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An efficient approach to homochiral indane nucleosides

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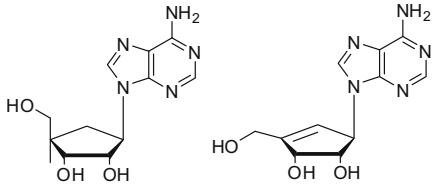
ABSTRACT

A series of new chiral 6-substituted purinyl and 8-aza-purinyl carbonucleosides based on indanol were synthesized from the commercially available (1*R*,2*S*)-1-amino-2-indanol and (1*S*,2*R*)-1-amino-2-indanol based on a well-known methodology.

1. Introduction

Over the past two decades, the search for new antitumoural and antiviral therapeutic agents has focused on carbocyclic analogues of nucleosides (CANs),[1–3] in which the sugar ring oxygen has been replaced by a methylene group. This modification endows them with greater biostability than nucleosides by making them more resistant to the hydrolytic action of phosphorylases.[4]

The first member of this class of compounds was the carbocyclic analogue of adenosine described by Shearly in 1966[5] and interest was spurred by the discovery of the natural carbocyclic nucleosides aristeromycin[6] and neplanocin A.[7]



Aristeromycin Neplanocin A

Since then, many synthetic compounds with antiviral or anticancer activity have been prepared, many of which are used in the clinical and although certain limited structure–activity relationships have been inferred for CANs there are as yet no general rules of this kind so, several synthetic CANs have been prepared.[8,9] Moreover, there still remain some problems with these drugs such as the development of drug resistance, cytotoxicity and enzymatic instability in vivo, which has led to the search for new nucleoside analogues with more potent activity and lower side-effects.[10]

Continuing our interest in the synthesis of indane structure derivatives with antiviral activity[11] we have focused our attention on the synthesis of an emergent class of mimetic carbonucleosides in which the sugar unit is replaced by an indanol core. In this way the lipophilicity of the CANs is enhanced and facilitates its access to the central nervous system, an important reservoir of the HIV and other viruses.[12]

Herein, we report the synthesis of homochiral indane carbonucleosides of 2-amino-6-substituted (chlorine or hydroxyl) purine and 8-azapurine **A** and 6-substituted (chlorine or hydroxyl) purine and 8-azapurine **B**, all of which were obtained from the commercially available (1*R*,2*S*)- and (1*S*,2*R*)-*cis*-1-amino-2-indanols **1** and **2**, respectively, as chiral starting materials (Fig. 1).

2. Results and discussion

Carbocyclic nucleosides were synthesized by construction of an adenine or 8-azaadenine on the amine group of enantiomerically pure amino alcohol **1** and **2**, using a classical approach to carbocyclic analogues of nucleosides (Scheme 1).[13,14]

Compound **1** was condensed with 2-amino-4,6-dichloropyrimidine affording compound **3**. An aza-derivative **4** was then obtained by reaction between **3** and 4-chlorobenzendiazonium. Reduction of **4** with zinc in acetic acid gave the triaminopyrimidinyl derivative **5.** Compound **5** was treated with triethylorthoformate in hydrochloric acid to give compound **6,** which was treated with sodium hydroxide to give nucleophilic substitution of the 6-chloro substituent by the hydroxy group to give **7.** Otherwise, the triazole ring of the 8-azapurinyl compound **8** was formed by diazotization of **5** with sodium nitrite in hydrochloric acid. The intermediate diazonium salt obtained spontaneously cyclized to analogue **8.** Compound **8** was treated with sodium hydroxide to afford **9** (Scheme 1).[15]

In a similar way the enantiomeric compounds of **6**–**9** named **13**–**16** were prepared from (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **2** (Scheme 1).

Condensation of **1** with 5-amino-4,6-dichloropyrimidine in refluxing *n*-butanol containing triethylamine afforded **17**. Then to form the imidazole ring of the purinyl analogues, compound **17** was treated with triethylorthoformate in hydrochloric acid giving compound **18**. Compound **18** was converted into the hydroxyl

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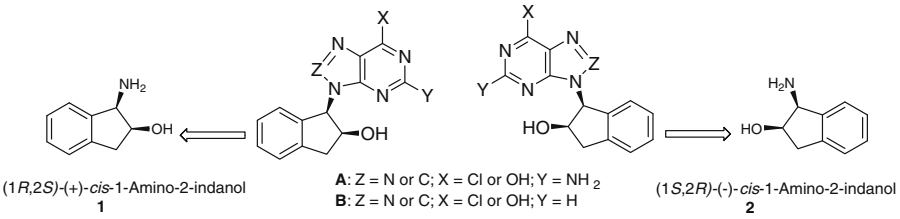


Figure 1.

derivative **19** by treatment with 0.25 M NaOH at reflux over 6 h. A triazole ring was also formed from **17** by intramolecular reaction of the diazonium salt of the primary amine group with sodium nitrite in an acidic medium, giving a highly unstable compound **20** [not isolated]. This compound was converted into the 8-aza purine derivative **21** by reaction with 1 M hydrochloric acid and refluxed for 1 h (Scheme 2).[15]

For the preparation of the enantiomeric nucleoside analogues **23–26** the same reaction sequence was repeated starting from (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **2** (Scheme 2).

