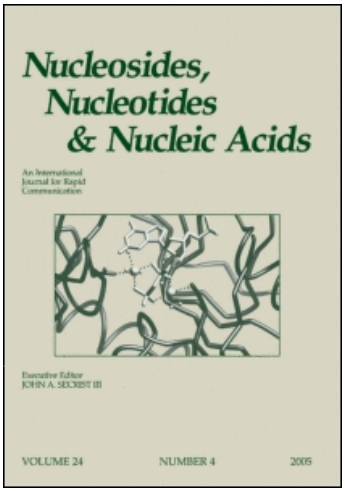

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Nucleosides LII[1], Synthesis and Properties of Quinazoline-3'-azidonucleosides

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NUCLEOSIDES LII[1], SYNTHESIS AND PROPERTIES OF QUINAZOLINE-3'-AZIDONUCLEOSIDES

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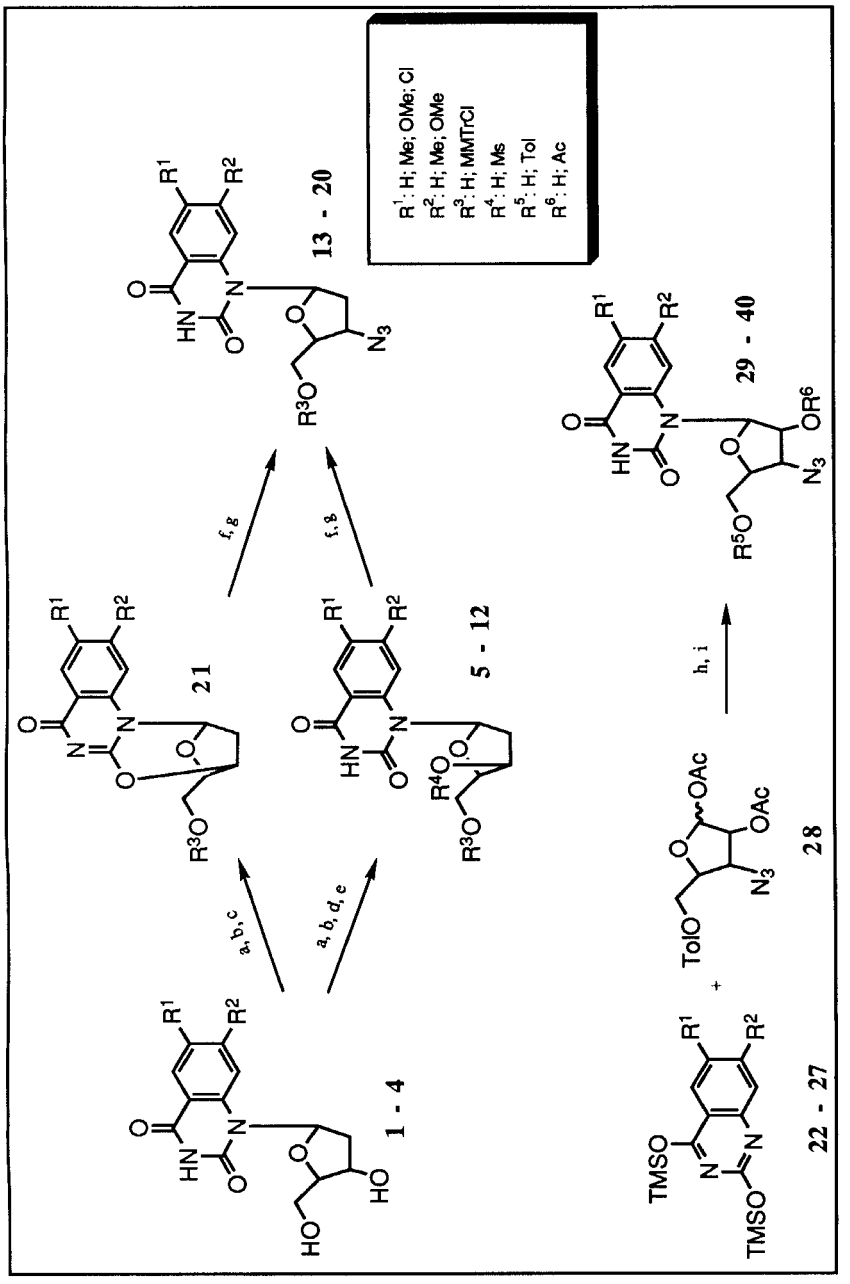
Abstract: A number of 6- and/or 7-substituted quinazoline-2,4-dione 3'-azido-3'-deoxyribo- and 3'-azido-2',3'-dideoxyribonucleosides have been synthesized. Chemical and physical properties of the novel compounds are briefly discussed.

