Synthesis of 1-[2-(Hydroxymethyl)cyclohexyl]pyrimidine Analogues of Nucleosides: A Comparative Study

Dolores Viña,*[a] Lourdes Santana,[a] Eugenio Uriarte,[a] Elías Quezada,[a] Laura Valencia[b]

[a] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
Fax +34(981)594912; E-mail: qovina@usc.es

[b] Departamento de Química Inorgánica, Facultad de Química, Universidad de Santiago de Compostela, Spain

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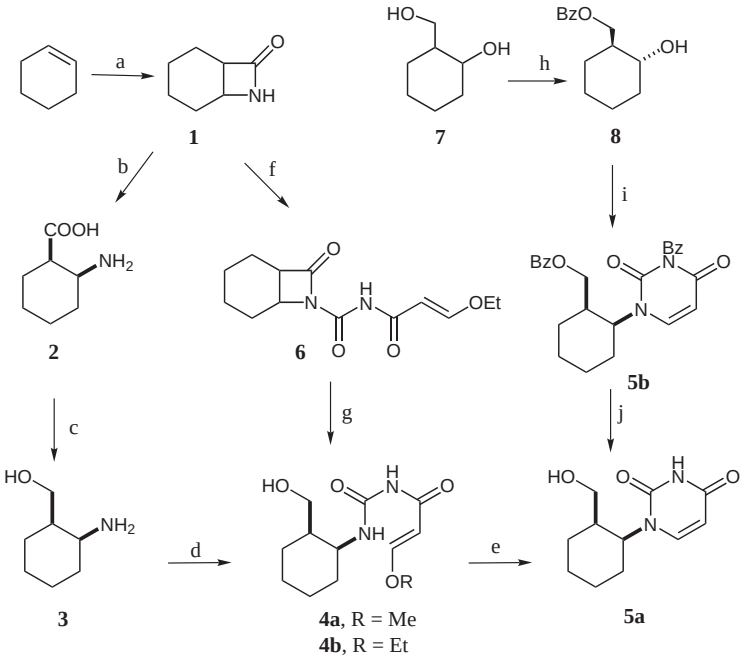
Abstract: The synthesis of a new series of 1,2-disubstituted carbonucleosides analogues of pyrimidine (cyclohexane derivatives) is reported. For the synthesis of the uridine analogue **5a**, either construction of the base on the amino group of the amino alcohol **3** or on the amido group of the predecessor β-lactam **1** was more efficient than condensation of the base with a protected diol. The *cis*-configuration of **5a** was confirmed by X-ray crystallography. Compound **5a** was halogenated with Cl, Br and I at uracil position 5.

Key words: amino alcohols, cyclizations, heterocycles, Mitsunobu reaction, nucleosides

Carbocyclic analogues of nucleosides, in which a methylene group replaces the furan oxygen of nucleosides, are generally more stable to hydrolysis than the corresponding furanyl compounds and in some cases have potent antiviral and/or anticancer activities.[1] For some years, we have been examining a group of such 2′,3′-dideoxy-cyclopentyl analogues which have the hydroxymethyl group and the heterocyclic base attached to contiguous positions of the carbocycle[2] (1,2-disubstituted carbonucleosides or OTCs) and yet retain stereochemistry similar to natural nucleosides and certain pharmacologically interesting nucleoside analogues. In this work, we extend this research to cyclohexyl OTCs,[3] reporting the synthesis of a representative pyrimidinyl compound, *cis*-1-[(2-hydroxymethyl)cyclohexyl]uridine, and their 5-haloderivatives. Despite the fact that carbocyclic nucleosides have been extensively studied, little effort has been directed toward the synthesis of six-membered carbocyclic analogues.[4] However, recent publications have described the potent antiviral activity of such compounds.[5] On the other hand, 5-halopyrimidines are not only of interest due to their potential chemotherapeutic properties[6] but also as synthetic



Scheme 1 *Reagents and conditions:* a) CSI, –78 °C, 43%; b) HCl 12 M, r.t., 99%; c) $LiAlH_4$, THF, reflux, 72 h, 55%; d) $O{=}C{=}NCOCH{=}CHOCH_3$–C_6H_6, DMF, r.t., **4a**: 53%; e) 2 M H_2SO_4, reflux, from **4a**: 86%, from **4b**: 90%; f) $O{=}C{=}NCOCH{=}CHOCH_2CH_3$–$C_6H_6$, DMF, r.t., 37%; g) $NaBH_4$–MeOH, r.t., **4b**: 76%; h) C_6H_5COCl–Et_3N–CH_2Cl_2, 32%; i) N^3-benzoyluracil–Ph_3P–$N_2(CO_2Et)_2$–THF, r.t., 18%; j) MeONa–MeOH, r.t., 60%

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intermediates in the formation of new carbon-carbon or carbon-heteroatom bonds.[7]

In this paper, we investigated the efficiency with which it was possible to prepare the *cis* uridine analogue **5a** as a racemic mixture, using the two routes that have been most widely employed in this field. These two routes are (i) construction of the heterocyclic base on the primary amino group of an appropriate amino alcohol by reaction with a β-alkoxyacryloyl isocyanate followed by acid-catalyzed cyclization according to published procedures[8,9] and (ii) direct condensation between the heterocyclic base and an appropriately functionalized carbocyclic moiety; in this case Mitsunobu condensation of N^3-benzoyluracil with the corresponding protected diol[10] (Scheme 1).