The compounds obtained were characterized by spectroscopic methods, and the structure of compound **3** was further confirmed by the aid of HMQC experiment. With this experiment it was possible to assign the hydrogen atoms of the O*H* group and the group N*H* unequivocally.

Biological evaluation as antileukemic agents, for all the prepared compounds, is in progress and will be reported in due course.

3. Conclusions

The synthesis of 14 enantiomerically pure carbonucleosides, with very good yields, has been performed from chiral 1-amino-2-indanols **1** and **2** using an easy methodology that allowed us to obtain both enantiomeric forms of each structure, a very important requirement to evaluate the biological activity of the compounds prepared.

4. Experimental

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AMX-500 and Bruker 300 spectrometers. Elemental analyses were performed on a Perkin–Elmer C, H, N, S-Analyzer 2400. Optical rotations were measured with Perkin–Elmer 141 polarimeter. IR spectra of samples in KBr disk (solids) were recorded on a Perkin–Elmer Spectrum 1 FTIR spectrometer. Preparative thin layer chromatography (p-TLC) and thin layer chromatography (TLC) analysis were performed on Kieselgel 60 F_{254} (Merck) plates. The reagents were purchased from Aldrich and used without purification. (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol $[\alpha]_D^{22} = +63$ (*c* 0.2, chloroform); (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol $[\alpha]_D^{20} = -61$ (*c* 0.5, chloroform), both with 99% of ee by GLC.

4.1. (1*R*,2*S*)-1-(2-Amino-6-chloro-pyrimidin-4-ylamino)-indan-2-ol 3

A mixture of **1** (300 mg, 2.02 mmol) and 5-amino-4,6-dichloropyrimidine (420 mg, 2.56 mmol) in dry triethylamine (2.3 mL) and 1-butanol (11.5 mL) was heated under reflux for 24 in argon atmosphere. Then, the reaction mixture was cooled and the solvent was removed under reduced pressure until dryness. The residue was purified by p-TLC (eluant EtOAc) to afford compound **3** as a white solid (390 mg, 70%); mp: 138–140 °C; $[\alpha]_D^{23} = -37.5$ (*c* 0.530, MeOH); IR: 3437, 3325, 3224, 2695, 1647 cm^{-1}; ^{1}H NMR (500 MHz) δ (ppm): 2.80 (d, *J* = 16.5 Hz, 1H, C*H*H), 3.05 (dd, *J* = 5.5 Hz, *J* = 16.7 Hz, 1H, C*H*H), 4.41 (t, *J* = 3.7 Hz, 1H, C*H*OH), 5.12 (br s, 1H, CHN*H*), 5.50 (br s, 1H, O*H*), 6.05 (s, 1H, C*H*NH), 6.41 (s, 2H, NH_2), 7.12–7.20 (m, 3H, Ar*H*), 7.22 (d, *J* = 6.9 Hz, 1H, Ar*H*), 7.31 (br s, 1H, Het*H*); ^{13}C NMR (125 MHz) δ (ppm): 40.1, 72.6, 95.3, 125.0, 125.7, 127.1, 128.3, 136.0, 138.3, 141.4, 162.4, 163.1, 166.5. Anal. Calcd for $C_{13}H_{13}ClN_4O$: C, 56.42; H, 4.74; N, 20.25. Found: C, 56.97; H, 4.44; N, 20.20.

4.2. (1*S*,2*R*)-1-(2-Amino-6-chloro-pyrimidin-4-ylamino)-indan-2-ol 10

Compound **2** (300 mg, 2.02 mmol) was converted into **10** (450 mg, 80%); $[\alpha]_D^{23} = +36.9$ (*c* 0.495, MeOH) according to the reported procedure to obtain compound **3**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**3**.