Many natural as well as synthetic quinazolinone derivatives have been found to exhibit significant biological activity[3]. For example, the quinazoline alkaloids Febrifugine and Isofebrifugine, to pick only two compounds from a long list, show effectiveness against malaria[4]. Quinazoline-2,4-dione on the other hand can be looked at as benzouracil. Nucleosides with this kind of base modification are of considerable interest. In continuation with our recent studies in chemical and physical properties as well as potential biological activity of quinazoline-2,4-dione nucleosides[5,6], we describe here the synthesis of quinazoline analogs of AZT (Retrovir, 3'-Azido-3'-deoxy-thymidine) and of the respective 2'-hydroxy analogs (quinazoline 3'-azido-3'-deoxyribonucleosides).

Synthesis

For the synthesis of the quinazoline-2,4-dione AZT analogs we followed well-known standard procedures. Starting from the corresponding quinazoline-2,4-dione-2'-deoxyribosides[6], the O^2,3'-anhydroxylofuranoside intermediates were prepared by blocking the 5'-hydroxyl function with MMTr, mesylation of the



a: MMTrCl, pyridine; b: MsCl, pyridine; c: DBU, THF; d: aq. NaOH, EtOH; e: MsCl, pyridine; f: LiN_3, DMF; g: TsOH, CH_2Cl_2; h: TMSOTfl, dichloroethane; i: NaOMe, MeOH

3'-hydroxyl, and treatment with DBU under anhydrous conditions[7]. Thus, in three subsequent steps, **2** was converted to **21** in an excellent overall yield. Ring opening of **21** with LiN_3 in DMF[8] followed by removal of the protective group gave **17** in only moderate yield. Attempts to increase the yield of **14** by prolonged reaction times or excess of LiN_3 failed. The strong tendency of quinazolinedione ribosides[5] to form anhydro derivatives prevents the ring opening reaction from going to completion. We therefore decided to circumvent anhydro intermediates by nucleophilic displacement at the sugar moiety to introduce the azido function. This has been demonstrated as early as 1964 by Horwitz et al.[9]. Thus **1 - 4** were converted to **5 - 8** in three subsequent steps in good overall yields. Treatment with MsCl gave the 3'-O-mesylxyloderivatives **9 - 12** in almost quantitative yield after crystallization. Reaction of **9 - 12** with LiN_3 in hot DMF gave the 2',3'-dideoxy derivatives **13 - 16** in a clean nucleophilic displacement. Removal of the MTr protective group afforded the title compounds **17 - 20**.

For the synthesis of the 3'-azido-ribo derivatives we chose a Vorbrüggen type glycosylation procedure[10] with use of an appropriate azidosugar derivative. Thus D-xylose was converted to 1,2-di-O-acetyl-3-azido-3-deoxy-5-O-p-toluoyl-D-ribofuranose **28** by known methods[11]. Silyl-Hilbert-Johnson reaction of **28** with the silylated quinazoline-2,4-diones **22 - 27**[5] under TMSOTf catalysis gave the blocked azidonucleosides **29 - 34** in low to moderate yields. Apparently all quinazoline-2,4-diones with a substituent in position 7 gave low while 6- or unsubstituted bases gave moderate glycosilation yields. Subsequent deblocking of the acylated nucleosides **29 - 34** with NaOMe in MeOH afforded the title compounds **35 - 40** in moderate to good yields as crystalline compounds.

UV spectroscopy

UV spectra of the 3'-azido-2',3'-dideoxy quinazolindione nucleosides (**17 - 20**) show no bathochromic shift of the characteristic bands when going from neutral to alkaline medium. This indicates heterocyclic substitution at N1 which is in accordance with the structure of the starting materials. The respective UV spectra of **17 - 20** are almost identical with the ones of the starting materials (**1 - 4**)[5]. The pK_a-values of **17 - 20** show a slightly increased acidity compared to the 2'-deoxy analogs (**1 - 4**). Likewise the UV spectra of the monoanions of **35 -40** show only a small bathochromic shift and thus indicate heterocyclic N1 substitution.