Following route (i) amino alcohol **3** was obtained by a [2+2]-cycloaddition between cyclohexene and chlorosulphonyl isocyanate (CSI)[11] followed by hydrolysis of the resulting lactam **1**. Amino acid **2** was either converted into the corresponding amino ester[12] and subsequently reduced with $NaBH_4$ or directly reduced with $LiAlH_4$ to afford **3** in a similar yield of 20% from cyclohexene. Treatment of **3** with 3-methoxyacryloyl isocyanate[13] in anhydrous benzene afforded the corresponding acyclic ureide **4a**, which by acidic cyclization turned out to afford **5a** in 46% yield from amino alcohol **3**.

Additionally, we have introduced a modification on route (i), which has been described previously with other carbocyclic analogues of nucleosides.[14] It involved initial reaction of the β-lactam **1** with a 3-ethoxyacryloyl isocyanate[2b,15] in anhydrous benzene affording the corresponding carbamoyl derivative **6**. Reduction of compound **6** with an excess of $NaBH_4$ in MeOH gave the corresponding acyclic ureide **4b** with *cis* stereochemistry and subsequent acidic ring closure afforded the desired uracil derivative **5a** in 25% yield from the β-lactam **1**. This alternative procedure is a more direct way and also avoids the preparation of amino alcohol **3**,[16] which is an unstable compound that is difficult to isolate and purify.

Alternatively, compound **5a** was obtained from alcohol **8** in two steps following the route (ii): direct condensation of N^3-benzoyluracil and (±)-*trans*-(2-hydroxy)cyclohexylmethyl benzoate (**8**) in the presence of triphenylphosphine and diethyl azodicarboxylate[17] gave the *cis* compound **5b** in 18% yield, which was deprotected by hydrolysis with MeONa–MeOH to give **5a** in 60% yield. Alcohol **8** was prepared in 23% overall yield by reduction of ethyl 2-oxocyclohexanecarboxylate with $NaBH_4$ to give a mixture of (±)-*cis*/*trans* diols **7**.[18] Subsequent benzoylation of the primary hydroxyl group using benzoyl chloride gave a mixture of (±)-*cis*/*trans*-(2-hydroxy)cyclohexylmethyl benzoate, which could be separated by silica gel column chromatography (1.2:1 ratio of compounds *trans* and *cis*, respectively).

The *cis* configuration of **5a** could be confirmed by X-ray structure determination of a crystal[19] obtained from $CHCl_3$ using Mo-Kα radiation as the X-ray source (Figure 1). The asymmetric unit cell contains two independent molecules of the compound. Both of them have the same *cis* configuration. The molecules are connected by a strong intermolecular hydrogen bond between the N2….O4 and N4….O1. The planarity of the uracil ring is maintained due to sp^2 character of the atoms of the ring (rms = 0.0077 Å and 0.0071 Å). Table 1 shows the bonds lengths (Å) and angles (°) for **5a**.

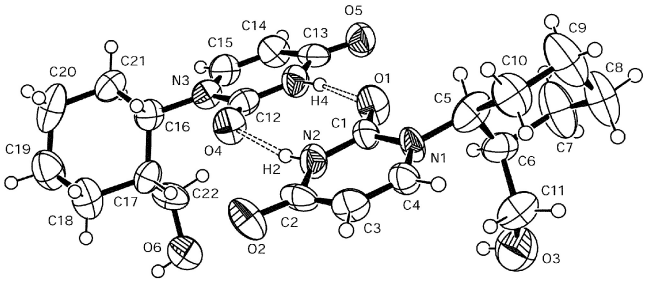


Figure 1 ORTEP plot of the molecular structure of compound **5a** in the crystal (crystallographic numbering does not correspond to the systematic numbering).