4.3. (1*R*,2*S*)-1-[2-Amino-6-chloro-5-(4-chloro-phenylazo)-pyrimidin-4-ylamino]-indan-2-ol 4

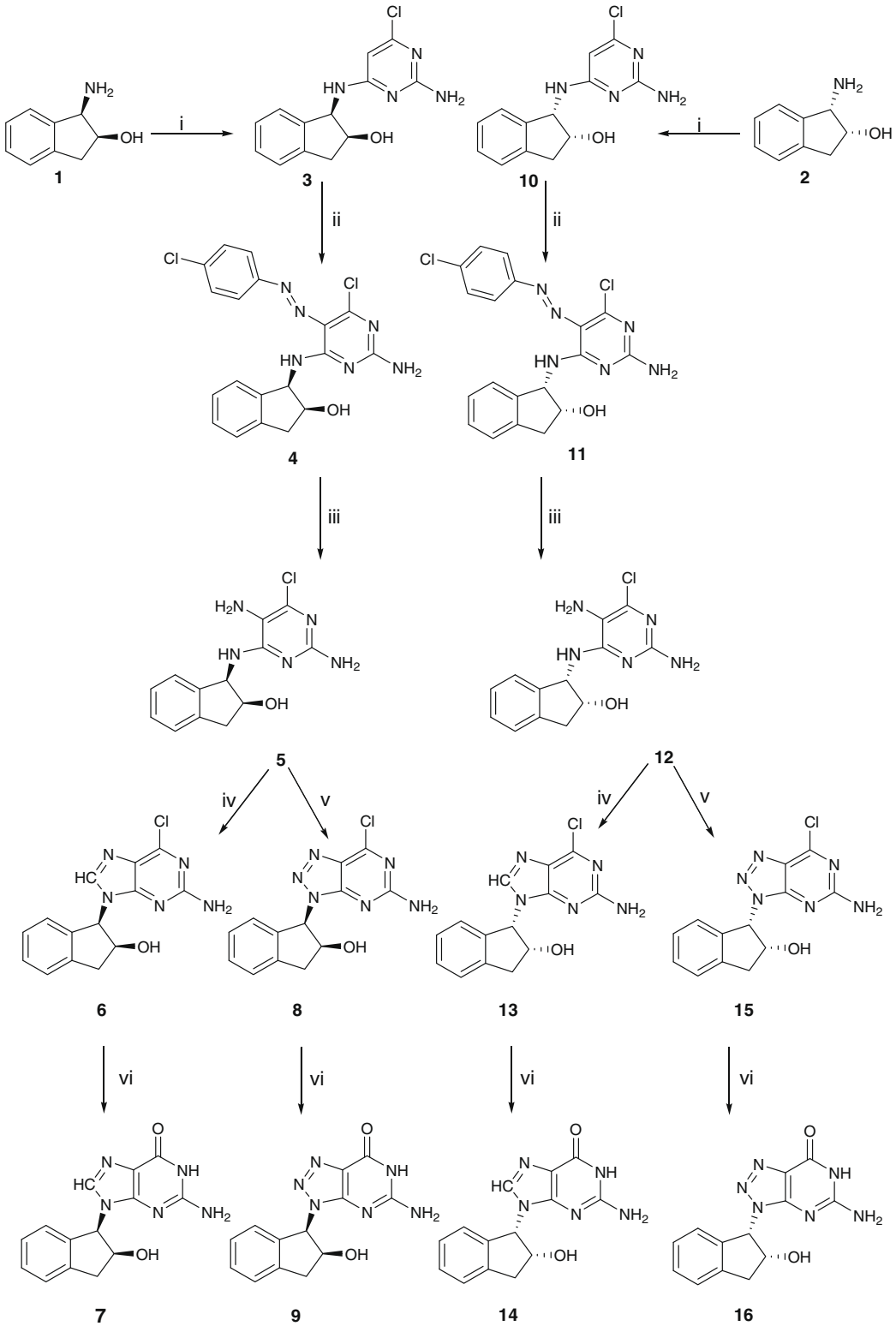
4-Chloroaniline (160 mg, 1.25 mmol) in 3 M HCl (1 mL) was treated at 0 °C with $NaNO_2$ (90 mg, 1.29 mmol) in water (1 mL). The diazonium salt obtained was added to a mixture of **3** (270 mg, 1.08 mmol), NaOAc (2.0 g), acetic acid (5.0 mL) and water (5.0 mL) and was stirred overnight at room temperature. The precipitate was filtered out, washed with water until the washings were neutral, to afford **4** as orange crystals (380 mg, 91%); mp: 226–229 °C; $[\alpha]_D^{23} = +42.3$ (*c* 0.180, MeOH); IR: 3551, 3467, 1568 cm^{-1}; ^{1}H NMR (500 MHz) δ (ppm): 2.83 (d, *J* = 16.5 Hz, 1H, C*H*H), 3.17 (dd, *J* = 5.0 Hz, *J* = 16.3 Hz, 1H, C*H*H), 4.60 (br s, 1H, C*H*OH), 5.60 (t, *J* = 5.5 Hz, 1H, –C*H*NH), 5.70 (br s, 1H, O*H*), 6.40 (br s, 2H, NH_2), 7.18–7.30 (m, 3H, Ar*H*), 7,32 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.45 (d, *J* = 7.8 Hz 1H, Ar*H*), 7.57 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.67 (d, *J* = 8.8 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz) δ (ppm): 40.0, 58.5, 72.3, 123.2, 125.0, 126.9, 127.9, 128.2, 129.9, 133.9, 134.5, 142.6, 145.2, 151.0, 152.4, 155.3, 158.1. Anal. Calcd for $C_{19}H_{16}Cl_2N_6O$: C, 54.95; H, 3.88; N, 20.24. Found: C, 54.90; H, 3.80; N, 20.04.

