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Regioselective synthesis of O^2- and O^6-cyclopyrimidine nucleoside analogues

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

[a]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain*
[b]*Departamento de Química Farmacéutica, Facultad de Farmacia, Universidad de Salamanca, 37008 Salamanca, Spain*

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Abstract—Regioselective synthesis of two new series of cyclonucleoside analogues from the 1,2-carbonucleoside of uracil **1a**: O^2,7′-cyclonucleosides (**3a–c**) and O^6,7′-cyclonucleosides (**4a–c**), analogues of pyrimidine (cyclohexane derivatives) is reported. Synthesis of O^2-cyclonucleoside analogues was performed by activation of the hydroxymethyl group of carbocyclic moiety and using the carbonyl group at position 2 of the heterocyclic base as a nucleophile. Synthesis of O^6-cyclonucleoside analogues was achieved by nucleophilic attack of the 7′-hydroxyl group on the electron-deficient 6-position and subsequently dehydrohalogenation in basic conditions.

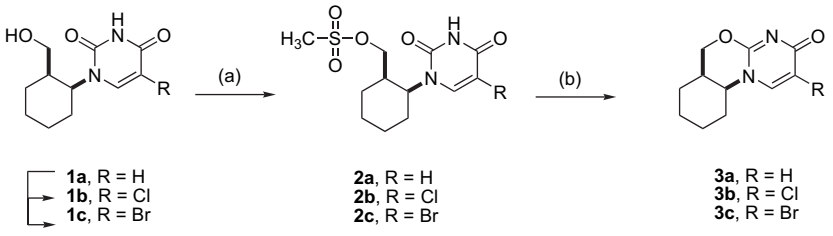
1. Introduction

Cyclic analogues of nucleosides are compounds in which the additional cycle is formed between the sugar ring and the nitrogen base. From the initial discovery by Todd and co-workers[1] many efforts have been focused on this area. Additionally, the discovery of antitumoral activity of O^2,7′-cyclocytidine and its analogues[2,3] has accelerated the synthetic studies of cyclonucleosides, specially in the pyrimidine series.[4–7]

Cyclonucleosides are also important due to their versatility as synthetic precursor of substituted derivatives on the pyrimidine base,[8,9] as well as on the carbohydrate ring.[10,11]

Furthermore, the shaping of O-bridge between the hydroxymethyl group and the position 2 or 6 of the pyrimidine allows the preparation of analogues in which the rotation of the heterocyclic base around the glycosidic bond is restricted and fixed in *syn* and *anti* conformation, respectively, important aspect as far as the enzyme–substrate interaction and their implication in the pharmacological activity is concerned.[12,13]

For some years, we have been interested in the synthesis and study of 1,2-disubstituted analogues of dideoxy-nucleosides, which have the hydroxymethyl group and the heterocyclic base attached to contiguous positions of the carbocycle (OTCs), being the pseudosugar a cyclopentane, cyclopentene, or cyclohexene ring. Some of them have shown an interesting profile of activity against the proliferation of murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt4/C8 and CEM/0).[14–17] Previously, we have reported the synthesis of 1-[2-(hydroxymethyl)cyclohexyl]-pyrimidine analogues of nucleosides **1a–c**.[18] In the present paper, we report the synthesis of O^2- (compounds **3a–c**, Scheme 1) and O^6-cyclonucleoside analogues (compounds



Scheme 1. Reagents and conditions: (a) $ClSO_2CH_3$, rt, **2a**: 55%, **2b**: 62%, **2c**: 57%; (b) DBU–acetonitrile, reflux, **3a**: 89%, **3b**: 93%, **3c**: 89%.

