Synthesis of 5'-Azido- and 5'-Amino-2',5'-dideoxynucleosides from Quinazoline-2,4(1*H*,3*H*)-diones

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Quinazoline-2,4(1*H*,3*H*)-diones **4** were silylated and condensed with methyl 5-azido-2,5-dideoxy-3-*O*-(4-methylbenzoyl)-α,β-D-*erythro*-pentofuranoside (**3**) using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst to afford the corresponding 5'-azidonucleosides **5**. 1-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-diones **6** and the corresponding β anomers were obtained by treating **5** with sodium methoxide in methanol at room temperature. 6-Methyl-1-(5-amino-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**8**) was obtained by treatment of the corresponding azido derivative **7** with triphenylphosphine in pyridine, followed by hydrolysis with ammonium hydroxide.

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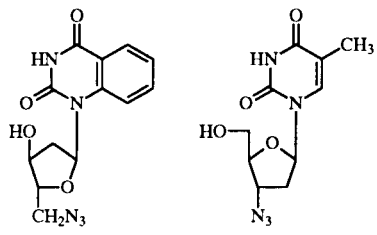
Many natural as well as synthetic quinazolinone derivatives exhibit significant biological activity [2] and their nucleosides have been of considerable interest since Stout and Robins [3] prepared the uridine analogue 1-β-D-ribofuranosylquinazoline-2,4(1*H*,3*H*)-dione in 1968. Recently, some 2'-deoxy-, 3'-deoxy-, and 2',3'-dideoxyquinazoline nucleosides were also synthesized [4,5]. In this context we were interested in the α anomers of 5'-azido-2',5'-dideoxynucleosides **1** because such compounds can be considered as distorted benzo analogues of 3'-azido-3'-deoxythymidine (AZT). Needless to say that all possible analogues of AZT are of interest for testing as antiviral compounds, because AZT itself is extremely potent against human immunodeficiency virus (HIV) [6].

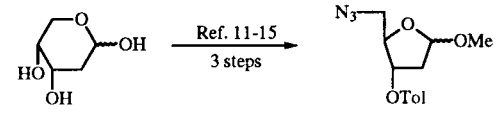
Scheme 1



1 **AZT**

Whenever possible to isolate the corresponding β anomers of 5'-azidonucleosides, we find it interesting to reduce them to the corresponding quinazoline-2,4(1*H*,3*H*)-dione 5'-aminonucleosides. The 5'-amino analogue of thymidine has demonstrated potent antiviral activity against herpes simplex virus type 1 (HSV-1) in complete absence of toxicity to the uninfected host Vero cells in culture [7,8]. This compound was therapeutically effective in the topical therapy of herpetic keratouveitis in rabbits, and systematic administration into the neonatal mouse revealed no adverse effect *in vivo* or by the histopathological examination [9]. 5'-Amino-3'-*O*-acylthymidine derivatives show significant antiviral activity by inhibition of the formation of infectious HSV-1 virions [10].

