44.17 (C3); 34.79 (C4); 25.60 (C5); 23.86 (CH_3); 20.97 (CH_3); 18.57 (CH_3). Anal. Calcd. for $C_{14}H_{23}ClN_4O$: C, 56.27, H, 7.76, N, 18.75. Found: C, 56.41, H, 8.01, N, 18.99.

(+)-(1*S*,3*R*)-3-(6-Chloro-9*H*-purin-9-ylmethyl)-2,2,3-trimethylcyclopentylmethanol (8). A mixture of **7** (0.84 g, 2.82 mmol), triethyl orthoformate (15.50 mL, 138.11 mmol) and 12N HCl (0.19 mL) was stirred at room temperature for 17 h and then concentrated under vacuum to obtain a residue that was treated with 0.5 N HCl (59 mL) for 3 h at room temperature. The resulting solution was brought to pH 8 with 1N NaOH, and evaporation of the solvents under reduced pressure left a residue that was taken into MeOH (12 mL) and filtered to remove undissolved NaCl. Evaporation of the MeOH under vacuum left a yellow solid (1.38 g) that upon purification by column chromatography on silica gel using 30:1 CH_2Cl_2/MeOH as eluent afforded **8** as a white solid (0.58 g, 65%) that was recrystallized from 2:1 hexane/EtOAc. Mp 153–155°C. $[\alpha]_D^{25}$+28.54 (*c* 0.48; MeOH). IR (KBr) ν (cm^{-1}): 3355, 2964, 2908, 2871, 1600, 1561, 1403, 1341, 1241, 1214, 944, 650. ^{1}H NMR (DMSO-d_6) δ (ppm): 8.77 and 8.67 (2s, 2H, purine 2-H+8-H); 4.34 (s, 1H, D_2O exchang., OH); 4.23 (s, 2H, NCH_2); 3.50 (dd, 1H, $J = 10.28$ Hz, $J = 6.12$ Hz, OC*H*H); 3.34–3.28 (m, 1H, OCH*H*); 2.13–1.94 (m, 2H), 1.79–1.66 (m, 1H); 1.36–1.21 (m, 1H); 1.14–1.06 (m, 1H); 0.99 (s, 3H, CH_3); 0.89 (s, 3H, CH_3); 0.66 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 153.06 (purine C4); 151.79 (purine C2); 149.40 (purine C6); 148.68 (purine C8); 130.71 (purine C5); 63.00 (OCH_2); 50.33 (NCH_2); 49.30 (C1); 49.06 (C2); 44.64 (C3); 35.03 (C4); 25.36 (C5); 23.04 (CH_3); 20.70 (CH_3); 18.40 (CH_3). EIMS *m/z* (%): 308 (10, M^+); 209 (20); 207 (11); 170 (23); 169 (14); 168 (67); 167 (20); 157 (32); 155 (100); 123 (39); 95 (15); 81 (39); 79 (17); 77 (10); 71 (12); 69 (32); 68 (15); 67 (30); 58 (17); 57 (18); 55 (36). Anal. Calcd. for $C_{15}H_{21}ClN_4O$: C, 58.34, H, 6.85, N, 18.14. Found: C, 58.49, H, 6.98, N, 18.23.