Table 1 - UV spectra of Quinazoline-N_1 3'-Azidonucleosides

	pKa in H_2O	λ max in nm				log ε				pH	molecular form
5		[218]	[241]	[274]	[302]	[4.73]	[4.22]	[3.74]	[3.68]	MeOH	o
6		[217]	[243]	[273]	311	[4.66]	[4.15]	[3.69]	3.60	MeOH	o
7		224	[252]		303	4.68	[3.83]		3.56	MeOH	o
8		225	[252]		310	4.70	[3.90]		3.64	MeOH	o
9			[236]	271	[302]		[4.36]	4.08	[3.77]	MeOH	o
10		218	[242]		312	4.67	[4.15]		3.63	MeOH	o
11		222	[253]		304	4.79	[3.98]		3.69	MeOH	o
12		224	[254]		309	4.75	[3.91]		3.66	MeOH	o
17	9.63	218	[242]		306	4.63	[3.91]	3.62		pH 7	o
		221	[240]	258	307	4.65	[4.08]	[[3.61]	3.65	pH12	-
18	9.57	220	[244]		315	4.63	[3.99]		3.61	pH 7	o
		223	[260]		315	4.67	[3.56]		3.64	pH12	-
19	9.99	224	[245]	[254]	305	4.65	[3.89]	[3.84]	3.64	pH 7	o
		225	[260]	305	[313]	4.71	[3.75]	3.68	[3.63]	pH12	-
20	9.89	225	[248]	[258]	313	4.66	[3.95]	[3.80]	3.65	pH 7	o
		225	[262]	312	[317]	4.72	[3.73]	3.70	[3.67]	pH12	-
21		224	[256]	305	[314]	4.65	[3.86]	3.71	[3.63]	MeOH	o
29		217	[237]		304	4.63	[4.36]		3.56	MeOH	o
30		219	[236]		311	4.63	[4.42]		3.54	MeOH	o
31		218	[237]		305	4.66	[4.41]		3.58	MeOH	o
32		225	[240]		311	4.68	[4.38]		3.58	MeOH	o
33			[238]	[260]	316		[4.67]	[4.02]	3.79	MeOH	o
34		220	[242]		315	4.70	[4.45]		3.55	MeOH	o
35	9.84	218	[240]		306	4.61	[3.92]		3.61	pH 7	o
		220	[240]	[258]	306	4.64	[4.07]	[3.60]	3.63	pH12	-
36	9.63	220	[244]		315	4.62	[3.98]		3.60	pH 7	o
		223		[262]	315	4.66		[3.55]	3.63	pH12	-
37	9.59	224	[245]	[255]	305	4.65	[3.90]	[3.86]	3.63	pH 7	o
		224		[259]	305	4.71		[3.77]	3.67	pH12	-
38	9.97	226	[247]	[260]	313	4.65	[3.96]	[3.76]	3.65	pH 7	o
		226		[261]	312	4.70		[3.73]	3.66	pH12	-
39	9.68	235		261	318	4.57		3.91	3.86	pH 7	o
		230	[257]	[270]	317	4.63	[3.84]	[3.68]	3.88	pH12	-
40	9.20	221	[243]	[252]	317	4.66	[4.07]	[3.87]	3.56	pH 7	o
		224	[250]	267	317	4.66	[3.99]	3.37	3.59	pH12	-

[]: shoulder; pK_a-values were measured spectrophotometrically according to the method described by A.Albert et al.[12]

^{1}H-NMR spectroscopy

The most striking feature in the proton resonance spectra of the title compounds **17 - 20** is the large difference in chemical shift of the signals of the protons 2' and 2 " (0.65 - 0.80 ppm). These compounds show also relatively large coupling constants $^3J_{1',2'(2")}$ of ≈ 7.5 Hz. The same effects were observed earlier with quinazolinedione 2'-deoxynucleosides and have been discussed in a previous paper[6].

NMR spectra of the 3'-azido-3'-deoxynucleosides **29 - 40** show no abnormalities and on the whole, correspond to the NMR spectra of the quinazolinedione ribofuranosides which also have been discussed in detail earlier[1].

