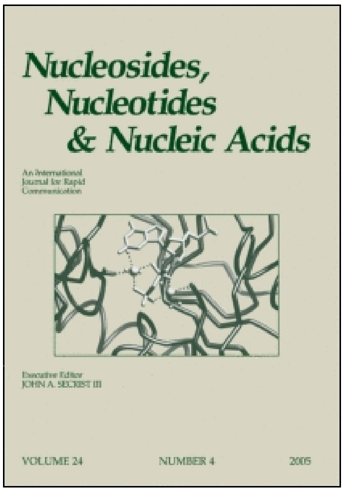

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Quinolone Nucleosides: 6,7-Dihalo-N-β- and α-Glycosyl-l 4-dihydro-4-oxo-quinoline-3-carboxylic Acids and Derivatives. Synthesis, Antimicrobial and Antiviral Activity

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QUINOLONE NUCLEOSIDES: 6,7-DIHALO-N-β- AND α-GLYCOSYL-1,4-DIHYDRO-4-OXO-QUINOLINE-3-CARBOXYLIC ACIDS AND DERIVATIVES. SYNTHESIS, ANTIMICROBIAL AND ANTIVIRAL ACTIVITY

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ABSTRACT. Reaction of the silylated 6,7-dihaloquinoline bases **10-12** with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**13**) gave ethyl 7-chloro-6-flouro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate (**14**) and the free acids **15** and **16**, respectively, which led on deblocking of the sugar moiety to the free nucleosides **17**, **18** and **20**, respectively. Treatment of **14** with methanolic ammonia afforded the amide derivative **19**. Ribosylation of **11** with 1,2-di-O-acetyl-3-azido-3-deoxy-5-p-toluoyl-β-D-ribofuranose (**21**) afforded the azido nucleoside **22**, which was again converted into the free nucleoside **23**. Analogously, reaction of **11** with the chloro deoxyribose derivative **24** led to a mixture of α / β (2:1) anomers of **25**. Deblocking and recrystallization of the product gave mainly the α-anomer **26**. Compounds **17-19**, **23** and **26** were evaluated against *Escherichia coli* and found inactive. Compound **16-18** and **22** were inactive aganist HIV-1 (III B) and HIV-2 (ROD) induced cytopathicity in human MT-4 lymphocyte cells.

Synthetic quinolones are widely accepted as useful and indispensable antibacterial [1] or antiviral agents [2] and dehydrogenase inhibitors [3], owing to their potent activity against various infectious diseases.[4,5] Since the introduction in 1963 of nalidixic acid (**1**) [6] as a systemic Gram-negative antibacterial agent, a large number of related analogues such as norfloxacin (**2**) [7], ciprofloxacin (**3**) [8], amifloxacin (**4**) [9] and sparfloxacin (**5**) [10] have been synthesized and widely used to treat a variety of infections.

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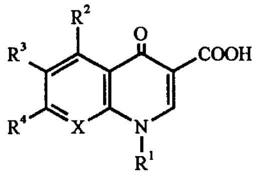