(+)-(1*R*,3*S*)-6,9-Dihydro-9-[3-(hydroxymethyl)-1,2,2-trimethylcyclopentylmethyl]-1*H*-purin-6-one (9). A mixture of **8** (0.53 g, 1.72 mmol) and 0.33N NaOH (37 mL) was refluxed for 6.5 h. Subsequent concentration to dryness by evaporation of the solvent afforded 1.65 g of a yellow solid that upon purification by column chromatography on silica gel (41 g) with successive 30:1 and 10:1 mixtures of CH_2Cl_2 and MeOH as eluents gave **9** as a white solid (0.44 g, 90%) that was recrystallized from MeOH, mp 286–288°C. $[\alpha]_D^{25}$+35.46 (*c* 0,52; MeOH). IR (KBr) ν (cm^{-1}): 3219, 2967, 1676, 1576, 1541, 1508, 1458, 1026. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.23 (s, 1H, D_2O exchang., purine 1-H); 8.02 (2s, 2H, purine 2-H+8-H); 4.30 (t, 1H, D_2O exchang., $J = 4.78$ Hz, OH); 4.06 (s, 2H, NCH_2); 3.53–3.46 (m, 1H, OC*H*H); 3.34–3.27 (m, 1H, OCH*H*); 2.08–2.01 (m, 2H); 1.80–1.67 (m, 1H); 1.33–1.22 (m, 1H); 1.15–1.07 (m, 1H); 0.97 (s, 3H, CH_3); 0.86 (s, 3H, CH_3); 0.64 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6) δ (ppm): 157.33 (purine C6); 149.74 (purine C4); 145.84 (purine C8); 141.75 (purine C2); 124.13 (purine C5); 63.29 (OCH_2); 50.02 (NCH_2); 49.67 (C3); 49.23 (C2); 44.84 (C1); 35.38 (C5); 25.63 (C4); 23.32 (CH_3); 20.93 (CH_3); 18.63 (CH_3). EIMS *m*/*z* (%): 290 (9, M^+); 191 (14); 151 (9); 150 (82); 149 (33); 137 (100); 136 (28); 123 (17); 109 (9); 95 (11); 81 (25); 79 (10); 69 (22); 67 (24); 58 (15); 57 (19); 55 (36); 53 (12). Anal. Calcd. for $C_{15}H_{22}N_4O_2$: C, 62.05, H, 7.64, N, 19.30. Found: C, 62.25, H, 7.76, N, 19.48.

(1*S*,3*R*)-3-(6-Amino-9*H*-purin-9-ylmethyl)-2,2,3-trimethylcyclopentylmethanol (10). A mixture of **8** (100 mg, 0.32 mmol) and 14M NH_4OH (11 mL) was heated at 90°C for 16 h and then concentrated to dryness, affording **10** as a white solid (80 mg, 83%) that was washed with acetone, mp 228–230°C. IR (KBr) ν (cm^{-1}) 3148, 1665, 1598, 1401, 1326, 1250, 1030, 796. ^{1}H NMR (DMSO-d_6) δ (ppm): 8.12 and 8.07 (2s, 2H, purine 2-H+8-H); 7.13 (s, H, D_2O exchang., NH_2); 4.32 (t, 1H, $J = 4.85$ Hz, D_2O exchang., OH), 4.06 (d, 2H, $J = 3.19$ Hz, NCH_2); 3.51–3.46 (m, 1H, OC*H*H); 3.33–3.26 (m, 1H, OCH*H*); 2.06–1.95 (m, 2H); 1.76–1.69 (m, 1H); 1.30–1.27 (m, 1H); 1.15–1.06 (m, 1H); 0.96 (s, 3H, CH_3); 0.87 (s, 3H, CH_3); 0.65 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 156.29 (purine C6); 152.66 (purine C2); 150.68 (purine C4); 142.02 (purine C8); 118.67 (purine C5); 63.05 ($HOCH_2$); 49.45 (C1); 49.30 (NCH_2); 49.08 (C2); 44.52 (C-3); 35.25 (C4); 25.42 (C5); 23.11 (CH_3); 20.81 (CH_3); 18.40 (CH_3). EIMS *m*/*z* (%): 289 (12, M^+); 258 (12); 190 (11); 188 (11); 149 (94); 148 (64); 136 (49); 135 (100); 108 (14); 81 (17); 79 (11); 69 (14); 67 (21); 58 (33); 57 (17); 55 (27); 53 (10). Anal. Calcd. for $C_{15}H_{23}N_5O$: C, 62.26, H, 8.01, N, 24.20. Found: C, 62.43, H, 8.24, N, 24.29.

(+)-(1*R*,3S)-6,7-Dihydro-3-[3-(hydroxymethyl)-1,2,2-trimethylcyclopentylmethyl]-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-one (12). A solution of $NaNO_2$ (63 mg, 0.90 mmol) in water (1.5 mL) was added to a solution of **7** (0.20 g,