Table 2 - ^{1}H-NMR spectra of Quinazoline-N$_1$ 3'-Azidonucleosides

	NH	1'-H	J1',2'	2'-H	3'-H	4'-H	5'-H	arom. H			subst H
5[c]	9.10	6.32t		2.60 (m,2H)	4.48m	3.90m	3.58 (d,2H)	7.25* 8.20d	7.65t	7.80d	-
6[c]	8.60	6.45t		2.60 (m,2H)	4.45m	3.91m	3.55 (m,2H)	7.25*	7.68d	7.98s	2.40 (s,3H)
7[c]	8.57	6.33dd		2.59 (m,2H)	4.53m	4.00m	3.48dd 3.63dd	7.10d	7.55s	8.07s	2.37 (s,3H)
8[c]	8.34	6.82		2.55 (m,2H)	4.52m	4.05m	3.47dd 3.63dd	7.25*	7.92s		2.28 2.29 (s,3H)
9[c]	8.52	6.77*		2.76 (m,2H)	5.36m	4.11m	3.42m 3.72m	7.25* 8.22dd	7.55t	each 7.81d	-
10[c]	9.05	6.60*		2.45 (m,2H)	5.38m	4.15m	3.43m 3.71m	7.25*	8.00s	8.63dd	2.35 (s,3H)
11[c]	8.43	6.70*		2.71 (m,2H)	5.37m	4.15m	3.38m 3.75*	7.10d	7.53s	8.09d	2.32 (s,3H)
12[c]	8.33	6.78*		2.72 (m,2H)	5.37m	4.15m	3.38m 3.75*	7.40*	7.93s		2.21 2.29 (s,3H)
17[d]	11.80	6.80t		2.30m 3.10m	4.75m	4.00m	3.80 (m,2H)	7.40m	7.90 (m,2H)	each 8.20d	-
18[d]	11.59	6.56t		2.15m 2.81m	4.49m	3.78m	3.65 (m,2H)	7.49dd	7.61d	7.81d	2.34 (s,3H)
19[d]	11.57	6.60t		2.18m 2.79m	4.53m	3.79m	3.67 (m,2H)	7.12d	7.61s	7.88d	2.40 (s,3H)
20[d]	11.51	6.60t		2.15m 2.80m	4.53m	3.78m	3.67 (m,2H)	7.74s	7.95s		2.31 2.49 (s,3H)
21[c]		6.20dd		2.45dd 2.62dd	5.13m	4.34m	3.25 (m,2H)	7.25*	7.44d	each 7.94s	2.35 (s,3H)
29[c]	9.07	6.08	.....	(m,2H)	4.81dd	4.26m	4.54dd 4.74dd	7.30t 8.22t	7.38d	7.60t	-
30[c]	8.35	6.35	.....	(m,2H)	4.25m	4.74	(m,2H) 4.52m	7.26*	(2H)	7.97*	2.38 (s,3H)
31[c]	9.54	5.93d	1.8	6.12d	4.87dd	4.27m	4.58dd 4.70dd	7.13*	(2H)	8.09d	2.46 (s,3H)
32[c]	8.65	5.93d	1.9	6.11d	4.75m	4.28m	4.70 (m,2H)	7.12s	7.52s		2.23 2.30 (s,3H)
33[c]	8.91	5.82d	1.7	6.14d	4.86dd	4.30m	4.52dd 4.71dd	6.74s	7.56s	each	3.94 4.00 (s,3H)
34[c]	9.64	6.02	.....	(m,2H)	4.25m	4.77	4.54dd (m,2H)	7.29*	7.44dd	each 8.16d	-
35[d]	11.72	6.14d		4.85pq	4.18t	3.88	3.64 (m,2H)	7.31pq 8.02d	7.67pq	7.78d	-
36[d]	11.70	6.11d		4.83pq	4.16t	3.87m	3.64 (m,2H)	7.47dd	7.65d	7.82d	2.34 (s,3H)
37[d]	11.63	6.16d		4.86pq	4.20t	3.87m	3.66 (m,2H)	7.12d	7.68s	7.89d	2.39 (s,3H)
38[d]	11.57	6.16d		4.86pq	4.20t	3.88m	3.67 (m,2H)	7.68s	7.76s		2.25 2.29 (s,3H)
39[d]	11.60	6.21d		4.80pq	4.18t	3.60 -	4.00 (m,3H)	7.04s	7.40s	each	3.81 3.89 (s,3H)
40[d]	11.90	6.12d		4.82pq	4.18t	3.87m	3.64 (m,2H)	7.68dd	7.85ds	each 7.94dd	-

*: covered by protective group signals; [c]: in $CDCl_3$, [d]: in DMSO-d_6; d; doublet; t: triplet; pq: pseudoquartet; m: multiplet

Experimental part

^{1}H-NMR spectra were measured with a Bruker WM 250 and a Bruker AC 250 spectrometer with tetramethylsilane as an internal standard and with a δ-scale in ppm. UV spectra were recorded on a Perkin-Elmer spectrophotometer Lambda 5. The pK-values were determined spectrophotometrically. Thin layer chromatography was performed on silica-gel sheets F 1550 LS 254 of Schleicher & Schüll. Silica gel 60 (Merck) was used for ordinary column chromatography. Flash chromatography was done on Flash silica gel (Baker) according to the procedure of Still et al.[13]. Drying of substances was achieved at 100°C at atmospheric pressure or in a Büchi TO-50 drying oven under vacuum at 40°C. Melting points were measured with a Gallenkamp melting point apparatus and are not corrected.