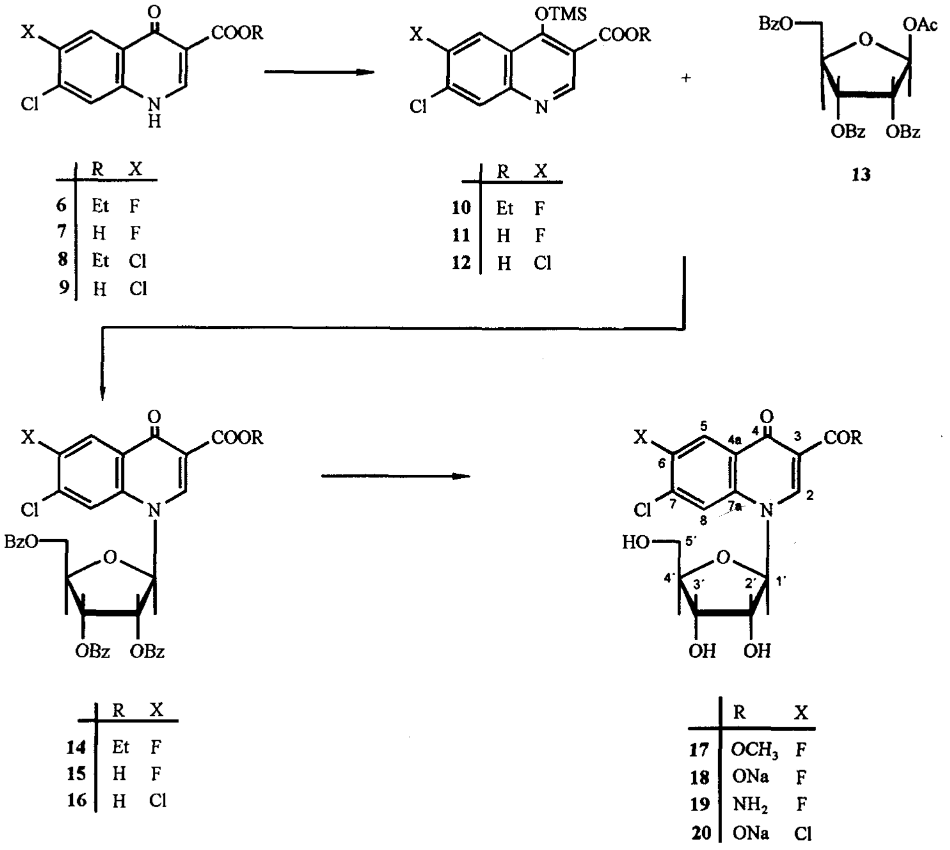
	R^1	X	R^2	R^3	R^4
1. nalidixic acid	Et	N	H	H	CH_3
2. norfloxacin	Et	CH	H	F	HN N
3. ciprofloxacin		CH	H	F	HN N
4. amifloxacin	CH_3NH	CH	H	F	CH_3N N
5. sparfloxacin		CF	NH_2	F	CH_3 HN N CH_3

Recent studies showed various modifications in the quinolone ring, particularly substitution with different groups at the aromatic ring of the quinolone moiety. [11-15] The synthesis of analogues of natural N-nucleosides, the building constituents of DNA and RNA and basis of many biologically active compounds, and their antiviral and anticancer treatment have been intensively investigated.[16] The potent pharmacological activities of quinolone bases prompted some laboratories to synthesize nucleosides carrying some of these bases. Goya *et al* [17] have reported recently the synthesis of the nucleosides **14** and **15** with their antiviral and antibacterial activity. In 1996 de Souza *et al.* [18] have reported also two examples of quinolone nucleosides without biological investigations. As part of our search for potent antibacterial or antiviral nucleosides of such bases, we report here the synthesis of some quinolone N-nucleosides along with the result of antibacterial and anti-HIV screening.

SYNTHESIS

The condensation of 4-chloro-3-fluoro-aniline with diethyl ethoxymethylene-malonate gave a product which, generally without purification, was cyclized in refluxing diphenyl ether to 7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline carboxylic acid ethyl ester **6**.[7] Saponification of the ester **6** with aqueous sodium hydroxide afforded the acid **7** [17] in 80% yield. Similarly, the 6,7-dichloro derivative **9** [19] was prepared from **8** in 70 % yield.

scheme 1



	R	X
6	Et	F
7	H	F
8	Et	Cl
9	H	Cl

	R	X
10	Et	F
11	H	F
12	H	Cl

	R	X
14	Et	F
15	H	F
16	H	Cl

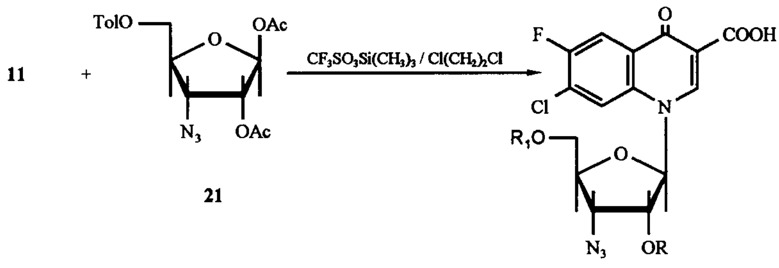
	R	X
17	OCH_3	F
18	ONa	F
19	NH_2	F
20	ONa	Cl

Ribosylation of the silylated quinolones **10-12** with the acylated sugar **13**, according to Hilbert-Johnson-Birkofer method [20] under trimethylsilyl triflate catalysis in boiling 1,2-dichloroethane afforded, regiospecifically, the 6,7-dihalo quinolone nucleosides **14-16** in 62%, 45% and 60%, respectively. Deblocking of **14-16** with sodium methoxide in methanol gave the methyl ester **17**, the sodium salts **18** and **20** in 82%, 77% and 85% respectively.

Reaction of **14** with methanolic ammonia at room temperature for 20 h proceeded with hydrolysis of the benzoyl groups and formation of the amido group at C-3 to give **19** in 65% yield. (scheme 1).