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* Corresponding author. Fax: +34 981 594912; e-mail: qovina@usc.es

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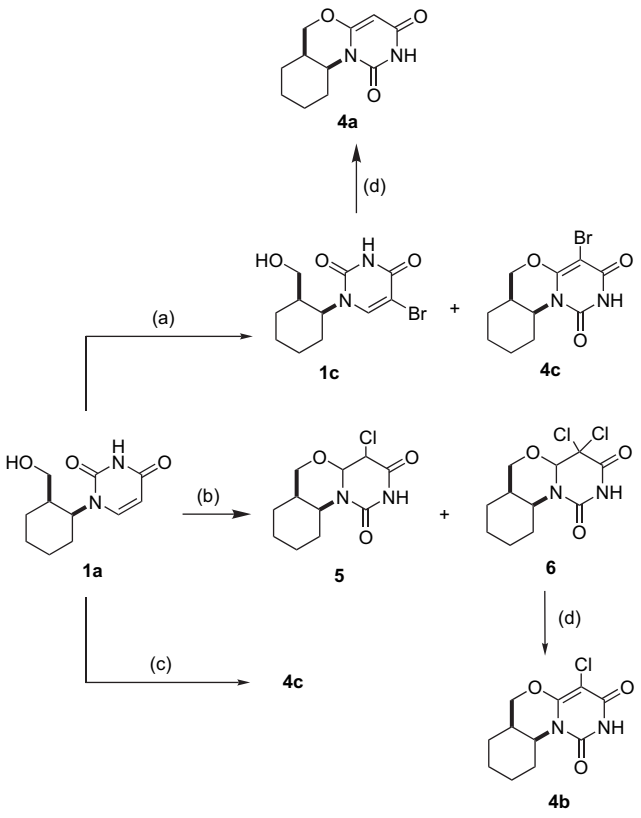
4a–c, Scheme 2) of the corresponding compounds above mentioned with H, Cl, or Br on the 5-position of the pyrimidine nucleus. Precursor compound for all of them was (±)-*cis*-1-[2-(hydroxymethyl)cyclohexyl]uracil (**1a**) and cyclization, in a regioselective and efficient way, could be forced at position 2 or 6 of the pyrimidine ring.



Scheme 2. Reagents and conditions: (a) NBS/HOAc, 80 °C, **1c**: 45%, **4c**: 10%; (b) NCS/DMF, rt, **5**: 5%, **6**: 92%; (c) NBS/DMF, rt, **4c**: 83%; (d) EtONa/EtOH, reflux, **4a**: 38%, **4b**: 31%.

Although some cyclonucleosides analogues had been synthesized previously, cyclocarbanucleoside analogues of pyrimidine are not so frequent in the literature.[19–21] Cyclization in our compounds is helped due to contiguous position of the hydroxymethyl group and the heterocyclic base, affording a stable six-membered ring.

2. Results and discussion

The synthesis of O^2,7′-cyclonucleosides was performed by activation of the hydroxymethyl group of carbocyclic moiety using the carbonyl group at position 2 of the heterocyclic base as a nucleophile. This is possible, because the 2-carbonyl group is close to the atom of carbon, on the carbocyclic ring, which is linked to the leaving group. Activation of the hydroxymethyl group was achieved by treatment of the corresponding derivative of uracil **1a**, 5-chlorouracil **1b**, and 5-bromouracil **1c** with methylsulphonyl chloride affording **2a**, **2b**, and **2c** in 55, 62, and 57% yield, respectively. Finally, the treatment of these intermediates with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile afforded the compounds **3a–c** in approximately 90% yield for all of them.

The O^6,7′-cyclonucleosides were achieved in different ways depending on the substituent at position 5. Treatment of **1a** with 1.2 equiv of *N*-bromosuccinimide (NBS) in acetic acid gave a mixture of 5-bromouracil derivative **1c** and an unexpected compound, which was identified as O^6-cyclonucleoside **4c** in 10% yield. A plausible mechanism for the formation of **4c** could be the following one: an additional bromination at the 5-position of the intermediate **1c** would be initiated by an electrophilic attack of the bromonium cation on the 5,6-double bond of the pyrimidine base, followed by nucleophilic attack of the 7′-hydroxyl group on the electron-deficient 6-position, which would result in the intramolecular 6,7′-O-cyclization. Finally, dehydrohalogenation took place in the basic conditions used to neutralize the acetic acid in the reaction.[9]

However, when compound **1a** was treated with *N*-chlorosuccinimide (NCS) in the conditions above mentioned, formation of cyclonucleoside **4b** was not observed. Then to afford **4b**, the conditions were changed using an excess of NCS (3 equiv) in DMF the 5,5-dichlorocyclonucleoside **6** could be isolated. One more compound, identified as **5** was additionally isolated in the same reaction, this compound subjected again to the same reaction conditions afforded **6** quantitatively after 5 h. Finally, dehydrohalogenation of **6** to afford **4b** was performed by treatment with EtONa. In sight of this result, **4c** was also prepared in only one step starting from **1a** with NBS (3 equiv) and DMF in 83% yield, without observing the presence of dibromo precursor.