1-(2'-Deoxy-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinediones (5 - 8), general procedure - To a solution of the respective 2'-deoxynucleosides (1 - 4)[6] (3 mmol) in pyridine (20 ml) was added monomethoxytritylchloride (3.6 mmol). The clear solution was stirred at rt overnight. After evaporation the residue was partitioned between chloroform (80 ml) and phosphate buffer (60 ml). Combined organic layers were dried with Na_2SO_4, filtered and evaporated. The crude product was dissolved in pyridine and cooled to 0°C. Mesylchloride (0.59 ml, 7.5 mmol) was added and the reaction mixture was stirred at this temperature for 3 hrs, then at r.t overnight. The mixture was poured over ice (100 g) and partitioned between chloroform (150 ml) and phosphate buffer (50 ml). Organic layers were evaporated after drying with Na_2SO_4. The residue was boiled in a mixture of NaOH (0.36 g), water (10 ml) and ethanol (20 ml) for 2 hrs. After cooling and evaporation of the residue was partitioned between chloroform (100 ml) and phosphate buffer (150 ml). Combined organic layers were dried over Na_2SO_4, filtered and evaporated. The respective crude products were purified by FCC (flash column chromatography).

1-(2'-Deoxy-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (5) - FCC (4.5 x 13 cm; dichloromethane/ethyl acetate 4:1), yield: 1.15 g (70%); Rf = 0.41 (silica gel - chloroform/ethyl acetate 4:1)
$C_{33}H_{30}N_2O_6 \cdot 0.5\ H_2O$: calc. for C: 70.83; H: 5.58; N: 5.01; found: C: 71.03; H: 5.73: N: 5.10

6-Methyl-1-(2'-Deoxy-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**6**) - FCC (4.5 x 13 cm, dichloromethane/ethyl acetate 4:1), yield: 1.30 g (77%); Rf = 0.26 (silica gel - chloroform/methanol 19:1)
$C_{34}H_{32}N_2O_6 \cdot H_2O$ (582.7): calc. for C: 70.09; H: 5.88; N: 4.81; found: C: 70.35; H: 5.73; N: 4.68

7-Methyl-1-(2'-Deoxy-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**7**) - FCC (4.5 x 13 cm, dichloromethane/ethyl acetate 4:1), yield: 1.20 g (71%); Rf = 0.38 (silica gel - chloroform/ethyl acetate 4:1)
$C_{34}H_{32}N_2O_6 \cdot 0.5\ H_2O$ (573.7): calc. for C: 71.19; H: 5.80; N: 4.88; found: C: 71.15; H: 5.91; N: 4.86

6,7-Dimethyl-1-(2'-Deoxy-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**8**) - FCC (4.5 x 13 cm, dichloromethane/ethyl acetate 4:1), yield: 1.11 g (64%); Rf = 0.80 (silica gel - chloroform/methanol 19:1)
$C_{35}H_{34}N_2O_6$ (578.8): calc. for C: 72.65; H: 5.92; N: 4.84; found: C: 72.27; H: 6.19; N: 4.60

1-(2'-Deoxy-3'-O-methanesulfonyl-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinediones (**9 - 12**), general procedure - To an ice-cold solution of the respective compounds **5 - 8** (2 mmol) in pyridine (10 ml) is added methanesulfonyl chloride (0.46 g, 4 mmol). The mixture is stirred at that temperature for 2 hrs, later at rt. After 18 hrs the mixture is poured on ice upon which crystallization occurs. The precipitate is filtered, washed thoroughly with water and dried under vacuum.