4.4. (1*S*,2*R*)-1-[2-Amino-6-chloro-5-(4-chloro-phenylazo)-pyrimidin-4-ylamino]-indan-2-ol 11

Compound **10** (160 mg, 1.25 mmol) was converted into **11** (300 mg, 67%); $[\alpha]_D^{23} = -40.5$ (*c* 0.160, MeOH) according to the reported procedure to obtain compound **4**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (+)-**4**.

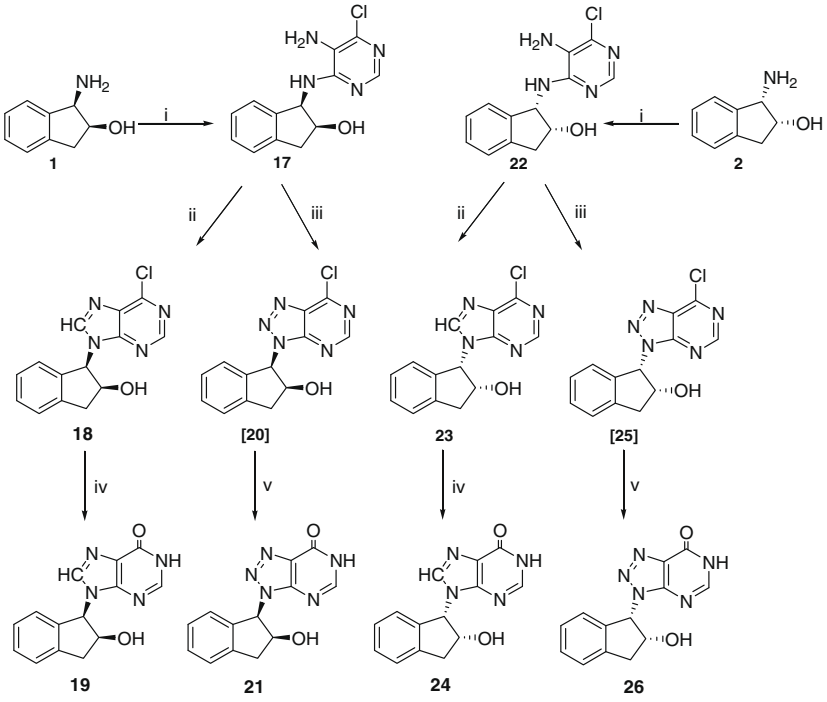
4.5. (1*R*,2*S*)-1-(2,5-Diamino-6-chloro-pyrimidin-4-ylamino]-indan-2-ol 5

A mixture of **4** (200 mg, 0.48 mmol), Zn powder (0.27 mg, 4.06 mmol), acetic acid (0.1 mL), water (3.0 mL) and ethanol



Scheme 1. Reagents and conditions: (i) 2-amino-4,6-dichloropyrimidine, $(CH_3CH_2)_3N$, *n*-butanol, reflux, 24 h; (ii) 4-chloroaniline, HCl, H_2O, $NaNO_2$, NaOAc, HOAc, overnight; (iii) Zn powder, HOAc, H_2O/EtOH, reflux, 3 h; (iv) triethylorthoformate, 12 N HCl, rt, overnight; (v) $NaNO_2$, H_2O, HOAc, 0 °C, 3 h; (vi) 0.25 N NaOH, reflux, 5 h.