0.67 mmol) in AcOH (2.24 mL) and water (2.5 mL) in an ice-bath with salt. After 10 min the ice-bath was removed and the suspension was left at room temperature for 72 h, after which the solvents were evaporated under reduced pressure. The solid residue (0.25 g) was purified by column chromatography on silica gel with successive 30:1 and 10:1 mixtures of CH_2Cl_2 and MeOH as eluents, affording **12** (0.14 g, 74%) as a white solid that was recrystallized from EtOH, mp. 225–227°C. $[\alpha]_D^{25}$ + 37.13 (*c* 0.53; MeOH). IR (KBr) ν (cm^{-1}): 3429, 2970, 1711, 1585, 1557, 1272, 1170, 1021, 609. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.66 (s an, 1H, D_2O exchang., 6-H); 8.23 (d, 1H, $J = 3.57$ Hz, triazolopyrimidine 5-H); 4.40 (d, 2H, $J = 2.99$ Hz, NCH_2); 4.31 (t, 1H, $J = 4.81$ Hz, D_2O exchang., OH); 3.50 (dd, 1H, $J = 10.25$ Hz, $J = 6.06$ Hz, OC*H*H); 3.31 (dd, 1H, $J = 10.25$ Hz, $J = 7.75$ Hz OCH*H*); 2.04–1.96 (m, 2H); 1.81–1.68 (m, 1H); 1.38–1.30 (m, 1H); 1.25–1.16 (m, 1H); 0.93 (s, 3H, CH_3); 0.91 (s, 3H, CH_3); 0.68 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 156.01 (triazolopyrimidine C7); 150.08 (triazolopyrimidine C3a); 149.96 (triazolopyrimidine C5); 129.74 (triazolopyrimidine C7a); 63.24 (OCH_2); 53.43 (NCH_2); 49.73 (C3); 49.36 (C2); 44.87 (C1); 35.62 (C5); 25.59 (C4); 23.44 (CH_3); 21.10 (CH_3); 18.68 (CH_3). EIMS *m/z* (%): 291 (1, M^+); 192 (8); 151 (15); 150 (7); 139 (15); 138 (100); 124 (21); 123 (26); 109 (6); 96 (17); 95 (16); 82 (8); 81 (34); 80 (6); 79 (22); 69 (26); 68 (18); 67 (30); 58 (12); 57 (19); 55 (37); 53 (12). Anal. Calcd. for $C_{14}H_{21}N_5O_2$: C, 57.71, H, 7.27, N, 24.04. Found: C, 57.94, H, 7.36, N, 24.16.

(+)-(1*S*,3*R*)-3-(7-Amino-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl-methyl)-2,2,3-trimethylcyclopentylmethanol (13). To a suspension of **7** (0.25 g, 0.83 mmol) in 1N HCl (2 mL) at 0°C, a solution of $NaNO_2$ (60 mg, 0.89 mmol) in water (7 mL) was added slowly enough to prevent the temperature rising above 0°C, and stirring was continued at this temperature for a further 15 min. Then 14M NH_4OH (4 mL) was added and the mixture was refluxed for 4 h, after which the solvents were removed. The resulting solid residue (0.2 g) was purified by column chromatography on silica gel with 2:3 hexane/EtOAc as eluent, giving **13** as a white solid (0.1 g, 40%) that was recrystallized from EtOH. Mp. 248–249°C. $[\alpha]_D^{25}$ + 37.00 (*c* 0.86; MeOH). IR (KBr) ν (cm^{-1}): 3282, 2968, 1668, 1605, 1577, 1508, 1458, 1271, 1064, 1022. ^{1}H NMR (DMSO-d_6) δ (ppm): 8.35 (s, 1H, D_2O exchang., N*H*H); 8.28 (s, 2H, triazolopyrimidine 5-H); 8.05 (s, 1H, D_2O exchang., NH*H*); 4.42 (d, 2H, $J = 5.54$ Hz, NCH_2); 4.32 (t, 1H, D_2O exchang., $J = 4.32$ Hz, OH); 3.53–3.47 (m, 1H, OC*H*H); 3.35–3.28 (m, 1H, OCH*H*); 2.07–1.95 (m, 2H); 1.78–1.70 (m, 1H); 1.37–1.30 (m, 1H); 1.24–1.16 (m, 1H); 0.93 (s, 6H, $2CH_3$); 0.68 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 156.62 (triazolopyrimidine C7); 156.22 (triazolopyrimidine C5); 149.57 (triazolopyrimidine C3a); 123.37 (triazolopyrimidine C7a); 62.68 (OCH_2); 52.33 (NCH_2); 49.15 (C1); 48.83