1-(2'-Deoxy-3'-O-methanesulfonyl-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**9**) - yield: 1.21 g (97%), m.p. 126°C; Rf = 0.23 (silica gel - chloroform/ethyl acetate 4:1)
$C_{34}H_{32}N_2O_8S$ (628.7): calc. forC: 64.96; H: 5.13; N: 4.46; found: C: 64.55; H: 5.08; N: 4.78

6-Methyl-1-(2'-deoxy-3'-O-methanesulfonyl-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**10**) - yield: 1.19 g (93%), m.p. 127-130°C; Rf = 0.26 (silica gel - chloroform/ethyl acetate 4:1)
$C_{35}H_{34}N_2O_8S$ (642.7): calc. for C: 65.41; H: 5.33; N: 4.36; found: C: 65.63; H: 5.29; N: 4.47

7-Methyl-1-(2'-deoxy-3'-O-methanesulfonyl-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**11**) - yield: 1.14 g (89%), m.p. 132-136°C; Rf = 0.27 (silica gel - chloroform/ethyl acetate 4:1)
$C_{35}H_{34}N_2O_8S$ (642.7): calc. for C: 65.41; H: 5.33; N: 4.36; found: C: 65.34; H: 5.36; N: 4.22

6,7-Dimethyl-1-(2'-deoxy-3'-O-methanesulfonyl-5'-O-monomethoxytrityl-β-D-xylofuranosyl)-2,4-quinazolinedione (**12**) - yield: 1.23 g (93%), m.p. 135-140°C; Rf = 0.24 (silica gel - chloroform/ethyl acetate 4:1)
$C_{36}H_{36}N_2O_8S$ (656.8): calc. for C: 65.84; H: 5.53; N: 4.27; found: C: 65.69; H: 5.42; N: 4.12

1-(3'-Azido-2',3'-dideoxy-β-D-ribofuranosyl)-2,4-quinazolinediones (**13** - **16**), general procedure - A mixture of lithiumazide (15 mmol) and the respective compound 9 -12 (1.5 mmol) in DMF (10 ml) was heated to 120°C for 1 hr. After cooling the reaction mixture was evaporated. The residue was partitioned between chloroform (50 ml) and phosphate buffer (40 ml). Combined organic layers were dried with Na_2SO_4, filtered and evaporated. The crude intermediate was dissolved in a 2% solution of toluenesulfonic acid in dichloromethane/ methanol 4:1 (20 ml) and stirred at rt for 30 min.

1-(3'-Azido-2',3'-dideoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**17**) The reaction was quenched by addition of a few drops of sat. aq. $NaHCO_3$, then evaporated. The residue was crystallized from ethanol (15 ml) to yield 0.42 g of colorless crystals, which were slightly contaminated by NaOTs. Recrystallization from water afforded the pure compound: 328 mg (72%), m.p. 169°C (decomp.)
$C_{13}H_{13}N_5O_4$ (303.3): calc. for C: 51.49; H: 4.32; N: 23.09; found: C: 51.47; H: 4.37; N: 23.11; IR: 2107 cm^{-1}

6-Methyl-1-(3'-azido-2',3'-dideoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**18**) - a) from **14** following the general procedure. The compound crystallizes from the detritylation solution. The precipitate was filtered, washed with ethanol and dried in vacuum. Additional material was obtained by evaporation and recrystallization of the mother liquor. Combined yield: 0.314 g (66%)

b) A solution of **21** (0.95 g, 1.73 mmol) and LiN_3 (0.42 g, mmol) was stirred at 125°C for 4 hrs. After cooling the mixture was evaporated under high vacuum. The residue was partitioned between chloroform (50 ml) and phosphate buffer pH 7 (30 ml). Combined organic layers were dried with Na_2SO_4, filtered and evaporated. The yellowish residue was dissolved in a 2% solution of toluenesulfonic acid in dichloromethane/methanol 4:1 and stirred for 20 min. The reaction solution was washed with phosphate buffer pH 7 (20 ml). The organic layer was dried over Na_2SO_4, filtered, evaporated and the residue is crystallized from ethanol to give 0.22 g of colorless crystals (40%).
Rf = 0.52 (silica gel - chloroform/methanol 19:1); m.p. 201 -202°C (decomp.)
$C_{14}H_{15}N_5O_4$: calc. for C: 52.99; H: 4.77; N: 22.07; found C: 53.03; H: 4.86; N: 21.93

7-Methyl-1-(3'-azido-2',3'-dideoxy-β-D-ribofuranosyl)-2,4-quinazoline-dione (**19**) - Colorless crystals separated from the reaction mixture, which are filtered off, washed with ethanol and dried in vacuum. The mother liquor is evaporated and the residue recrystallized from ethanol to give a combined yield of 338 mg (71%), m.p. 207 - 209°C (decomp.)
$C_{14}H_{15}N_5O_4 \cdot 0.25\ H_2O$ (321.8): calc. for C: 52.25; H: 4.86; N: 21.76; found: C: 52.24; H: 4.65; N: 21.80; IR: 2107 cm^{-1}