(3.0 mL) was refluxed under argon for 3 h. Then, the reaction mixture was filtered, the solvent was removed under reduced pressure until dryness and the residue was purified by p-TLC (eluant AcOEt) to afford **5** as a brown solid (130 mg, 92%); mp: 207–209 °C; $[\alpha]_D^{23} = -1.6$ (*c* 0.257, MeOH); IR: 3429, 1565, 1449 cm^{-1}; ^1H NMR (500 MHz) δ (ppm): 2.87 (d, *J* = 16.0 Hz, H, C*H*H), 3.06 (dd, *J* = 5.0 Hz, *J* = 16.5 Hz, 1H, C*H*H), 3.98 (br s, 2H, NH_2), 4.53 (dt, *J* = 1.6 Hz, *J* = 5.0 Hz, 1H, C*H*OH), 5.52 (dd, *J* = 4.6 Hz, *J* = 8.0 Hz, 1H, C*H*NH), 5.73 (s, 2H, NH_2), 6.67 (d, *J* = 8.5 Hz, 1H, N*H*), 7.17–7.27 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz) δ (ppm): 40.2, 58.7, 72.4, 113.7, 124.9, 125.2, 126.7,



Scheme 2. Reagents and conditions: (i) 5-amino-4,6-dichloropyrimidine, $(CH_3CH_2)_3N$, *n*-butanol, reflux, 24 h; (ii) triethylorthoformate, 12 N HCl, rt, 36 h; (iii) 1 N HCl, $NaNO_2$, H_2O; (iv) 0.25 N NaOH, reflux, 6 h; (v) H_2O, reflux, 1 h.

127.7, 131.7, 138.2, 143.0, 141.2, 156.4. Anal. Calcd for $C_{13}H_{14}ClN_5O$: C, 53.52; H, 4.84; N, 24.01. Found: C, 54.07; H, 4.64; N, 23.90.

4.6. (1*S*,2*R*)-1-(2,5-Diamino-6-chloro-pyrimidin-4-ylamino]-indan-2-ol 12

Compound **11** (200 mg, 0.48 mmol) was converted into **12** (120 mg, 85%); $[\alpha]_D^{23} = +1.8$ (*c* 0.260, MeOH) according to the reported procedure to obtain compound **5**. The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**5**.

4.7. (1*R*,2*S*)-1-(2-Amino-6-chloro-9*H*-purin-9-yl)-2,3-dihydro-1*H*-inden-2-ol 6

A mixture of **5** (40 mg, 0.137 mmol), triethylorthoformate (0.8 mL) and 12 M HCl (0.04 mL) under argon was stirred overnight at room temperature. The mixture reaction was concentrated under reduced pressure until dryness and the residue was purified by p-TLC (eluant EtOAc). The compound **6** was isolated as an amorphous solid (30 mg, 73%); mp: 207–209 °C; $[\alpha]_{365}^{23} = +38.1$ (*c* 0.010, MeOH); IR: 3411, 1626, 1384, 1094 cm^{-1}; ^1H NMR (500 MHz) δ (ppm): 2.96 (d, *J* = 15.9 Hz, 1H, C*H*H), 3.11 (dd, *J* = 5.2 Hz, *J* = 16.0 Hz, 1H, C*H*H), 5.30 (m, 1H, –C*H*OH), 5.73 (d, *J* = 5.7 Hz, 1H, C*H*NH), 6.41 (s, 2H, N*H*$_2$), 7.01 (m, 4H, Ar*H*), 8.32 (s, 1H, N=CH-N); ^{13}C NMR (125 MHz) δ (ppm): 40.7, 68.9, 74.3, 124.4, 125.3, 127.1, 127.6, 130.3, 137.4, 139.6, 142.1, 149.2, 153.7, 158.5. Anal. Calcd for $C_{14}H_{12}ClN_5O$: C, 55.73; H, 4.01; N, 23.21. Found: C, 55.47; H, 4.04; N, 23.10.

4.8. (1*S*,2*R*)-1-(2-Amino-6-chloro-9*H*-purin-9-yl)-2,3-dihydro-1*H*-inden-2-ol 13

Compound **12** (50 mg, 0.164 mmol) was converted into **13** (35 mg, 71%); $[\alpha]_{365}^{23} = -38.9$ (*c* 0.010, MeOH) according to the reported procedure to obtain compound **6**. The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (+)-**6**.