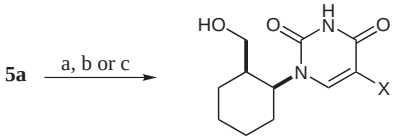
Table 1 Bonds Lengths (Å) and Angles (°) of **5a**

O(1)-C(1)	1.216 (7)	N(2)-C(1)-N(1)	114.0 (6)
O(2)-C(2)	1.225 (7)	O(2)-C(2)-N(2)	120.5 (7)
O(3)-C(11)	1.505 (7)	O(2)-C(2)-C(3)	127.6 (7)
N(1)-C(4)	1.352 (7)	N(2)-C(2)-C(3)	111.9 (6)
N(1)-C(1)	1.371 (7)	C(4)-C(3)-C(2)	121.5 (6)
N(1)-C(5)	1.520 (8)	C(3)-C(4)-N(1)	122.3 (6)
N(2)-C(1)	1.366 (7)	C(6)-C(5)-N(1)	106.6 (6)
N(2)-C(2)	1.381 (7)	C(6)-C(5)-C(10)	115.6 (6)
C(2)-C(3)	1.430 (9)	N(1)-C(5)-C(10)	113.5 (5)
C(3)-C(4)	1.316 (7)	C(5)-C(6)-C(11)	115.2 (6)
C(5)-C(6)	1.435 (8)	C(5)-C(6)-C(7)	105.7 (6)
C(5)-C(10)	1.549 (8)	C(11)-C(6)-C(7)	110.0 (6)
C(6)-C(11)	1.525 (9)	C(8)-C(7)-C(6)	113.5 (6)
C(6)-C(7)	1.631 (9)	C(7)-C(8)-C(9)	106.3 (7)
C(7)-C(8)	1.442 (9)	C(10)-C(9)-C(8)	111.2 (7)
C(8)-C(9)	1.638 (10)	C(9)-C(10)-C(5)	108.3 (6)
C(9)-C(10)	1.474 (9)	O(3)-C(11)-C(6)	109.4 (6)
O(4)-C(12)	1.216 (7)	C(15)-N(3)-C(12)	120.1 (6)
O(5)-C(13)	1.215 (7)	C(15)-N(3)-C(16)	122.3 (5)
O(6)-C(22)	1.453 (6)	C(12)-N(3)-C(16)	117.6 (5)
N(3)-C(15)	1.361 (8)	C(12)-N(4)-C(13)	129.0 (6)
N(3)-C(12)	1.380 (7)	O(4)-C(12)-N(4)	123.6 (6)
N(3)-C(16)	1.495 (7)	O(4)-C(12)-N(3)	122.0 (6)

Table 1 Bonds Lengths (Å) and Angles (°) of **5a** (continued)

N(4)-C(12)	1.354 (7)	N(4)-C(12)-N(3)	114.4 (6)
N(4)-C(13)	1.396 (7)	O(5)-C(13)-N(4)	120.5 (7)
C(13)-C(14)	1.417 (8)	O(5)-C(13)-C(14)	127.1 (7)
C(14)-C(15)	1.335 (8)	N(4)-C(13)-C(14)	112.4 (6)
C(16)-C(17)	1.522 (8)	C(15)-C(14)-C(13)	120.2 (7)
C(16)-C(21)	1.531 (7)	C(14)-C(15)-N(3)	123.9 (6)
C(17)-C(22)	1.485 (7)	N(3)-C(16)-C(17)	110.4 (5)
C(17)-C(18)	1.557 (8)	N(3)-C(16)-C(21)	113.0 (5)
C(18)-C(19)	1.508 (8)	C(17)-C(16)-C(21)	112.3 (5)
C(19)-C(20)	1.533 (10)	C(22)-C(17)-C(16)	114.4 (5)
C(20)-C(21)	1.532 (8)	C(22)-C(17)-C(18)	112.3 (5)
C(4)-N(1)-C(1)	121.7 (5)	C(16)-C(17)-C(18)	109.6 (5)
C(4)-N(1)-C(5)	121.9 (5)	C(19)-C(18)-C(17)	110.7 (6)
C(1)-N(1)-C(5)	116.2 (5)	C(18)-C(19)-C(20)	110.0 (6)
C(1)-N(2)-C(2)	128.5 (6)	C(19)-C(20)-C(21)	111.6 (6)
O(1)-C(1)-N(2)	123.8 (6)	C(20)-C(21)-C(16)	108.1 (5)
O(1)-C(1)-N(1)	122.2 (6)	O(6)-C(22)-C(17)	112.4 (5)

Finally, we proceeded to investigate the halogenation of uracil position 5 (Scheme 2). Bromination and chlorination reactions, were carried out with the corresponding *N*-halosuccinimide in HOAc[20] at 80 °C; these reactions gave yields of 45% and 51%, respectively. However, as one would expect, iodination of **5a** under the same conditions was not possible and yielded a complex mixture of compounds. Then it was carried out with iodine monochloride[21] in MeOH at 50 ºC to afford **11** in 20% yield.