In this study, different ribo sugar moieties are utilized to investigate the chemical and biological properties of the quinolone nucleosides. Thus, reaction of **11** with the azido

scheme 2



	R	R$_1$
22	Ac	Tol
23	H	H

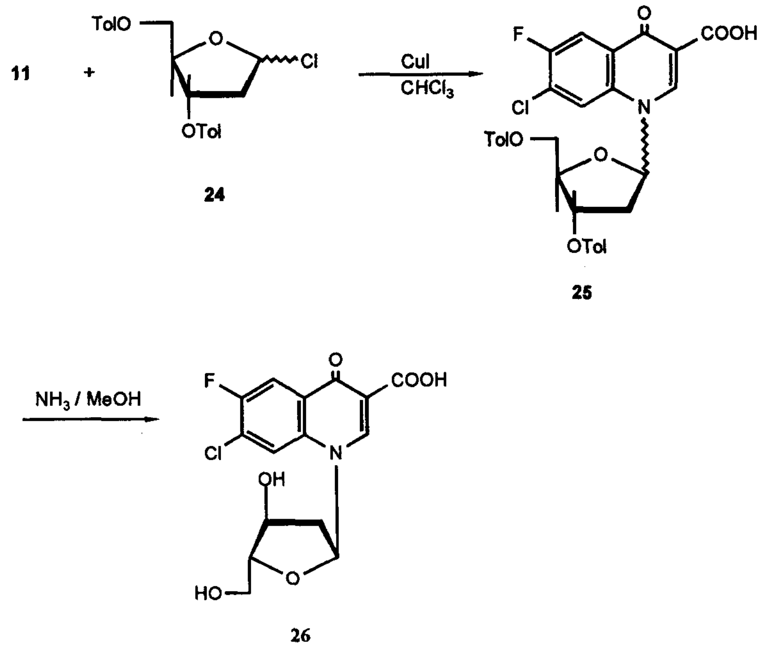
ribose **21** under the same above condition resulted in the formation of **22** in 49% yield, which on deblocking with methanolic ammonia afforded the free nucleoside **23** in 72% yield. (scheme 2).

Further study was made with the 2-deoxyribose. Thus, condensation of the silylated base **11** with the chloro sugar **24** in the presence of copper iodide in chloroform gave the α- and β- nucleoside mixture **25** in 2:1 ratio (58% yield). The separation of these anomers by chromatography was unsucccessful. Removal of the toluoyl groups was performed by treating **25** with methanolic ammonia for 16 h at room temperature to yield a mixture of α- and β- anomers of free nucleosides (75%), which on recrystallization from ethanol gave mainly the α-anomer **26** in 45% yield.(scheme 3).

PHYSICAL PROPERTIES

The structures of the newly synthesized quinolone N-nucleosides were assigned on the basis of their UV, ^{1}H-NMR (ROESY, COSY, HMQC)[21], ^{13}C-NMR and mass spectra. From the UV spectra, it has been observed that the formation of the monoanion was associated with a hypsochromic shift for the long wavelength band. The ^{1}H-NMR spectra of **14** and **26** (^{1}H-ROESY and HMQC) proved that the ribosylation was regiospecific at the N-site of the quinolone base and no trace of reaction at the oxygen site observed.[21] The anomeric protons of **14** and **26** showed clear rotating frame NOE with H-2 and H-8 since no any ROESY was observed with H-5 indicating the ribosylation at N-1 with the β-

scheme 3



configuration. The ^{1}H-NMR spectra of the amide **19** revealed clearly the presence of two doublets at δ 9.02 and 7.56 with J 4.2 Hz which were attributed to NH_2 group. ^{13}C-NMR spectra [21] of the newly compounds showed similar pattern since the C-5, C-6 , C-7 and C-4a showed doublets due to the coupling with fluorine atom at C-6. The carbon chemical shifts of C-2, C-3 and C-4 are almost identical.

BIOLOGICAL EVALUATION

The antibacterial activity of the free nucleosides **17-19**, **23** and **26** were tested by using the *Escherichia coli* K12 wild-type strain D10 (ma met). 10^4 cells / ml were inocubated into LB medium containing the indicated amounts of a compound. After growth overnight at 37 °C, the O.D. of the culture was determined. The MIC of compounds **26** was determined in the range of 600 µg / ml. All other compounds did not inhibit growth at concentration up to 1 mg / ml.