4.9. 2-Amino-9-[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-1*H*-purin-6(9*H*)-one 7

A mixture of **6** (100 mg, 0.330 mmol) and 0.33 M NaOH (5.9 mL) was refluxed for 6 h, whereupon the solvent was removed under reduced pressure until dryness. The residue was purified by p-TLC (eluant EtOAc) to afford compound **7** as yellow crystals (65 mg, 70%); mp: 280 °C (d); $[\alpha]_D^{23} = +20.5$ (*c* 0.203, MeOH); IR: 3440, 3380, 3050, 2882, 1740, 1612 cm^{-1}; ^1H NMR (500 MHz) δ (ppm): 3.01 (d, *J* = 16.0 Hz, 1H, CHH), 3.22 (dd, *J* = 5.3 Hz, *J* = 16.1 Hz, 1H, CHH), 4.62 (m, 1H, –CHOH), 5.97 (d, *J* = 5.5 Hz, 1H, CHNH), 7.12–7.30 (m, 3H, ArH), 7.72 (d, *J* = 7.1 Hz, 1H, ArH), 8.00 (s, 1H, N=CH–N), 10.61 (s, 1H, N*H*CO); ^{13}C NMR (125 MHz) δ (ppm): 41.0, 59.7, 73.3, 117.4, 125.9, 126.8, 127.6, 131.3, 137.3, 140.7, 143.5, 145.6, 152.0, 156.8. Anal. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.64; N, 24.72. Found: C, 59.47; H, 4.44; N, 24.50.

4.10. 2-Amino-9-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-1*H*-purin-6(9*H*)-one 14

Compound **13** (100 mg, 0.330 mmol) was converted into **14** (60 mg, 65%); $[\alpha]_D^{23} = -19.4$ (*c* 0.213, MeOH) according to the reported procedure to obtain compound **7**. The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (+)-**7**.

4.11. (1*R*,2*S*)-1-(5-Amino-7-chloro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-2,3-dihydro-1*H*-inden-2-ol 8

Sodium nitrite (34.2 mg, 0.498 mmol) in water (1.3 ml) was added to a cooled (0 °C) solution of **5** (146 mg, 0.499 mmol) in acetic acid (0.80 ml) and water (0.80 ml), and was stirred for 3 h. After working-up, a white solid was obtained, which was purified by p-TLC (eluant EtOAc) to afford compound **8** (115 mg, 76%); mp: 228–231 °C; $[\alpha]_D^{23} = -1.5$ (*c* 0.501, MeOH); IR: 3429, 1565, 1449 cm^{-1}; ^1H NMR (500 MHz) δ (ppm): 2.97 (d, *J* = 10.0 Hz, H, C*H*H), 3.12 (dd, *J* = 6.2 Hz, *J* = 10.1 Hz, 1H, C*H*H), 4.69 (m, 1H, C*H*OH), 5.85 (d,

J = 5.85 Hz, 1H, C*H*NH), 7.10 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.18 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.30 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz) δ (ppm): 40.0, 62.3, 74.9, 124.7, 127.0, 128.2, 129.6, 129.9, 137.4, 140.0, 143.4, 157.8, 163.1. Anal. Calcd for $C_{13}H_{11}ClN_6O$: C, 51.58; H, 3.66; N, 27.76. Found: C, 51.47; H, 3.74; N, 27.60.

4.12. (1*S*,2*R*)-1-(5-Amino-7-chloro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-2,3-dihydro-1*H*-inden-2-ol 15

Compound **12** (150 mg, 0.513 mmol) was converted into **15** (120 mg, 79%); $[\alpha]_D^{23} = +1.1$ (*c* 0.537, MeOH) according to the reported procedure to obtain compound **8**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**8**.

4.13. 5-Amino-3-[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one 9

A mixture of **8** (50 mg, 0.164 mmol) and 0.25 M NaOH (2.1 ml) was refluxed for 5 h, whereafter the reaction mixture was cooled and the solvent was removed under reduced pressure until dryness and the residue was purified by p-TLC (eluant AcOEt) to afford **9** as white crystals (27 mg, 61%); mp: >300 °C; $[\alpha]_D^{23} = -12.6$ (*c* 0.150, MeOH); IR: 3465, 2426, 1642, 1565, 1384 cm^{-1}; ^{1}H NMR (500 MHz) δ (ppm): 2.96 (d, *J* = 16.2, H, C*H*H), 3.40 (dd, *J* = 4.9, *J* = 16.0, 1H, C*H*H), 4.69 (br s, 1H, O*H*), 5.45 (m, 1H, –C*H*OH), 5.88 (d, *J* = 5.5, 1H, C*H*NH), 6.85 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.10–7.31 (m, 3H, Ar*H*), 8.50 (s, 2H, N*H*$_2$), 9.57 (d, *J* = 6.9 Hz, 1H, N*H*CO); ^{13}C NMR (125 MHz) δ (ppm): 40.5, 59.2, 71.8, 125.4, 126.5, 127.9, 130.2, 131.3, 139.0, 141.6, 145.8, 153.9, 156.4. Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.67; H, 4.34; N, 29.60.