9, X = Br
10, X = Cl
11, X = I

Scheme 2 *Reagents and conditions:* a) NBS–HOAc, 80 °C, 45%; b) NCS–HOAc, 80 °C, 51%; c) ClI–MeOH, 50 °C, 20%

Conclusion

For the synthesis of the uridine analogue **5a**, either construction of the base on the amino group of the amino alcohol **3** or on the amido group of the predecessor β-lactam **1** was more efficient than condensation of the base with the corresponding diol **8**. The synthesis of uridine analogue **5a** starting from the lactam **1** via amino alcohol leads to a longer synthetic strategy. Therefore intermediate amino alcohol **3** is difficult to manipulate and purify. Treatment of β-lactam **1** with a 3-ethoxyacryloyl isocyanate is a more direct procedure and also avoids the preparation of amino alcohol **3**.

Mitsunobu reaction between the protected diol **8** and uracil involves the same number of the steps than the last alternative and although the uridine analogue derivative **5a** is afforded in a lower yield, synthesis of β-alkoxyacryloyl isocyanate could be avoided. The *cis*-configuration of **5a** was confirmed by X-ray crystallography. Selective halogenation at uracil position 5 of **5a** was achieved in an efficient way.

Melting points were determined using a Stuart Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1640 FT spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX (250 MHz) and Bruker AMX (500 MHz) spectrometers, using TMS as internal standard (chemical shifts as δ in ppm, *J* in Hz). Mass spectra and HRMS (EI) were obtained using a Hewlett Packard 5988A spectrometer and Micromass Autospec spectrometer, respectively. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Crystal data were collected on a Bruker Smart CCD-1000 area detector diffractometer using Mo-Kα radiation and the absorption effects were corrected using the SADABS program. Figures were obtained using the programs ORTEP III and PLATON.

(±)-7-Azabicyclo[4.2.0]octan-8-one (1); Typical Procedure

CSI (3.25 g, 2 mL, 22.98 mmol) was added dropwise to cyclohexene (2.03 g, 2.5 mL, 24.68 mmol) under Ar at –78 °C. The temperature was maintained at 0 °C for 8 h, then overnight at 25 °C. After this period the reaction mixture was poured into a solution of 25% sodium bisulfite and treated with KOH (10%) to pH 8. The resulting solution was extracted with EtOAc, the organic phase was evaporated under vacuum and the residue was chromatographed on silica gel (hexane–EtOAc, 6:4) to give **1**; yield: 1.3 g (43%); mp 52–54 °C.

IR (KBr): 3200, 2934, 2866, 1734, 1447.9, 1303, 1218, 715 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20–1.65 [m, 8 H, $(CH_2)_4$], 2.92–3.05 (m, 1 H, CHCO), 3.55–3.66 (m, 1 H, CHN), 6.85 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 17.1, 19.2, 20.0, 25.6, 46.9, 47.5, 173.2.

MS: *m*/*z* (%) = 127 (63) [M + 2]$^+$, 125 (100) [M$^+$], 96 (37) [M$^+$ – HCO], 81 (100) [M$^+$ – CONH].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_7H_{11}NO$: 125.0841; found: 125.0840.

(±)-*cis*-2-Aminocyclohexanecarboxylic Acid (2); Typical Procedure

To compound **1** (3.73 g, 29.84 mmol) was slowly added, under ice-cooling and stirring, 12 M HCl (75 mL). The reaction mixture was stirred for 30 min at r.t. and then evaporated to dryness to give the crude hydrochloride of **2**, which was submitted to ion exchange chromatography on Dowex 50X8-100 resin. Elution with aq NH_4OH (1 M) afforded **2**; yield: 4.22 g (99%); mp 216–218 °C.

IR (KBr): 3502, 2952, 1654, 1584, 1154 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.30–1.85 [m, 8 H, $(CH_2)_4$], 2.30 (dt, *J* = 4.1, 6.4 Hz, 1 H, CHCO), 3.17 (dt, *J* = 4.1, 8.1 Hz, 1 H, CHN).

^{13}C NMR (DMSO-d_6): δ = 22.0, 22.7, 26.4, 27.4, 42.9 (1), 49.9 (2), 178.5.

MS: *m*/*z* (%) = 144 (56) [M + 1]$^+$, 143 (58) [M$^+$], 126 (15) [M$^+$ – OH], 100 (86) [(M + 1)$^+$ – CO_2].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_7H_{13}NO$: 143.0946; found: 143.0946.