The quinolone nucleoside **17-19** and **23** were evaluated for their inhibitory activity of HIV-1 (III B) and HIV-2 (ROD) induced cytopathicity in Human MT-4 lymphocyte cells. All compounds were inactive against both HIV-1 and HIV-2.

TABLE 1. UV data * of some quinolone-N-nucleosides.

	λmax						log ε					
14	331	321	[304]	[281]	259	228	4.06	4.10	[3.92]	[3.91]	[4.40]	4.79
15	333	320	[305]	259	251	229	4.04	4.00	[3.79]	4.46	4.46	4.68
16	337	324	[310]	263	254	229	4.08	4.00	[3.83]	4.36	4.36	4.67
17	333	322	[306]	260	252	215	4.02	3.96	[3.80]	4.18	4.17	4.20
18	333	322	[306]	260	252	216	3.95	3.98	[3.76]	4.32	4.29	4.23
19	334	323	[305]	261	252	215	4.01	3.98	[3.82]	4.34	4.29	4.33
20	336	326	[310]	263	[356]	221	3.95	3.87	[3.72]	4.23	[4.20]	4.24
22	334	320	[305]	260	[250]	205	3.99	3.86	[3.60]	[4.17]	4.27	4.26
23	334	321	[306]	260	251	215	3.92	3.79	[3.77]	4.27	4.24	4.23
26	334	321	[307]	260	252	215	4.02	4.02	[3.84]	4.37	4.33	4.31

[ ]: shoulder; Molecular form = 0 (neutral form), * Solvent = MeOH.

EXPERIMENTAL

The melting points are uncorrected. The UV spectra were measured on a Perkin-Elmer spectrophotometer Lambda 5. The ^{1}H-NMR and ^{13}C -NMR spectra were acquired on Bruker AC 250 spectrometers (unless otherwise stated) with tetramethylsilane as an internal standard and on a δ scale in ppm. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 from Merck. Silica gel 60 (Merck) was used for column chromatography. EI and FAB mass spectra were recorded on a MAT 312 mass spectrometer using 3-nitrophenol (NBOH) or glycerol as matrix. Some molecular ions were detected by droping the samples with Na$^+$ ion.

6,7-Dihalo-quinolone-N-nucleosides (14-16)

General method. A suspension of quinolone bases **6**,**7** and **9** (6.20 mmol) in hexamethyldisilazane (20 ml) containing a few crystals of $(NH_4)_2SO_4$ was boiled for 5 h. After cooling, the solution was removed under reduced pressure to give crude **10-12**. To the solutions of silylated products in dry 1,2-dichloroethane (20 ml) was added a solution of the sugar **13** (6.20 mmol) in dry 1,2-dichloroethan (20 ml), followed by dropwise addition of trimethylsilyl triflate catalyst (6.20 mmol). After stirring for 3.5 h at room temperature, the mixture was partitioned between diluted aqueous solution of $NaHCO_3$

(20 ml) and $CHCl_3$ (3× 25 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness as amorphous. Recrystallization from EtOH / hexane gave the crystalline desired nucleosides.

***Ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)quinoline -3-carboxylate* (14)^{17}.** Yield : 2.74 g (62%) ; R_f ($CHCl_3$-MeOH 99 : 1) 0.56 ; m.p. 138-140 °C.

***7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) quinoline-3- carboxylic acid* (15)^{17}.** Yield: 1.91 g (45%); R_f (CH_2Cl_2-MeOH 99:1) 0.32; m.p. 157-160 °C dec. at 217 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz) : δ 14.08 (br, 1 H, CO_2H); 9.23 (s, 1 H, H-2); 8.21 (d, 1 H, $J_{5,F}$ 8.4 Hz); 8.02 (d, 1 H, $J_{8,F}$ 5.5 Hz, H-8); 8.08 (2 s, 2 H, Ar); 7.96-7.92 (4 s, 3 H, ortho-Ph), 7.61-7.55 (6 s, 3 H, para-Ph), 7.45-7.39 (7 s, 6 H, meta-Ph); 6.51 (d, 1 H, $J_{1',2'}$ 5.4 Hz, H-1'); 5.91 (t, 1 H, $J_{2',3'}$ 5.5 Hz, H-2'); 5.87 (t, 1 H, $J_{3',4'}$ 4.3 Hz, H-3') 4.98 (dd, 1 H , $J_{4',5'}$, 3.5 Hz, H-4'); 4.93 (dd, 1 H, $J_{4',5''}$, 3.0 Hz, H-5'); 4.88 (dd, 1 H, $J_{5',5''}$ 12.7 Hz).