The O^6-cyclonucleoside **4a** was obtained by reaction of **1c** with alkoxide (EtONa/EtOH) in 38% yield. The reaction proceeded via dihydropyrimide intermediate formed as a result of nucleophilic attack of the 2′-hydroxymethyl group on C-6 of the pyrimidine ring.

Cyclic formation at different positions has been determined by spectroscopic analysis. O^2,7′-Cyclonucleosides show the signals corresponding to the vinylic protons in the ^{1}H NMR experiment (**3a**: δ 5.84 and 7.60) while in the ^{13}C NMR experiment the signal corresponding to the carbonyl at position 2 of **2a** is shifted from δ 150.7 to 154.5 for **3a**, the shift for α,β-unsaturated carbonyl (4-position) let us to confirm that cyclization takes place in 2-position as we previously expected instead of 4-position. For O^6,7′-cyclonucleosides, the signals corresponding to the vinylic protons in the ^{1}H NMR experiment have disappeared. On the other hand, the mass spectrum of **3a–c** shows that H_2O is lost in relation to the acyclic precursors, whereas for **4a–c**, M^+ ion peaks are 2 units lower than for the corresponding **1a–c**.

In conclusion, a suitable methodology has been developed and it will let to synthesize a large series of this type of cyclic analogues of OTCs for their pharmacological evaluation.

3. Experimental

3.1. General

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 (ν in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX (250 MHz) and Bruker AMX (500 MHz) spectrometers, using TMS as an internal standard (chemical shifts as δ in parts per million, J in hertz). 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).

3.2. (±)-*cis*-1-[2-[[(Methylsulfonyl)oxy]methyl]cyclohexyl]uracil (2a)

Compound **1a**[14] (130 mg, 0.58 mmol) was dissolved in pyridine (8 mL) and CH_3SO_2Cl (0.08 mL) was dropwise added at 0 °C. Then, the reaction was stirred at room temperature for 2 h. As soon as the reaction had finished, the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to give **2a** (96 mg, 55%) as a white solid. Mp 164 °C. IR (KBr): 3330, 2959, 2852, 1676, 1330, 1142, 932, 864. ^1H NMR ($CDCl_3$) δ: 1.11–2.09 (m, 8H, $(CH_2)_4$), 2.72 (m, 1H, C*H*-CH_2-O), 2.96 (s, 3H, CH_3), 4.29 (m, 2H, CH_2-O), 4.60 (m, 1H, CH-N), 5.73 (d, 1H, H-5, J=8.1 Hz), 7.24 (d, 1H, H-6, J=8.1 Hz), 8.41 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 25.7, 29.7, 31.2, 36.1, 37.6, 56.8, 66.3, 101.6, 141.4, 150.7, 162.5. MS *m/z* (%): 302 (M^+, 10), 223 ($M^+-CH_3SO_2$, 23), 207 ($M^+-CH_3SO_3$, 9), 111 ($N_2C_4O_2H_3$, 17), 95 (100).

3.3. (±)-*cis*-5-Chloro-1-[2-[[(methylsulfonyl)oxy]-methyl]cyclohexyl]uracil (2b)

According to the procedure described for **2a** from **1a**, reaction of **1b** (25 mg, 0.09 mmol) afforded **2b** (20 mg, 62%) as a white solid. Mp 186–189 °C. IR (KBr): 3114, 2955, 2830, 2795, 1659, 1330, 1102, 926. ^1H NMR ($CDCl_3$) δ: 1.20–2.05 (m, 8H, $(CH_2)_4$), 2.68 (m, 1H, C*H*-CH_2-O), 2.88 (s, 3H, CH_3), 4.25 (m, 2H, CH_2-O), 4.52 (m, 1H, CH-N), 7.43 (s, 1H, H-6), 8.22 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 25.2, 29.1, 29.4, 32.4, 37.7, 63.9, 76.2, 110.6, 143.9, 148.2, 158.5. MS *m/z* (%): 336 (M^+, 3), 240 (6), 205 (16), 147 (12), 95 (100).