(±)-*cis*-2-Amino-3-cyclohexanemethanol (3); Typical Procedure

$LiAlH_4$ (719 mg, 18.92 mmol) was added portion wise to a cooled (0 °C) solution of **2** (770 mg, 5.38 mmol) in anhyd THF (100 mL) with stirring under Ar. The mixture was heated under reflux for 72 h, cooled to 0 °C and quenched by slow addition of H_2O–ice mixture. After a further 30 min stirring at r.t., the resulting solid was filtered off, organic phase was washed with H_2O, dried with Na_2SO_4 and the filtrate was concentrated in vacuo to give **3** as a colourless oil, which was used in the next step without further purification; yield: 1.5 g (55%).

IR (KBr): 3286, 2924, 2841, 1574, 1455, 1040 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.80 [m, 9 H, $(CH_2)_4$ + CHCO], 3.29 (br s, 1 H, OH), 3.60–4.10 (m, 5 H, CHN + CH_2O + NH_2)

^{13}C NMR ($CDCl_3$): δ = 21.8, 24.4, 25.1, 32.6, 41.2, 51.4, 66.2.

MS: *m*/*z* (%) = 129 (30) [M$^+$], 112 (12) [M$^+$ – OH], 86 (60), 56 (100).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_7H_{15}NO$: 129.1154; found: 129.1173.

(±)-*cis*-*N*-[2-(Hydroxymethyl)cyclohexylcarbamoyl]-3-methoxy-2-propenamide (4a); Typical Procedure

A solution of 3-methoxyacryloyl isocyanate in benzene (1.08 g, 25 mL, 8.56 mmol) was added very slowly to a solution of amino alcohol **3** (1.10 g, 8.56 mmol) in DMF (32 mL) at –20 °C under Ar. This mixture was stirred overnight arriving slowly to r.t. The solvent was evaporated under vacuum below 40 °C (by forming an azeotropic mixture with EtOH–toluene), and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to give **4a**; yield: 600 mg (53%); mp 167–169 °C.

IR (KBr): 3432, 3228, 3101, 2928, 1672, 1613, 1566, 1152, 810 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.15–1.47 [m, 9 H, $(CH_2)_4$ + CHCO], 3.16–3.24 (m, 1 H, *H*CHO), 3.32–3.47 (m, 1 H, HC*H*O), 3.70 (s, 3 H, OCH_3), 4.10–4.21 (m, 1 H, OH), 4.29–4.31 (m, 1 H, CHN), 5.21 (d, *J* = 12.2 Hz, 1 H, =CHO), 7.75 (d, *J* = 12.2 Hz, 1 H, =CHCO), 9.08 (s, 1 H, NH imide), 9.16 (d, 1 H, NH amide, *J* = 8.8 Hz).

MS: *m*/*z* (%) = 256 (3) [M$^+$], 226 (12) [M$^+$ – CH_2O], 183 (8), 145 (83) [M$^+$ – $C_7H_{11}O$], 128 (26), 65 (100).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{20}N_2O_4$: 256.1423; found: 256.1433.

***N*-(3-Ethoxy-2-propenoyl)-8-oxo-7-azabicyclo[4.2.0]octan-7-carboxamide (6); Typical Procedure**

According to the procedure described for the preparation of **4a**, a solution of 3-ethoxyacryloyl isocyanate (846 mg, 6.00 mmol) in anhyd benzene (20 mL) was treated with a solution of **1** (500 mg, 4.00 mmol) in anhyd benzene (5 mL). The solid residue was purified by FC (hexane–EtOAc, 9:1) to give **3** as a colorless oil which later became solid; yield: 393 mg (37%); mp 74 °C.

IR (KBr): 3305, 3121, 2973, 2871, 1766, 1732, 1683, 1607, 1397 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.52–1.63 [m, 4 H, $(CH_2)_2$], 1.80–2.22 (m, 4 H, $(CH_2)_2$], 3.37–3.46 (m, 1 H, CHC=O), 4.00 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.27–4.33 (m, 1 H, CHN), 6.32 (d, *J* = 12.3 Hz, 1 H, =CH), 7.77 (d, *J* = 12.3 Hz, 1 H, =CH), 8.90 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.7, 16.9, 19.0, 19.7, 23.3, 27.6, 51.1, 67.6, 98.5, 147.2, 164.9, 166.9, 171.4.

MS: *m*/*z* (%) = 266 (2) [M$^+$], 237 (10) [M$^+$ – C_2H_5], 221 (26) [M$^+$ – C_2H_5O], 109 (29), 99 ($C_5H_7O_2$, 100), 71 (64).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{18}N_2O_4$: 266.1267; found: 266.1274.

(±)-*cis*-*N*-[2-(Hydroxymethyl)cyclohexylcarbamoyl]-3-ethoxy-2-propenamide (4b); Typical Procedure

To a stirred solution of **3** (130 mg, 0.49 mmol) in anhyd MeOH (4 mL) at 0 °C was added $NaBH_4$ (64 mg, 1.69 mmol) portion wise. The mixture was stirred for 1 h at r.t. and the excess reducing reagent was destroyed by the addition of HOAc–MeOH (1:10). The solvent was evaporated under reduced pressure and the residue was purified by FC (EtOAc) to afford **4b**; yield: 100 mg (76%); mp 137–138 °C.