(C2); 44.16 (C3); 35.10 (C4); 24.98 (C5); 22.82 (CH_3); 20.61 (CH_3); 18.05 (CH_3). EIMS m/z (%): 290 (8, M^+); 275 (9); 259 (6); 191 (10); 150 (13); 149 (13); 137 (100); 123 (20); 95 (29); 94 (12); 81 (14); 79 (15); 69 (8); 67 (16); 55 (11). Anal. Calcd. for $C_{14}H_{22}N_6O$: C, 57.91, H, 7.64, N, 28.94. Found: C, 58.11, H, 7.72, N, 29.05.

(+)-(1*R*,3*S*)-*N*-[(3-Hydroxymethyl-1,2,2-trimethyl)cyclopentylmethyl]-*N'*-(3-ethoxypropenoyl)urea (14). Silver cyanate (48.0 g, 320 mmol), previously dried at 100°C under vacuum over P_2O_5, was added to dry benzene (321 mL) in the dark under argon, and the suspension was refluxed with vigorous stirring for 0.5 h. A solution of 3-methoxypropenoyl chloride (19.28 g, 160 mmol) in dry benzene (60 mL) was then added dropwise, and the resulting suspension was refluxed for a further 0.5 h with vigorous stirring and then allowed to settle at room temperature for 3 h. A sample of the supernatant (15 mL, theoretically containing 6.25 mmol of 3-ethoxypropenoyl isocyanate) was transferred to a dry dropping funnel and added dropwise to a solution of aminoalcohol **6** (0.72 g; 4.19 mmol) in dry dimethylformamide (22 mL) at −15°C. The mixture was allowed to warm to room temperature over 1 h, stirred overnight at room temperature, and concentrated under reduced pressure (oil pump) at a temperature below 40°C by driving off the solvent by repeated co-evaporation with EtOH. The residue (1.63 g) was chromatographed on silica gel with 5:3 EtOAc/hexane as eluent, and the pooled **14**-containing fractions afforded a white solid (0.89 g, 68%), a sample of which was recrystallized from EtOAc/hexane. Mp. 98–100°C. $[\alpha]_D^{25}$ +27.15 (*c* 0.50; MeOH). IR (KBr) ν (cm^{-1}): 3304, 3097, 2968, 1700, 1675, 1616, 1560, 1500, 1473, 1251, 1170, 1102, 816. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.63 (s, 1H, D_2O exchang., CONHCO); 8.,10 (s, 1H, D_2O exchang., CON*H*CH_2); 7.65 (d, 1H, $J = 12.13$ Hz, CH_3CH_2OCH); 5.53 (d, 1H, $J = 12.13$ Hz, COCH); 3.99 (c, 2H, $J = 7.03$ Hz, CH_3CH_2); 3.76–3.71 (m, 1H, OC*H*H); 3.55–3.50 (m, 1H, OCH*H*); 3.27 (d, 2H, $J = 5.82$ Hz, NCH_2); 2.13–2.08 (m, 1H); 1.98–1.91 (m, 1H); 1.76–1.66 (m, 1H); 1.50–1.40 (m, 1H); 1.36 (t, 3H, $J = 7.05$ Hz, CH_2CH_3); 1.31–1.23 (m, 1H); 1.15 (s, 1H D_2O exchang., OH); 1.01 (s, 3H, CH_3); 0.99 (s, 3H, CH_3); 0.81 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.33 (NH*C*OCH); 163.33 (CH_3CH_2OCH); 155.18 (NHCONH); 98.28 (CO*C*H); 68.04 (CH_3CH_2); 65.45 (OCH_2); 50.62 (C1); 48.25 (C3); 46.42 (NCH_2); 44.56 (C2); 35.18 (C5); 25.64 (C4); 23.94 (CH_3); 21.37 (CH_3); 19.10 (CH_3); 14.92 (CH_3). Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51, H, 9.03, N, 8.97. Found: C, 61.67, H, 9.15, N, 8.99.

(−)-(1*R*,3*S*)-1-[(3-Hydroxymethyl-1,2,2-trimethyl)cyclopentylmethyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (15). A suspension of **14** (0.24 g, 0.77 mmol) in 14M NH_4OH (2.3 mL) was refluxed for 28 h, and the solvent was removed.