3.4. (±)-*cis*-5-Bromo-1-[2-[[(methylsulfonyl)oxy]-methyl]cyclohexyl]uracil (2c)

Prepared from **1c** (42 mg, 0.14 mmol) in an analogous way to **2a** from **1a**, giving **2c** (30 mg, 57%). Mp 181–184 °C. IR (KBr): 3114, 2955, 2830, 2795, 1659, 1330, 1102, 926. ^1H NMR (DMSO-d_6) δ: 1.25–2.20 (m, 8H, $(CH_2)_4$), 2.17 (m, 1H, C*H*-CH_2O), 3.15 (s, 3H, CH_3), 4.33 (m, 3H, CH_2-O+ CH-N), 7.98 (s, 1H, H-6), 11.78, (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.1, 24.8, 25.8, 27.2, 36.4, 36.9, 57.4, 68.5, 95.4, 142.4, 150.8, 159.5. MS *m/z* (%): 382 ([M+2]$^+$, 21), 380 (M^+, 25), 303 ($M^+-CH_3SO_2$, 7), 286 ($M^+-CH_4SO_3$, 45), 205 (75), 190 ($C_4N_2O_2H_2Br$, 34), 149 (26), 95 (100).

3.5. (±)-*cis*-3*H*,6*H*-6a,7,8,9,10,10a-Hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3a)

Compound **2a** (30 mg, 0.10 mmol) was dissolved in acetonitrile (3.3 mL) and DBU (0.22 mL) was added. The reaction was refluxed for 1.5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 95:5) to give **3a** (18 mg, 89%) as a white solid. Mp 207–208 °C. IR (KBr): 2886, 2761, 1631, 1608, 1511, 1438, 1295, 1250, 1182, 1080, 1034. ^1H NMR (DMSO-d_6) δ: 1.30–1.92 (m, 9H, $(CH_2)_4$+C*H*-CH_2-O), 4.03 (q, 1H, CH-N, J=5.3 Hz), 4.31 (dd, 1H, *H*CH-O, J=3.6 and 11.2 Hz), 4.55 (t, 1H, HC*H*-O, J=11.2 Hz), 5.84 (d, 1H, C*H*=CH, J=7.4 Hz), 7.60 (d, 1H, CH=C*H*, J=7.4 Hz). ^{13}C NMR (DMSO-d_6) δ: 20.3, 23.5, 24.7, 28.4, 29.8, 57.8, 66.5, 109.8, 142.3, 154.5, 166.0. MS *m/z* (%): 206 (M^+, 99), 178 (8), 150 (20), 95 (100), 70 (73), 67 (54). HRMS (EI) (M^+) calcd for $C_{11}H_{14}N_2O_2$: 206.1055, found: 206.1058.

3.6. (±)-*cis*-2-Chloro-3*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3b)

Prepared from **2b** (30 mg, 0.09 mmol) in an analogous way to **3a** from **2a**, affording **3b** (20 mg, 93%). Mp 209–211 °C. IR (KBr): 3001, 2864, 2773, 1631, 1499, 1466, 1307, 1233, 1159, 943. ^1H NMR ($CDCl_3$) δ: 1.25–2.10 (m, 8H, $(CH_2)_4$), 2.70 (m, 1H, C*H*-CH_2-O), 3.87 (m, 1H, CH-N), 4.30 (dd, 1H, *H*CH-O, J=4.6 and 11.2 Hz), 4.53 (t, 1H, HC*H*-O, J=11.2 Hz), 7.29 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 20.4, 23.3, 24.8, 29.3, 30.0, 59.0, 66.8, 118.5, 137.0, 153.5, 165.8. MS *m/z* (%): 242 ([M+2]$^+$, 3), 240 (M^+, 31), 205 (45), 95 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{15}ClN_2O_2$: 242.0822, found: 242.0820.