IR (KBr): 3430, 3224, 3119, 2925, 2856, 1674, 1606, 1564, 1164 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.96–1.39 [m, 4 H, $(CH_2)_2$], 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.57–1.89 (m, 5 H, $(CH_2)_2$ + CHCO], 3.16–3.41 (m, 2 H, C*H*$_2$OH), 3.99 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.15 (dd, *J* = 4.2, 6.4 Hz, 1 H, CHN), 4.28–4.32 (m, 1 H, OH), 5.23 (d, *J* = 12.2 Hz, 1 H, =CH), 7.67 (d, *J* = 12.2 Hz, 1 H, =CH), 9.17 (br s, 1 H, NH), 9.21 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.9, 21.6, 23.6, 25.5, 30.9, 43.7, 45.4, 64.2, 68.0, 97.7, 125.5, 156.6, 163.9.

MS: *m*/*z* (%) = 270 (0.5) [M$^+$], 240 (6) [(M + 1)$^+$ – CH_3O], 159 (62), 128 (26) [M$^+$ – $C_6H_8O_3N$], 99 (100) [$C_5O_2H_7$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{22}N_2O_4$: 270.1580; found: 270.1586.

(±)-*cis*/*trans*-(2-Hydroxy)cyclohexylmethanol (7); Typical Procedure

Anhydrous EtOH (75 mL) was cooled to –30 °C and treated with $NaBH_4$ (6.05 g, 160 mmol). To this solution was added dropwise a solution of ethyl cyclohexanone-2-carboxylate (5.46 g, 5.1 mL, 32.09 mmol) in EtOH (15 mL) so that the temperature did not rise to more than –20 °C. After stirring for 1 h at temperature between –20 °C and –30 °C the cooling bath was removed and stirring was continued at r.t. for another 20 h. Thereafter the reaction mixture was treated dropwise with glacial HOAc (25 mL). The resulting solution was concentrated under reduced pressure. The residue was treated with brine (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by FC using hexane–EtOAc (20:80) to give **7**; yield: 2.98 g (71%).

(±)-*trans*-(2-Hydroxy)cyclohexylmethyl Benzoate (8); Typical Procedure

Benzoyl chloride (605 mg, 0.5 mL, 4.31 mmol) was added to a solution of diol **7** (500 mg, 3.84 mmol) and Et_3N (1.8 mL) in anhyd CH_2Cl_2 (10 mL) under Ar. The mixture was stirred at r.t. for 3 h. The organic layer was washed with $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated under vacuum. The residue was purified by FC using hexane–EtOAc (85:15) to give first compound *cis*-**8**[22] and then compound *trans*-**8**; yield of **8**: 290 mg (32%).

IR (KBr): 3434, 2921, 2846, 1713, 1446, 1275, 1114, 708 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.28–1.35 (m, 2 H, CH_2), 1.58–1.90 [m, 5 H, $(CH_2)_2$ + *H*CH], 2.01–2.06 (m, 1 H, HC*H*), 2.64–2.66 (m, 1 H, C*H*CH$_2$OBz), 3.32–3.44 (m, 1 H, C*H*OH), 4.27 (dd, *J* = 11.2, 4.3 Hz, 1 H, *H*CHOBz), 4.70 (dd, *J* = 11.2, 4.7 Hz, 1 H, HC*H*OBz), 7.42–7.46 (m, 2 H, ArH), 7.54–7.61 (m, 1 H, ArH), 8.03–8.07 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 25.2, 25.7, 28.7, 35.3, 45.9, 67.1, 71.5, 128.8, 130.0, 130.4, 133.5, 166.8.

MS: *m*/*z* (%) = 235 (100) $[M + 1]^+$, 217 (92) $[(M + 1)^+ – H_2O]$, 123 (45), 105 (86), 95 (64) $[C_7H_5O]$.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1256.

(±)-*cis*-1-[2-(Benzoyloxymethyl)cyclohexyl]-*N*^{3}-benzoyluracil (5b); Typical Procedure

N^3-Benzoyluracil (1.14 g, 5.30 mmol) was added to a solution of Ph_3P (1.39 g, 5.30 mmol) and diethyl azodicarboxylate (885 mg, 0.8 mL, 5.30 mmol) in anhyd THF (40 mL) at 0 °C, and the mixture was stirred for 10 min. Alcohol **8** (999 mg, 4.27 mmol) in anhyd THF (4 mL) was added dropwise, and the mixture was stirred overnight at r.t. The solvent was evaporated under vacuum and the residue purified by FC (hexane–EtOAc, 8:2) to give **5b**; yield: 320 mg (18%); mp 84–86 °C.