4.14. 5-Amino-3-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl] (1*S*,2*R*)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one 16

Compound **15** (50 mg, 0.164 mmol) was converted into **16** (20 mg, 45%); $[\alpha]_D^{23} = +13.3$ (*c* 0.163, MeOH) according to the reported procedure to obtain compound **9**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**9**.

4.15. (1*R*,2*S*)-1-(5-Amino-6-chloro-pyrimidin-4-ylamino)-indan-2-ol 17

A mixture of **1** (300 mg, 2.02 mmol) and 5-amino-4,6-dichloropyrimidine (420 mg, 2.56 mmol) in dry triethylamine (2.3 mL) and 1-butanol (11.5 mL) was heated under reflux conditions for 24 h under an argon atmosphere. Then, the reaction mixture was cooled and the solvent was removed under reduced pressure until dryness. The residue was purified by p-TLC (eluant EtOAc) to afford compound **17** as a white solid (370 mg; 67%); mp: 195–197 °C; $[\alpha]_D^{23} = +76.6$ (*c* 0.419, MeOH); IR: 3450, 3359, 3201, 2932, 1638 cm^{-1}; ^{1}H NMR (500 MHz) δ ppm): 2.86 (d, *J* = 16.1 Hz, 1H, C*H*H), 3.09 (dd, *J* = 5.0 Hz, *J* = 16.3 Hz, 1H, C*H*H), 4.59 (t, *J* = 4.4 Hz, 1H, C*H*OH), 5.15 (br s, 1H, CHO*H*), 5.25 (br s, 2H, N*H*$_2$), 5.60 (dd, *J* = 4.8 Hz, *J* = 8.4 Hz, 1H, C*H*NH), 6.92 (d, *J* = 8.2 Hz, 1H, N*H*), 7.16–7.27 (m, 4H, Ar*H*), 7.77 (s, 1H, N=C*H*–N); ^{13}C NMR (125 MHz) δ (ppm): 40.0, 59.5, 72.1, 124.4, 124.9, 125.3, 126.6, 127.8, 137.5, 141.4, 142.4, 145.8, 152.7. Anal. Calcd for $C_{13}H_{13}ClN_4O$: C, 56.42; H, 4.74; N, 20.25. Found: C, 56.47; H, 4.64; N, 20.40.

4.16. (1*S*,2*R*)-1-(5-Amino-6-chloro-pyrimidin-4-ylamino)-indan-2-ol 22

Compound **2** (300 mg, 2.02 mmol) was converted into **22** (350 mg, 63%); $[\alpha]_D^{23} = -75.6$ (*c* 0.473, MeOH); according to the reported procedure to obtain compound **17**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (+)-**17**.

4.17. (1*R*,2*S*)-1-(6-Chloro-purin-9-yl)-indan-2-ol 18

A mixture of **17** (100 mg, 0.36 mmol), triethylorthoformate (2.1 mL) and 12 M HCl (0.1 mL) was stirred at room temperature for 36 h. Then, the solvent was removed under reduced pressure until dryness, and the solid residue was purified by p-TLC (eluant EtOAc) affording chloropurine **18** as a white solid (90 mg, 87%); mp: 168–170 °C; $[\alpha]_D^{23} = +110.2$ (*c* 0.108, MeOH); IR: 3649, 3338, 3100, 1589, 1567 cm^{-1}; ^{1}H NMR (500 MHz) δ (ppm): 3.05 (d, *J* = 16.0 Hz, 1H, CH*H*), 3.31 (dd, *J* = 6.0 Hz, *J* = 16.7 Hz, 1H, C*H*H), 4.65 (m, 1H, C*H*OH), 5.34 (d, *J* = 4.8 Hz, 1H, O*H*), 6.26 (d, *J* = 5.5 Hz, 1H, C*H*N), 7.18 (d, *J* = 7.5, 1H, Ar*H*), 7.25 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.37 (t, *J* = 7.1 Hz, 1H, Ar*H*), 7.41 (d, *J* = 7.4, 1H, Ar*H*), 8.21 (s, 1H, =N–C*H*=N), 8.82 (1H, s, N=C*H*–N); ^{13}C NMR (125 MHz) δ (ppm): 39.2, 62.4, 72.1, 125.1, 126.3, 128.1, 129.9, 131.0, 137.7, 142.1, 147.6, 149.8, 152.1, 152.8. Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.47; H, 3.94; N, 19.40.