Scheme 2



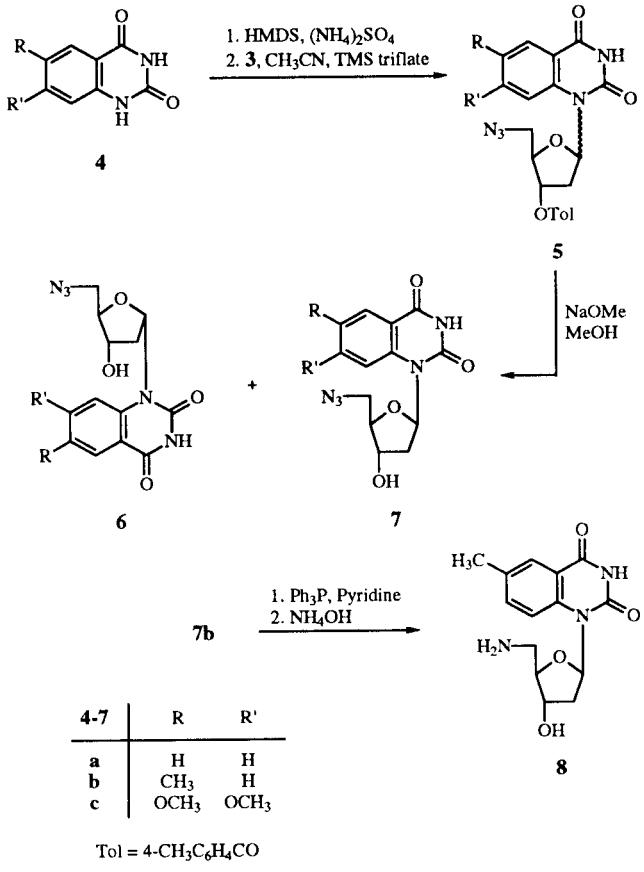
2 **3**

Tol = 4-$CH_3C_6H_4CO$

Methyl 5-azido-2,5-dideoxy-3-*O*-(4-methylbenzoyl)-α,β-D-*erythro*-pentofuranoside (**3**) was prepared by treatment of 2-deoxy-D-ribose (**2**) with hydrogen chloride in methanol [11,12] to give the corresponding methyl furanoside which was reacted with sodium azide [13,14] in the presence of carbon tetrabromide and triphenyl phosphine in anhydrous *N,N*-dimethylformamide and subsequently with 4-methylbenzoyl chloride in pyridine to give **3** [15].

Quinazoline-2,4-diones **4a-c** were prepared [16-19] and silylated [19] with 1,1,1,3,3,3-hexamethyldisilazane (HMDS). The trimethylsilylated derivatives were condensed with **3** using the trimethylsilyl trifluoromethanesulfonate (TMS triflate) method of Vorbrüggen *et al.* [20] to give an (α/β) anomeric mixture of protected nucleosides **5a-c** in 35-51% yields. Removal of the protecting toluoyl group from the glycon moiety of **5a-c** was

Scheme 3



4-7	R	R'
a	H	H
b	CH_3	H
c	OCH_3	OCH_3

achieved by treatment with sodium methoxide in methanol at room temperature to afford 1-(5-azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-diones **6a-c** in 24-31% yields and its β anomers **7a-c** in 55-63%. Treatment of compound **7b** with triphenylphosphine in pyridine [21] followed by hydrolysis with concentrated aqueous ammonia, yielded 6-methyl-1-(5-amino-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**8**) in 70% yield.

The protons in the ^1H nmr spectra were assigned by ^1H-^1H-homonuclear shift correlated (COSY) 2D nmr. Compounds **6a,7a** were selected for ^1H Nuclear Overhauser Effect (^1H NOE difference spectroscopy) to assign the site of glycosylation on the quinazoline ring and the anomeric configuration. *N*[1] Glycosylation of the quinazoline derivatives was proven by strong NOE enhancements in 8-H (9% in **6a** and 9% in **7a**) when 1'-H was irradiated. A typical decisive feature for β configuration **7a** was irradiations of 2'α-H at the α site and 2'β-H at the β site which resulted in strong NOE enhancements in 1'-H (10%) and 3'-H (8%), respectively. In compound **7a** irradiation of 1'-H generated a large NOE in 2'α-H (8%); irradiation of 2'β-H generated NOE in 8-H (5%); irradiation of 3'-H generated a large NOE in 2'β-H (5%), a small one in 2'α-H (0.3%), and a significant one in 8-H (3%). The NOE contact between 2'β-H or 3'-H and 8-H in the β anomer indicated a possible anti orientation of the nucleobase around the glycosidic bond. 3'-H and 4'-H are overlapping in the ^1H nmr spectrum of the α anomer **6a** and the only useful information we obtained from its NOE spectrum was assignment of a possible anti orientation around the glycosidic bond. This was ascribed to a large NOE (4%) generated in 8-H when the peak of 3'-H and 4'-H was irradiated.

Compounds **6a-c**, **7a-c** and **8b** did not show any significant activity at 100 μ*M* against HIV-1 in MT-4 cells. Expression of HIV in culture medium was quantified by HIV antigen detection ELISA. The same compounds were also devoid af any activity at 100 μ*M* against herpes simplex virus, type 1 (HSV-1), strain McIntyre when tested in African green monkey kidney cell line Vero.