IR (KBr): 3079, 2927, 2851, 1747, 1704, 1660, 1443, 1270, 1107, 711 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.30–2.01 [m, 8 H, $(CH_2)_4$], 2.70–2.90 (m, 1 H, C*H*CH_2), 4.35–4.41 (m, 1 H, *H*CHO), 4.49–4.53 (m, 1 H, HC*H*O), 4.61–4.66 (m, 1 H, CHN), 5.65 (d, *J* = 8.1 Hz, 1 H, H-5), 7.29–8.00 (m, 11 H, 10 ArH + H-6).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{25}H_{24}N_2O_5$: 432.1685; found: 432.1672.

(±)-*cis*-1-[2-(Hydroxymethyl)cyclohexyl]uracil (5a); Typical Procedure

A mixture of imide **4a** (600 mg, 2.68 mmol) and 2 M H_2SO_4 (18 mL) was refluxed for 3 h. After cooling, it was neutralized with 2 M NaOH, the solvent was evaporated under vacuum (by forming an azeotropic mixture with EtOH–toluene) and the resulting residue was purified by FC ($CHCl_3$–MeOH, 98:2) to give **5a**; yield: 450 mg (86%); mp 188–190 °C. The same procedure was used to get **5a** from **4b** (600 mg, 2.26 mmol); yield: 450 mg (90%). Compound **5a** was also obtained in 60% yield from **5b** by hydrolysis of the benzoyl derivative **5b** with 1 M MeONa–MeOH at r.t. overnight.

IR (KBr): 3383, 3010, 2922, 2855, 1698, 1281 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.25–2.08 [m, 9 H, $(CH_2)_4$ + CHCO], 3.30–3.35 (m, 1 H, *H*CHO), 3.44–3.49 (m, 1 H, HC*H*O), 4.32–4.38 (m, 2 H, CHN + OH), 5.50 (d, *J* = 8.9 Hz, 1 H, H-5), 7.45 (d, *J* = 8.9 Hz, 1 H, H-6), 11.10 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 19.8, 25.3, 25.8, 26.8, 38.8, 57.3, 58.1, 100.2 (5), 144.0 (6), 151.4 (2), 164.6 (4).

MS: *m*/*z* (%) = 224 (32) $[M^+]$, 193 (16) $[M^+ – CH_3O]$, 150 (9), 113 (100) $[M^+ – C_7H_{11}O]$, 95 (24), 79 (22), 67 (23), 63 (22).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{11}H_{16}N_2O_3$: 224.1161; found: 224.1163.

X-Ray Crystal Analysis of 5a

Formula: $C_{11}H_{16}N_2O_3$. *Crystal Data:* Monoclinic, space group Cc, *a* = 17.481 (4), *b* = 15.673 (4), *c* = 18.203 (4) Å, β = 115.64 (5)°, V = 4496.3 (18) Å^3, Z = 16, Dc = 1. Mg m^{-3}, F(000) = 1920, μ = 0.097 mm^{-1}, T = 293 K. *Data collection*: Structure of a single crystal of ca. 0.47 × 0.19 × 0.08 mm was performed on a Bruker Smart CCD-1000 area detector diffractometer using graphite monochromated MoK radiation, λ = 0.71073 Å. Absorption corrections were carried out using SADABS.[23] The structure was resolved by direct methods. *Structure Refinement*: The structure was refined by a full-matrix least-squares based on F^2, using anisotropic displacement parameters for all non-hydrogen atoms[24] to *wR*2 = 0.1913, *R*1 = 0.0982 for 286 parameters and 5052 independent reflections; max. Δρ = 0.413 eÅ^{-3}, S = 0.946. Hydrogen atoms were included using a riding model or rigid methyl groups.

(±)-*cis*-1-[2-(Hydroxymethyl)cyclohexyl]-5-bromouracil (9); Typical Procedure

NBS (55 mg, 0.31 mmol) in HOAc (3.5 mL) was added to a solution of the uracil derivative **5a** (63 mg, 0.28 mmol) in HOAc (2.5 mL) at r.t. The mixture was heated at 80 °C for 1 h, the solvent was evaporated (azeotropic mixture with EtOH–toluene), and the residue was re-dissolved in 0.5 M NaOH and neutralized with 0.5 M HCl. The solvent was evaporated under vacuum (azeotropic mixture with EtOH–toluene) and the residue was chromatographed on silica gel [hexane–*i*-PrOH, 90:10] to give **9**; yield: 38 mg (45%); mp 174 °C.