The residual paste (0.23 g) was purified by column chromatography on silica gel with 30:1 CH_2Cl_2/MeOH as eluent, affording **15** (0.14 g, 70%) as a white solid that was recrystallized from EtOAc/hexane. Mp 161–163°C. $[\alpha]_D^{25}$ − 11.74 (*c* 0.50; MeOH). IR (KBr) ν (cm^{-1}): 3396, 2966, 1715, 1673, 1458, 1377, 1260, 1169, 1023, 550. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.95 (s, 1H, D_2O exchang., NH); 7.13 (d, 1H, $J = 7.94$ Hz, pyrimidine 6-H); 5.66 (dd, 2H, $J = 7.94$ Hz, $J = 2.40$ Hz, pyrimidine 5-H); 3.92 and 3.54 (AB system, 2H, $J = 13.85$ Hz, NCH_2); 3.81–3.76 (m, 1H, OC*H*H); 3.60–3.55 (m, 1H, OCH*H*); 2.15–2.10 (m, 1H); 2.00–1.87 (m, 2H); 1.49–1.40 (m, 2H); 1.16 (s, 1H, D_2O exchang., HO); 1.04 (s, 3H, CH_3); 0.86 (s, 3H, CH_3); 0.84 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.98 (pyrimidine C4); 163.46 (pyrimidine C2); 145.58 (pyrimidine C6); 102,00 (pyrimidine C5); 65.15 (OCH_2); 54.52 (NCH_2); 49.68 (C-3); 49.49 (C1); 45.57 (C2); 35.94 (C5); 25.66 (C4); 23.15 (CH_3); 19.91 (CH_3); 18.69 (CH_3). Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.14, H, 8.33, N, 10.52. Found: C, 63.31, H, 8.45, N, 10.49.

(+)-(1*R*,3*S*)-1-[(3-Hydroxymethyl-1,2,2-trimethyl)cyclopentylmethyl]-5-iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione (16). A mixture of **15** (0.53 g, 1.99 mmol), dioxan (20 mL), I_2 (0.51 g, 4.06 mmol) and 0.75N HNO_3 (2.67 mL) was refluxed for 3 h. After cooling, the solvents were removed under vacuum and the residual paste (0.76 g) was purified by column chromatography on silica gel with 19:1 CH_2Cl_2/MeOH as eluent, affording **16** as a white porous solid (0.52 g, 67%) that when washed with ether (10 mL) was recovered as a white solid of mp 217–219°C. $[\alpha]_D^{25}$+10.28 (*c* 0.78; MeOH). IR (KBr) ν (cm^{-1}): 3419, 2965, 1674, 1608, 1430, 1370, 1328, 1262, 1022. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (s, 1H, D_2O exchang., NH); 7.57 (s, 1H, pyrimidine 6-H); 3.93 and 3.56 (AB system, 2H, $J = 13{,}69$ Hz, NCH_2); 3.74 (dd, 1H, $J = 10{,}29$ Hz, $J = 5.83$ Hz, OC*H*H); 3.58 (dd, 1H, $J = 10.29$ Hz, $J = 7.70$ Hz, OCH*H*); 2.17–2.08 (m, 1H); 2.04–1.84 (m, 2H); 1.52–1.24 (m, 3H one of them D_2O exchang., OH); 1.04 (s, 3H, CH_3); 0.87 (s, 3H, CH_3); 0.84 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 160.49 (pyrimidine C2); 151.16 (pyrimidine C4); 150.02 (pyrimidine C6); 67.39 (pyrimidine C5); 65.10 ($HOCH_2$); 54.97 (NCH_2); 49.64 (C1); 49.47 (C3); 45.64 (C2); 35.77 (C5); 25.65 (C4); 23.16 (CH_3); 19.90 (CH_3); 18.68 (CH_3). EIMS *m/z* (%): 392 (20, M^+), 252 (64), 239 (36), 238 (24), 208 (33), 124 (12), 123 (100), 95 (17), 81 (38), 79 (11), 69 (21), 67 (18), 58 (15), 55 (24), 53 (21).