EXPERIMENTAL

The nmr spectra were recorded on a Bruker 250 FT nmr spectrometer, tetramethylsilane as internal standard. Mass spectra were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer and fast atom bombardment (FAB) on a Kratos MS 50 spectrometer. The ir spectra were recorded on a Perkin-Elmer 1720 spectrometer. The silica gel (0.040-0.063 mm) used for column chromatography was purchased from Merck.

1-[5-Azido-2,5-dideoxy-3-*O*-(4-methylbenzoyl)-α,β-D-*erythro*-pentofuranosyl]quinazoline-2,4(1*H*,3*H*)-diones **5a-c**.

A mixture of quinazoline-2,4(1*H*,3*H*)-diones **4a-c** (5 mmoles), ammonium sulfate (60 mg) and 1,1,1,3,3,3-hexamethyldisilazane (40 ml) was refluxed (140°) overnight. The clear solution obtained was cooled and the solvent was removed *in vacuo*. The resulting residue was dissolved in anhydrous acetonitrile (15 ml) and a solution of methyl 5-azido-2,5-dideoxy-3-*O*-(4-methylbenzoyl)-α,β-D-*erythro*-pentofuranoside (**3**) (0.93 g, 3.2 mmoles) in anhydrous acetonitrile (15 ml) was added with stirring. The mixture was cooled to -50° and a solution of trimethylsilyl trifluoromethanesulfonate (0.75 ml, 3.9 mmoles) in anhydrous acetonitrile (5 ml) was added dropwise during 5 minutes at -50° and the mixture was stirred as follows depending on the base: **4a,c**, 5 hours at -20°; **4b**, 2 hours at -30°. The mixture was diluted with dichloromethane (200 ml), washed with a cold saturated aqueous sodium bicarbonate (150 ml), cold water (3 x 150 ml) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with chloroform to afford **5a**, white foam, yield 0.48 g (36%, α/β 2:3); **5b**, white foam, yield 0.7 g (51%, α/β 1:2), and **5c**, white foam, yield 0.54 g (35%, α/β 1:2).

1-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**6a**) and 1-(5-Azido-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)quinazoline-2,4(1*H*,3*H*)-dione (**7a**).

Sodium methoxide (39 mg, 0.72 mmole) in anhydrous methanol (5 ml) was added dropwise with stirring to a suspension of the protected nucleoside **5a** (0.3 g, 0.7 mmole) in methanol (15

ml) at 0°. The reaction mixture was stirred overnight at room temperature. After neutralization with ammonium chloride (41 mg, 0.76 mmole), the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with the gradient 0-2% methanol in chloroform to give **6a** and **7a**.

Compound **6a**. A white solid was obtained, yield 66 mg (31%), mp 211°; ^{1}H nmr (DMSO-d_6): δ 2.50 (m, 2H, 2'-H), 3.47 (dd, 1H, J = 5.3, 13.2 Hz, 5'-H), 3.55 (dd, 1H, J = 2.0, 13.3 Hz, 5'-H), 4.28 (s, 2H, 3'-H, 4'-H), 5.54 (s, 1H, OH), 6.66 (s, 1H, J = 7.9 Hz, 1'-H), 7.31 (m, 1H, H_{arom}), 7.73 (d, 2H, J = 3.8 Hz, H_{arom}), 8.02 (d, 1H, J = 7.9 Hz, 5-H), 11.48 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 35.5 (C-2'), 51.4 (C-5'), 71.0 (C-3'), 83.2, 83.9 (C-1', C-4'), 116.4 (C-4a), 115.9, 123.0, 127.6, 134.5 (C_{arom}), 139.3 (C-8a), 149.8 (C-2), 161.4 (C-4); ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (EI) m/z (%) = 303 (M^+, 2.5).

Anal. Calcd. for $C_{13}H_{13}N_5O_4$: M, 303.0967. Found: m/z 303.0947.