IR (KBr): 3500, 3283, 3109, 2957, 1658, 1614 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.29–1.87 [m, 7 H, $(CH_2)_3$ + *H*CH], 2.05–2.20 (m, 2 H, HC*H* + CHCO), 3.40–3.60 (m, 2 H, CH_2O), 4.29–4.39 (m, 1 H, OH), 4.44–4.46 (m, 1 H, CHN), 7.98 (s, 1 H, H-6), 11.75 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.3, 25.3, 26.1, 27.5, 38.9 (2′), 57.9 (1′), 58.6 (7′), 94.5 (5), 143.2 (6), 150.7 (2), 159.5 (4).

MS: *m*/*z* (%) = 304 (2) $[M + 2]^+$, 302 (6) $[M^+]$, 193 (32) $[(M + 2)^+ – C_7H_{11}O]$, 192 (32) $[(M + 2)^+ – C_7H_{12}O]$, 191 (31) $[M^+ – C_7H_{11}O]$, 190 (31) $[M^+ – C_7H_{12}O]$, 158 (19), 95 (61), 58 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{11}H_{15}BrN_2O_3$: 302.0266; found: 302.0269.

(±)-*cis*-1-[2-(Hydroxymethyl)cyclohexyl]-5-chlorouracil (10); Typical Procedure

NCS (32 mg, 0.24 mmol) in HOAc (1.8 mL) was added to a solution of the uracil derivative **5a** (48 mg, 0.21 mmol) in HOAc (2.9 mL) at r.t. The mixture was heated at 80 °C for 6 h, the solvent was evaporated (azeotropic mixture with EtOH–toluene), and the residue was re-dissolved in 0.5 M NaOH and neutralized with 0.5 M HCl. The solvent was evaporated under vacuum (azeotropic mixture with EtOH–toluene) and the residue was chromatographed on silica gel [hexane–*i*-PrOH, 96:4] to give **10**; yield: 28 mg (51%); mp: 193–195 °C.

IR (KBr): 3205, 3068, 2943, 1772, 1205, 1045 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.28–1.86 [m, 7 H, $(CH_2)_3$ + *H*CH], 2.02–2.18 (m, 2 H, HC*H* + CHCO), 3.41–3.50 (m, 2 H, CH_2O), 4.31–4.35 (m, 1 H, CHN), 4.40 (t, *J* = 4.8 Hz, 1 H, OH), 7.89 (s, 1 H, H-6), 11.07 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.3, 25.2, 26.1, 27.5, 40.9 (2′), 57.8 (1′), 58.6 (7′), 105.9 (5), 140.9 (6), 150.5 (2), 159.4 (4).

MS: *m*/*z* (%) = 260 (2) $[M + 2]^+$, 258 (7) $[M^+]$, 149 (52) $[(M + 2)^+ - C_7H_{11}O]$, 147 (14) $[M^+ – C_7H_{11}O]$, (6) $[(M + 2)^+ – C_7H_{12}O]$, 111 (54) $[C_7H_{11}O]$, 109 (60), 97 (89), 95 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{11}H_{15}ClN_2O_3$: 258.0771; found: 258.0777.

(±)-*cis*-1-[2-(Hydroxymethyl)cyclohexyl]-5-iodouracil (11); Typical Procedure

Iodine monochlorure (41.4 mg, 0.25 mmol) was added to a stirred solution of **5a** (38 mg, 0.17 mmol) in MeOH (4 mL). The resulting solution was heated at 50 °C for 1.5 h. The solution was cooled and decolorized by careful washing with the minimum required volume of 2% $NaHSO_3$–H_2O solution. The solvent was evaporated under vacuum and the residue purified by FC [hexane–*i*-PrOH, 98:2]; yield: 12 mg (29%); mp: 189–191 °C.

IR (KBr): 3432, 3045, 2932, 2841, 1716, 1670, 1278, 1051 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.43–1.99 [m, 7 H, $(CH_2)_3$ + *H*CH], 2.23–2.33 (m, 2 H, HC*H* + CHCO), 3.51–3.60 (m, 1 H, *H*CHO), 3.68–

3.88 (m, 1 H, HC*H*O), 4.47–4.51 (m, 1 H, CHN), 4.57 (t, *J* = 5.1 Hz, 1 H, OH), 8.05 (s, 1 H, H-6), 11.89 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.2, 25.3, 26.2, 27.3, 57.7 (1′), 58.4 (7′), 67.9, 74.7, 147.6 (6), 151.1 (2), 160.9 (4).

MS: *m*/*z* (%) = 350 (53) [M^+], 239 (43) [$M^+ - C_7H_{11}O$], 238 (90) [$M^+ - C_7H_{12}O$], 195 (91), 181 (83), 95 (100), 83 (19), 85 (46).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{11}H_{15}IN_2O_3$: 350.0126; found: 350.0127.

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