6,7-Dimethyl-1-(3'-azido-2',3'-dideoxy-β-D-ribofuranosyl)-2,4-quinazoline-dione (**20**) - Colorless crystals separate from the reaction mixture, which are filtered off, washed with ethanol and dried under vacuum. The mother liquor is evaporated and recrystallized from ethanol to give a combined yield of 370 mg (73%), m.p. 214°C (decomp.)
$C_{15}H_{17}N_5O_4 \cdot H_2O$ (331.3): calc. for C: 54.38; H: 5.17; N: 21.14; found: C: 53.85; H: 5.12; N: 20.90; IR: 2095 cm^{-1}

O^2,3'-Anhydro-6-methyl-1-(5'-O-monomethoxytrityl-β-D-xylofuranosyl)-4-quinazolone (**21**) - 6-Methyl-1-(2'-deoxy-b-D-ribofuranosyl)-2,4-quinazoline-dione (0.584 g, 2 mmol) (**2**) was dissolved in pyridine (15 ml). MMTrCl (0.741 g, 2.5 mmol) was added and the yellowish, clear solution was stirred overnight at rt. The mixture was evaporated and the yellowish residue was partitioned between chloroform (100 ml) and phosphate buffer pH 7 (50 ml). Combined organic layers were dried over Na_2SO_4, filtered and evaporated. The yellowish foam was dissolved in pyridine (20 ml) and cooled in an ice-bath. Mesylchloride

(0.39 ml, 5 mmol) was added dropwise. After 3 hrs. the mixture was warmed to r.t. and stirred at that temperature. After 16 hrs the brownish solution was poured on ice (50 g). The mixture was partitioned between chloroform (100 ml) and phosphate buffer pH 7 (50 ml). Organic layers were dried over Na_2SO_4, filtered and evaporated. The yellowish foam was dissolved in THF (50 ml), DBU (0.30 ml, 2 mmol) was added and the reaction mixture was stirred under reflux for 1 hr. After cooling to r.t. the mixture was evaporated. The residue was partitioned between chloroform (100 ml) and phosphate buffer (50 ml). Combined organic layers were dried with Na_2SO_4, filtered and evaporated. The crude product was purified by FCC (30 g, chloroform/methanol 19:1) to give a colorless foam (1.04 g, 94%).

$C_{34}H_{30}N_2O_5 \cdot 2H_2O$ (582.1): calc. for C: 70.16; H: 5.89; N: 4.81; found. C: 70.26; H: 5.79; N: 4.88

1-(2'-O-Acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofuranosyl)-2,4-quinazolinediones (29 - 34), general procedure - A suspension of the respective 2,4-quinazolinedione (2 mmol)[5], some crystals of ammonium sulfate and of acetamide in HMDS (20 ml) was refluxed overnight to give a colorless, clear solution. After cooling to rt the mixture was evaporated to give an amorphous residue which was dissolved in a solution of **28** (2 mmol) in 1,2-dichloroethane (40 ml). TMSOTf (2.2 mmol) was added dropwise to the stirred, clear solution. After 3 hrs at 75°C 60 ml of saturated aqueous $NaHCO_3$ was added and the mixture was extracted twice with chloroform (50 ml each). Combined organic layers were dried with Na_2SO_4, filtered and evaporated to give the crude products.

1-(2'-O-Acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (29) - FCC (2.5 x 15 cm, dichloromethane/ethyl acetate 6:1) yields 0.70 g of a colorless foam (73%); R_f = 0.51 (silica gel - chloro-form/ethyl acetate 4:1)

$C_{23}H_{21}N_5O_7$ (479.5): calc. for C: 57.62; H: 4.42: N: 14.61; found: C: 56.93; H: 4.71; N: 14.37

6-Methyl-1-(2'-O-acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofurano-syl)-2,4-quinazolinedione (30) - FCC (2.5 x 15 cm, dichlorometha-ne/ethyl acetate 6:1) yields 0.60 g of a colorless foam (73%); R_f = 0.57 (silica gel - chloroform/ethyl acetate 4:1)

$C_{24}H_{23}N_5O_7 \cdot H_2O$ (511.5): calc. for C: 56.36; H: 4.93: N: 13.69; found: C: 56.85; H: 4.72; N: 13.27