Compound **7a**. A white solid was obtained, yield 123 mg (57%), mp 189°; ^{1}H nmr (DMSO-d_6): δ 2.06 (ddd, 1H, J = 5.1, 8.1, 13.2 Hz, 2'α-H), 2.8 (m, 1H, 2'β-H), 3.59 (dd, 1H, J = 6.6, 13.2 Hz, 5'-H), 3.65 (dd, 1H, J = 3.3, 13.2 Hz, 5'-H), 3.83 (m, 1H, 4'-H), 4.43 (s, 1H, 3'-H), 5.38 (s, 1H, OH), 6.62 (t, 1H, J = 7.3 Hz, 1'-H), 7.30 (t, 1H, J = 7.6 Hz, 6-H), 7.61-8.04 (m, 3H_{arom}), 11.59 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 36.2 (C-2'), 51.2 (C-5'), 70.4 (C-3'), 83.6, 84.0 (C-1', C-4'), 116.3 (C-4a), 115.7, 123.0, 127.5, 134.6 (C_{arom}), 139.7 (C-8a), 149.5 (C-2), 161.4 (C-4); ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (FAB) (DMSO + 1% CH_3COOH, 3-nitrobenzylalcohol): m/z = 304 (M + H^+).

Anal. Calcd. for $C_{13}H_{13}N_5O_4$ (303.28): C, 51.48; H, 4.32; N, 23.09. Found: C, 51.30; H, 4.53; N, 22.56.

1-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**6b**) and 1-(5-Azido-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**7b**).

Nucleoside **5b** (0.9 g, 2 mmoles) was treated similarly as described for the preparation of **6a** and **7a**.

Compound **6b**. A white solid was obtained, yield 154 mg (24%), mp 207°; ^{1}H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3) 2.49 (m, 2H, 2'-H), 3.47 (dd, 1H, J = 5.3, 13.3 Hz, 5'-H), 3.55 (dd, 1H, J = 2.3, 13.2 Hz, 5'-H), 4.27 (m, 2H, 3'-H, 4'-H), 5.52 (d, 1H, J = 4.7 Hz, OH), 6.64 (t, 1H, J = 8.0 Hz, 1'-H), 7.57 (m, 2H, 7-H, 8-H), 7.84 (s, 1H, 5-H), 11.50 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.8 (CH_3), 35.6 (C-2'), 51.5 (C-5'), 71.0 (C-3'), 83.2, 83.8 (C-1', C-4'), 116.2 (C-4a), 115.8, 127.2, 132.3, 135.4, (C_{arom}), 137.1 (C-8a), 149.8 (C-2), 161.4 (C-4), ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (EI) m/z (%) = 317 (M^+, 1.5).

Anal. Calcd. for $C_{14}H_{15}N_5O_4$: M, 317.1124. Found: m/z 317.1121.

Compound **7b**. A white solid was obtained, yield 412 mg (63%), mp 203°; ^{1}H nmr (DMSO-d_6): δ 2.05 (ddd, 1H, J = 5.0, 8.2, 13.2 Hz, 2'α-H), 2.35 (s, 3H, CH_3), 2.78 (m, 1H, 2'β-H), 3.59 (dd, 1H, J = 6.2, 13.2 Hz, 5'-H), 3.64 (dd, 1H, J = 3.4, 13.2 Hz, 5'-H), 3.82 (dt, 1H, J = 3.4, 5.9 Hz, 4'-H), 4.42 (m, 1H, 3'-H), 5.37 (d, 1H, J = 5.1 Hz, OH), 6.59 (dd, 1H, J = 6.9, 7.8 Hz, 1'-H), 7.53 (s, 2H, 7-H, 8-H), 7.82 (s, 1H, 5-H), 11.52 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.8 (CH_3), 36.2 (C-2'), 51.2 (C-5'), 70.4 (C-3'), 83.5, 83.9 (C-1', C-4'), 116.1 (C-4a), 115.7, 127.1, 132.4, 135.4, (C_{arom}), 137.5 (C-8a), 149.5 (C-2), 161.4 (C-4); ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (EI) m/z (%) = 317 (M^+, 1.4).

Anal. Calcd. for $C_{14}H_{15}N_5O_4$: M, 317.1124. Found: m/z 317.1128.

1-(5-Azido-2,5-dideoxy-α-D-*erythro*-pentofuranosyl)-6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (**6c**) and 1-(5-Azido-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (**7c**).

The nucleoside **5c** (336 mg, 0.7 mmole) was treated similarly as described in the preparation of **6a**, **7a**.