(1*R*,3*S*)-5-Bromo-1-[(3-hydroxymethyl-1,2,2-trimethyl)cyclopentylmethyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione acetate (17a). A mixture of acetic anhydride (0.90 mL) and compound **15** (85 mg, 0.32 mmol) was refluxed until the solid dissolved, cooled to room temperature, and then maintained

at 25°C with stirring while a solution of bromine (80 mg, 0.50 mmol) in acetic acid (0.10 mL) was added dropwise. The resulting solution was stirred at room temperature for 3 h and then stored overnight at about 5°C. Volatile components were evaporated under reduced pressure, and the crystalline residue (100 mg) was chromatographed on silica gel with 10:0.1 CH_2Cl_2/MeOH as eluent, affording **17a** (70 mg; 64%). Mp. 214–215°C. IR (KBr) ν (cm^{-1}): 2967, 2835, 1744, 1682, 1615, 1464, 1431, 1374, 1257, 1045, 893, 750. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.17 (s, 1H, D_2O exchang., NH); 7.47 (s, 1H, pyrimidine 6-H); 4.12–4.00 (m, 2H, NCH_2), 3.95 and 3.55 (AB system, 2H, $J = 13.70$ Hz, OCH_2); 2.29–2.17 (m, 2H); 2.05 (s, 3H, $COCH_3$); 1.99–1.86 (m, 2H); 1.50–1.44 (m, 2H, one of them D_2O exchang., OH); 1.03 (s, 3H, CH_3); 0.87 (s, 3H, CH_3); 0.85 (s, 3H, CH_3). EIMS *m/z* (%): 388 (3), 386 (3), 247 (3), 206 (6), 205 (3), 204 (6), 192 (7), 191 (7), 162 (10), 136 (14), 124 (10), 123 (100), 121 (15), 107 (8), 105 (7), 95 (13), 93 (9), 82 (7), 81 (27), 79 (7), 69 (12), 67 (14), 55 (13), 53 (8).

(+)-(1*R*,3*S*)-5-Bromo-1-[(3-hydroxymethyl-1,2,2-trimethyl)cyclopentylmethyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (17b). A solution of acetate **17a** (57 mg, 0.15 mmol) in 20% methanolic ammonia (6 mL) was refluxed for 72 h and then concentrated to dryness under reduced pressure. The residue was dissolved in hot water and stored at about 5°C, which afforded **17b** as a white precipitate that was filtered out of solution and dried in vacuo (40 mg; 79%). Mp. 189–191°C. $[\alpha]_D^{25}$ + 4.72 (*c* 0.46; MeOH). IR (KBr) ν (cm^{-1}): 2966, 2871, 1718, 1684, 1654, 1616, 1508, 1458, 1430, 1046, 630. ^{1}H NMR (DMSOd_6) δ (ppm): 11.75 (s, 1H, D_2O exchang., NH); 8.10 (s, 1H, pyrimidine 6-H); 4.28 (m, 1H, D_2O exchang., OH); 3.77 and 3.57 (AB system, 2H, $J = 13.65$ Hz, OCH_2); 3.47–3.42 (m, 1H, N*H*H); 3.07–3.00 (m, 1H, NH*H*); 1.98–1.89 (m, 2H); 1.81–1.71 (m, 1H); 1.29–1.14 (m, 2H); 0.93 (s, 3H, CH_3); 0.73 (2s, 6H, $2CH_3$). ^{1}C NMR (DMSOd_6) δ (ppm): 159.96 (pyrimidine C4); 151.28 (pyrimidine C2); 146.41 (pyrimidine C6); 94.55 (pyrimidine C5), 63.06 ($HOCH_2$); 53.37 (NCH_2); 49.26 (C1); 48.95 (C3); 44.81 (C2); 34.62 (C5); 25.52 (C4); 22.95 (CH_3); 19.68 (CH_3); 18.18 (CH_3). EIMS *m/z* (%): 288 (1, M^+), 206 (6), 204 (3), 193 (2), 123 (100), 95 (8), 82 (4), 81 (56), 79 (11), 78 (61), 69 (34), 67 (39), 63 (79), 58 (60), 57 (15), 55 (40), 53 (14). Anal. Calcd. for $C_{15}H_{23}BrN_2O_3$: C, 50.15, H, 6.45, N, 7.80. Found: C, 50.36, H, 6.58, N, 7.93.

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