7-Methyl-1-(2'-O-acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribfuranosyl)-2,4-quinazolinedione (**31**) - FCC (2.5 x 15 cm, dichlorometha-ne/ethyl acetate 6:1) yields 0.23 g of a colorless foam (23%); R_f = 0.47 (silica gel - chloroform/ethyl acetate 4:1)
$C_{24}H_{23}N_5O_7$ (493.5): calc. for C: 58.41; H: 4.70; N: 14.19; found: C: 58.47; H: 4.58; N: 14.01

6,7-Dimethyl-1-(2'-O-acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (**32**) - FCC (2.5 x 15 cm, dichlorometha-ne/ethyl acetate 6:1) yields 0.38 g of a colorless foam (39%); R_f = 0.52 (silica gel - chloroform/ethyl acetate 4:1)
$C_{25}H_{25}N_5O_7 \cdot 0.5\ H_2O$ (516.5): calc. for C: 58.14; H: 5.07: N: 13.56; found: C: 58.41; H: 5.49; N: 13.13

6,7-Dimethoxy-1-(2'-O-acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (**33**) - FCC (2.5 x 15 cm, dichlorometha-ne/ethylacetate 6:1) yields 0.36 g of a colorless foam (26%); R_f = 0.35 (silica gel - chloroform/ethyl acetate 4:1)
$C_{25}H_{25}N_5O_9$ (539.5): calc. for C: 55.71; H: 4.67: N: 12.98; found: C: 55.76; H: 4.79; N: 12.87

6-Chloro-1-(2'-O-acetyl-3'-azido-3'-deoxy-5'-O-p-toluoyl-β-D-ribofurano-syl)-2,4-quinazolinedione (**34**) - FCC (2.5 x 15 cm, dichloromethane/ethyl acetate 6:1) yields 0.66 g of a colorless foam (64%); R_f = 0.62 (silica gel - chloroform/ethyl acetate 4:1)
$C_{23}H_{20}ClN_5O_7$ (513.9): calc. for C: 53.76; H: 3.92: N: 13.63; found: C: 53.89; H: 4.01; N: 13.53

1-(3'-Azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinediones **35 - 40**, general procedure - The respective nucleoside (**29 - 34**) (1 mmol) was added to a solution of sodium (28 mg, 1.15 mmol) in methanol (20 ml). The mixture was stirred at rt overnight. The solution was concentrated and the residue was partitioned between water (2 x 10 ml) and diethylether (50 ml). Combined aqueous layers were neutralized (pH 7) with conc. acetic acid and left in the

refrigerator overnight. The next day colorless crystals were filtered, washed with water and dried in the vacuum.

1-(3'-Azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**35**) - yield: 182 mg (57%), m.p. 189°C (decomp.); IR: 2124 cm^{-1}
$C_{13}H_{13}N_5O_5$ (319.3): calc. for C: 48.91; H: 4.10; N: 21.94; found C: 48.82; H: 4.02; N: 21.93

6-Methyl-1-(3'-azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**36**) - yield: 207 mg (62%), m.p. 194°C (decomp.); IR: 2118 cm^{-1}
$C_{14}H_{15}N_5O_5$ (333.3): calc. for C: 50.45; H: 4.54; N: 21.01; found C: 50.57; H: 4.53; N: 21.10

7-Methyl-1-(3'-azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**37**) - yield: 290 mg (87%), m.p. 212°C (decomp.); IR: 2115 cm^{-1}
$C_{14}H_{15}N_5O_5$ (333.3): calc. C: 50.45; H: 4.54; N: 21.01; found C: 50.51; H: 4.49; N: 21.03

6,7-Dimethyl-1-(3'-azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**38**) - yield: 177 mg (51%), m.p. 205 - 207°C (decomp.); IR: 2111 cm^{-1}
$C_{15}H_{17}N_5O_5$ (347.3): calc. C: 51.87; H: 4.93; N: 20.16; found C: 51.50; H: 4.95; N: 19.81

6,7-Dimethoxy-1-(3'-azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**39**) - yield: 265 mg (70%), m.p. 207°C (decomp.); IR: 2111 cm^{-1}
$C_{15}H_{17}N_5O_7$ (379.3): calc. C: 47.50; H: 4.52; N: 18.46; found C: 47.58; H: 4.50; N: 18.36

6-Chloro-1-(3'-azido-3'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (**40**) - yield: 194 mg (55%), m.p. 188°C (decomp.); IR: 2112 cm^{-1}
$C_{13}H_{12}ClN_5O_5$ (353.7): calc. C: 44.14; H: 3.42; N: 19.80; found C: 44.13; H: 3.47; N: 19.51

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