Compound **6c**. A white solid was obtained, yield 74 mg (29%), mp 196°; ^{1}H nmr (DMSO-d_6): δ 2.49 (m, 2H, 2'-H), 3.52 (m, 2H, 5'-H), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.29 (m, 2H, 3'-H, 4'-H), 5.60 (d, 1H, J = 3.9 Hz, OH), 6.71 (t, 1H, J = 8.0 Hz, 1'-H), 7.25 (s, 1H, 8-H), 7.41 (s, 1H, 5-H); ^{13}C nmr (DMSO-d_6): δ 35.9 (C-2'), 51.4 (C-5'), 55.6 (OCH_3), 56.3 (OCH_3), 71.3 (C-3'), 84.0, 84.2 (C-1', C-4'), 99.8, 108.0 (C-5, C-8), 108.7 (C-4a), 134.6 (C-8a), 145.1, 154.0 (C-6, C-7), 150.1 (C-2), 161.0 (C-4); ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (EI) m/z (%) = 363 (M^+, 2.3).

Anal. Calcd. for $C_{15}H_{17}N_5O_6$: M, 363.1179. Found: m/z 363.1183.

Compound **7c**. A white solid was obtained, yield 139 mg (55%), mp 213°; ^{1}H nmr (DMSO-d_6): δ 2.06 (m, 1H, 2'α-H), 2.79 (m, 1H, 2'β-H), 3.67 (m, 3H, 4'-H, 5'-H), 3.82 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.41 (m, 1H, 3'-H), 5.39 (s, 1H, OH), 6.65 (t, 1H, J = 7.7 Hz, 1'-H), 7.02 (s, 1H, 8-H), 7.41 (s, 1H, 5-H), 11.42 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 36.2 (C-2'), 51.0 (C-5'), 55.6 (OCH_3), 56.0 (OCH_3), 70.3 (C-3'), 83.4, 83.5 (C-1', C-4'), 99.1, 108.0 (C-5, C-8), 108.5 (C-4a), 135.2 (C-8a), 145.2, 154.1 (C-6, C-7), 149.8 (C-2), 161.0 (C-4); ir (potassium bromide): ν = 2104 cm^{-1} (N_3); ms: (EI) m/z (%) = 363 (M^+, 2.8).

Anal. Calcd. for $C_{15}H_{17}N_5O_6 \cdot 1.0H_2O$ (381.35): C, 47.24; H, 5.02; N, 18.36. Found: C, 47.34; H, 5.15; N, 17.89.

1-(5-Amino-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**8**).

1-(5-Azido-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**7b**) (250 mg, 0.79 mmole) and triphenylphosphine (340 mg, 1.3 mmoles) were dissolved in pyridine (7 ml) and kept at room temperature for 1 hour. Concentrated aqueous ammonia (10 ml) was added and the reaction mixture was allowed to stand for an additional 2 hours. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with the gradient 5-15% methanol in chloroform to obtain the title compound **8** as a white solid, yield 163 mg (71%), mp 181°; ^{1}H nmr (DMSO-d_6): δ 1.96 (ddd, 1H, J = 4.6, 8.1, 12.7 Hz, 2'α-H), 3.34 (s, 3H, CH_3), 2.63-2.94 (m, 3H, 2'β-H, 5'-H), 3.61 (q, 1H, J = 5.1 Hz, 4'-H), 4.36 (td, 1H, J = 4.5, 9.1 Hz, 3'-H), 6.61 (t, 1H, J = 7.6 Hz, 1'-H), 7.52 (m, 2H, 7-H, 8-H), 7.81 (s, 1H, 5-H); ^{13}C nmr (DMSO-d_6): δ 19.8 (CH_3), 36.2 (C-2'), 43.0 (C-5'), 70.4 (C-3'), 82.9 (C-1'), 86.7 (C-4'), 116.2 (C-4a), 116.3, 127.1, 132.2, 135.2 (C_{arom}), 137.2 (C-8a), 149.8 (C-2), 161.5 (C-4); ms: (FAB) (DMSO + 3-nitrobenzylalcohol) m/z = 292 (M + H^+).

Anal. Calcd. for $C_{14}H_{17}N_3O_4 \cdot 1.0H_2O$ (309.32): C, 54.36; H, 6.19; N, 13.58. Found: C, 54.21; H, 6.33; N, 13.23.

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