3.7. (±)-*cis*-2-Bromo-3*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3c)

Prepared from **2c** (30 mg, 0.09 mmol) in an analogous way to **3a** from **2a** affording **3c** (20 mg, 89%). Mp 207–209 °C. IR (KBr): 2886, 2807, 1614, 1489, 1432, 1273, 1227, 1142, 920. ^1H NMR ($CDCl_3$) δ: 1.39–2.12 (m, 8, $(CH_2)_4$), 2.63 (m, 1H, C*H*-CH_2-O), 3.94 (m, 1H, CH-N), 4.39 (dd, 1H, *H*CH-O, J=4.8 and 11.3 Hz), 4.53 (t, 1H, HC*H*-O, J=11.3 Hz), 7.42 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 22.8, 23.8, 25.3, 29.7, 30.5, 59.5, 67.0, 108.2, 139.7, 153.8, 159.5. MS *m/z* (%): 287 ([M+2]$^+$, 3), 286 ([M+1]$^+$, 25), 285 (M^+, 4), 284 (25), 205 (46), 149 (15), 95 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{13}BrN_2O_2$: 284.0160, found: 284.0157.

3.8. (±)-*cis*-4-Bromo-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4c)

NBS (55 mg, 0.31 mmol) in AcOH (3.5 mL) was added to a solution of the uracil derivative **1a** (63 mg, 0.28 mmol) in OHAc (2.5 mL) at room temperature. The mixture was heated at 80 °C for 1 h, the solvent was evaporated (azeotropic mixture with EtOH–toluene), and the residue was redissolved in 0.5 M NaOH and neutralized with 0.5 M HCl. The solvent was evaporated under vacuum (azeotropic mixture with EtOH–toluene) affording a mixture of **1c**[14] and **4c**, which was isolated by FC [hexane–(2-propanol), 9:1] to give **4c** (9 mg, 10%) as a white solid. Mp 246 °C. IR (KBr): 3182, 3091, 2977, 1784, 1705. ^1H NMR (DMSO-d_6) δ: 1.10–1.81 (m, 8H, $(CH_2)_4$), 1.95 (m, 1H, C*H*-CH_2-O), 4.18 (m, 1H, *H*CH-O-), 4.28 (m, 1H, HC*H*-O), 4.50 (t, 1H, CH-N-, J=12.6 Hz), 10.94 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 19.9, 24.2, 25.2, 26.0, 29.7, 51.6, 67.6, 76.1, 148.9, 156.4, 159.5. MS *m/z* (%): 302 ([M+2]$^+$, 27), 300 (M^+, 27), 149 (34), 95 (100), 80 (6). HRMS (EI) (M^+) calcd for $C_{11}H_{13}BrN_2O_3$: 300.0110, found: 300.0070. Compound **4c**

was also obtained in 83% yield from **1a** (1 mmol) and NBS (3 mmol) in DMF (25 mL) at room temperature for 5 h.

3.9. (±)-*cis*-1*H*,6*H*-6a,7,8,9,10,10a-Hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4a)

A solution of 5-bromopyrimidine nucleoside **1c** (36 mg, 0.12 mmol) in 1 N EtONa/EtOH (2 mL) was refluxed for 17 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to afford **4a** (10 mg, 38%) as a white solid. Mp 234 °C. IR (KBr): 3003, 2932, 2850, 1714, 1644, 1591, 1485, 1244. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.87 (m, 7H, $(CH_2)_3$+*H*CH), 2.19 (m, 1H, HC*H*), 2.21 (m, 1H, C*H*-CH_2-O), 4.23 (dd, 1H, CH-N, J=5.4 and 11.0 Hz), 4.45 (m, 2H, CH_2-O), 5.1 (s, 1H, CH═), 8.5 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.5, 24.6, 26.2, 26.9, 30.7, 51.2, 66.6, 82.0, 150.1, 160.0, 163.6. MS *m*/*z* (%): 222 (M^+, 100), 192 (M^+-CH_2O), 150 (5), 129 (30), 95 (72), 69 (71). HRMS (EI) (M^+) calcd for $C_{11}H_{14}N_2O_3$: 222.1004, found: 222.1001.