4.18. (1*S*,2*R*)-1-(6-Chloro-purin-9-yl)-indan-2-ol 23

Compound **22** (100 mg, 0.36 mmol) was converted into **23** (100 mg, 97%); $[\alpha]_D^{23} = -111.4$ (*c* 0.114, MeOH); according to the reported procedure to obtain compound **18**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (+)-**18**.

4.19. 9-[(1*R*,2*S*)-2-Hydroxy-indan-1-yl]-1,9-dihydro-purin-6-one 19

A mixture of **18** (50 mg, 0.17 mmol) and 0.25 M NaOH (2.5 mL) was heated under reflux conditions for 6 h, whereafter the reaction mixture was cooled and the solvent was removed under reduced pressure until dryness. The solid residue was purified by p-TLC (eluant EtOAc), affording purinone **19** (27 mg, 59%) as a white solid; mp: 213 °C (d); $[\alpha]_D^{23} = -28.2$ (*c* 0.137, MeOH); IR: 3440, 3050, 2882, 1760, 1602 cm^{-1}; ^{1}H NMR (500 MHz) δ (ppm): 2.90 (d, *J* = 17.9 Hz, 1H, CH*H*), 3.30 (dd, *J* = 5.5 Hz, *J* = 17.0 Hz, 1H, C*H*H), 4.58 (m, 1H, C*H*OH), 5.10 (br s, 1H, O*H*), 5.90 (d, *J* = 5.0 Hz, 1H, C*H*N), 6.98 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.21 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.30 (t, *J* = 7.3 Hz, 1H, Ar*H*), 7.37 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.40 (s, 1H, =N–CH=N), 7.92 (1H, s, –N=CH–N), 11.70 (s, 1H, N*H*CO); ^{13}C NMR (125 MHz) δ (ppm): 40.0, 58.7, 73.3, 122.6, 126.1, 126.8, 127.2, 129.0, 132.0, 137.3, 142.0, 146.1, 150.9, 156.0. Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.47; H, 4.44; N, 20.60.

4.20. 9-[(1*S*,2*R*)-2-Hydroxy-indan-1-yl]-1,9-dihydro-purin-6-one 24

Compound **23** (50 mg, 0.17 mmol) was converted into **24** (30 mg, 66%); $[\alpha]_D^{23} = +26.7$ (*c* 0.153, MeOH) according to the reported procedure to obtain compound **19**. The IR, ^{1}H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**19**.

4.21. 3-[(1*R*,2*S*)-2-Hydroxy-indan-1-yl]-3,6-dihydro-[1.2.3]triazolo[4,5-*d*]pyrimidin-7-one 21

A cooled (0 °C) solution of aminochloropyrimidine **17** (100 mg, 0.36 mmol) in 1 M HCl (1.3 mL) was treated with a solution of sodium nitrite (36 mg, 0.48 mmol) in water (10 mL). The mixture was stirred and allowed to warm up to room temperature, refluxed for 1 h, and then, the solvent was removed under reduced pressure

until dryness and the solid residue was purified by p-TLC (eluant EtOAc) affording 8-azapurinone **21** (65 mg, 67%), mp: 235–238 °C; $[\alpha]_D^{23} = -9.0$ (*c* 0.110, MeOH); IR: 3447, 3065, 2885, 1720, 1640 cm^{-1}; ^1H NMR (500 MHz) δ (ppm): 3.10 (dd, *J* = 6.9 Hz, *J* = 15.6 Hz, 1H, CH*H*), 3.25 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, CH*H*), 4.80 (q, *J* = 6.6 Hz, *J* = 7.3 Hz, 1H, C*H*OH), 5.33 (br s, 1H, O*H*), 6.20 (d, *J* = 6.6 Hz, 1H, C*H*N), 7.18–7.27 (m, 2H, Ar*H*), 7.33–7.39 (m, 2H, Ar*H*), 8.24 (d, *J* = 3.9 Hz, 1H, N=C*H*–NH), 12.70 (br s, 1H, N*H*CO); ^{13}C NMR (125 MHz) δ (ppm): 40.0, 64.3, 72.3, 125.6, 126.3, 127.4, 127.5, 129.7, 137.9, 142.9, 149.7, 149.8, 155.9. Anal. Calcd for $C_{13}H_{11}N_5O2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.87; H, 4.24; N, 26.10.

4.22. 3-[(1*S*,2*R*)-2-Hydroxy-indan-1-yl]-3,6-dihydro-[1.2.3]triazolo[4,5-*d*]pyrimidin-7-one 26

Compound **22** (100 mg, 0.36 mmol) was converted into **26** (70 mg, 72%); $[\alpha]_D^{23} = +9.3$ (*c* 0.107, MeOH) according to the reported procedure to obtain compound **21**. The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**21**.

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