3.10. (±)-*cis*-4-Chloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6*a*][3,1]benzoxazin-1,3-(2*H*,4*H*)-dione (5) and (±)-*cis*-4,4-dichloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6*a*][3,1]benzoxazin-1,3-(2*H*,4*H*)-dione (6)

To a solution of **1a** (54 mg, 0.24 mmol) in dry DMF (2 mL) was added NCS (96 mg, 0.72 mmol) and the solution was stirred at room temperature for 5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (hexane–EtOAc, 8:2) to afford **5** (4 mg, 5%) and **6** (64 mg, 92%), both of them, as white solids.

Compound **5**: mp 242 °C. IR (KBr): 3156, 3070, 1777, 1691, 1371, 1291, 1184, 842, 815, 639. ^{1}H NMR ($CDCl_3$) δ: 1.25–2.20 (m, 9H, $(CH_2)_4$+C*H*-CH_2-O), 3.85 (dd, 1H, *H*CH-O, J=11.7 and 4.9 Hz), 4.11 (t, 1H, HC*H*-O, J=11.9 Hz), 4.52–4.72 (m, 1H, CH-N), 4.90 (d, 1H, CH-Cl, J=8.0 Hz), 5.01 (d, 1H, CH-O, J=8.0 Hz), 10.90 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.7, 22.8, 25.1, 26.5, 33.1, 51.9, 54.6, 66.4, 82.0, 150.9, 164.4. MS *m*/*z* (%): 258 (M^+, 37), 223 (2), 140 (34), 95 (18), 84 (31), 78 (32), 76 (87), 66 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{15}ClN_2O_3$: 258.0771, found: 258.0776.

Compound **6**: mp 296 °C. IR (KBr): 3027, 2921, 2846, 1745, 1664, 1440, 1269, 1114, 879, 666. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.91 (m, 8H, $(CH_2)_4$), 2.33 (m, 1H, C*H*-CH_2-O), 3.95 (dd, 1H, *H*CH-O, J=11.7 and 4.9 Hz), 4.11 (t, 1H, HC*H*-O, J=11.9 Hz), 4.52–4.72 (m, 1H, CH-N), 5.12 (s, 1H, CH-O), 8.25 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.3, 22.5, 24.6, 25.9, 32.3, 52.3, 54.9, 79.8, 82.9, 149.9, 160.8. MS *m*/*z* (%): 294 ([M+2]$^+$, 21), 292 (M^+, 37), 257 (7), 140 (100), 95 (91), 67 (70). HRMS (EI) (M^+) calcd for $C_{11}H_{14}Cl_2N_2O_3$: 292.0381, found: 292.0368.

3.11. (±)-*cis*-4-Chloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4b)

A solution of **6** (70 mg, 0.24 mmol) in 1 N EtONa/EtOH (4 mL) was refluxed for 5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to afford **4b** (19 mg, 31%) as a white solid. Mp 277 °C. IR (KBr): 2932, 1713, 1654, 1584, 1483, 1184, 853, 655. ^{1}H NMR ($CDCl_3$) δ: 1.52–1.80 (m, 7H, $(CH_2)_3$+*H*CH), 2.13 (m, 1H, HC*H*), 2.15 (m, 1H, C*H*-CH_2-O), 4.36–4.41 (m, 2H, CH_2-O), 4.45 (t, CH-N, J=12.6 Hz), 8.1 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 24.5, 26.0, 26.9, 30.5, 52.1, 67.6, 79.23, 148.1, 158.1, 159.70. MS *m*/*z* (%): 258 ([M+2]$^+$, 11), 256 (M^+, 45), 103 (44), 95 (100), 83 (19). HRMS (EI) (M^+) calcd for $C_{11}H_{13}ClN_2O_3$: 256.0615, found: 256.0613.

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