***6,7-Dichloro-1,4-dihydro-4-oxo-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl) quinoline-3-carboxylic acid* (16).** Yield: 2.61 (60%); R_f (CH_2Cl_2-MeOH 99:1) 0.16; m.p. 185-187 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz) : δ 13.95 (br, 1 H, CO_2H); 9.21 (s, 1 H, H-2); 8.45 (s, 1 H, H-5); 8.06, 8.08, 7.94, 7.93, 7.91, 7.90 (6 s, 6 ortho protons, -OBz); 8.02 (s, 1 H, H-8); 7.59-7.53 (m, 3 para protons, -OBz); 7.41-7.23 (m, 6 meta proton, -OBz); 6.51 (d, 1 H, $J_{1',2'}$ 4.9 Hz, H-1'); 5.89-5.83 (m, 2 H, H-2',H-3'); 4.97 (d, 1 H, $J_{4',5'}$ 2.9 Hz, H-4'); 4.93 (dd, 1 H, $J_{4',5''}$ 2.5 Hz, H-5') ; 4.87 (dd, 1 H, $J_{5',5''}$ 12.5 Hz, H-5'').

Anal. Calc. for $C_{36}H_{25}Cl_2NO_{10}$ (702.5) : C, 61.55; H, 3.59; N, 1.99. Found : C, 61.45; H, 3.48; N, 2.01. m/z : (FAB>0) 725 $(M+Na)^+$.

***Methyl 7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-1-β-D-ribofuranosyl-3-carboxylate* (17).** A solution of **14** (0.54 g , 0.75 mmol) in 0.3 M sodium methoxide solution (25 ml) was stirred at room temperature for 15 h. After neutralization the solution with HOAc to pH 5, it was evaporated to dryness and the residue was partitioned between H_2O (15 ml) and ether (3 × 15 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 10 ml). Recrystallization from EtOH / ether gave **17** (0.24 g, 82 %); R_f ($CHCl_3$-MeOH 9:1) 0.35; m.p. 165-170 °C, dec. at 245 °C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 9.22 (s, 1 H, H-2); 8.16 (d, 1 H, $J_{5\text{-}F}$ 9.4 Hz; H-5); 8.02 (d, 1 H, J 6.0 Hz, H-8); 6.07 (d, 1 H, $J_{1',2'}$ 3.2 Hz, H-1'); 4.13 (d, 1 H, $C_{2'}$-OH); 4.10 (d, 1 H, H-2'); 4.08 (d, 1 H, $C_{3'}$-OH); 4.02 (t, 1H, $C_{5'}$-OH); 3.78 (t, 1 H, H-3'); 3.67 (m, 1 H, H-4'); 3.46 (dd, 1 H, $J_{4',5''}$ 4.7 Hz, H-5'); 3.42 (m, 2 H, H-5''); 1.67 (s, 3 H, -CO_2CH_3).

Anal. Calc. for $C_{16}H_{15}ClFNO_7{\cdot}2H_2O$ (423.77) : C, 45.35; H, 4.52; N, 3.31. Found : C, 45.21; 4.16; N, 2.96. m/z : (FAB>0) 388 $(M+H)^+$, 410 $(M+Na)^+$.

7-Chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-1-β-D-ribofuranosyl-3-carboxylic acid sodium salt **(18).** A solution of **15** (2.50 g, 3,64 mmol) in 0.3 M sodium methoxide (50 ml) was stirred at room temperature for 15 h. The solution was neutrallized with HOAc to pH 5 and then evaporated to dryness. The residue was partitioned between H_2O (50 ml) and ether (3 × 40 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 40 ml) to give crude product (1.60 g). Recrystallization from MeOH gave **18** (1.11 g, 77 %); R_f ($CHCl_3$-MeOH 9:1) 0.28; m.p. 157-160 °C dec. ^{1}H-NMR (DMSO-d_6, 600 MHz) : δ 9.37 (s, 1 H, H-2); 7.87 (d, 1 H, $J_{5,F}$ 8.5 Hz, H-5); 7.51 (d, 1 H, $J_{8,F}$ 6.3 Hz, H-8); 6.20 (bs, 1 H, H-1'); 6.00 (bs, 1 H, $C_{2'}$-OH); 5.44 (bs, 1 H, $C_{3'}$-OH); 5.27 (bs, 1 H, $C_{5'}$-OH); 4.22 (bs, 1 H, H-2'); 4.13 (bs, 1 H, H-3'); 4.03 (bs, 1 H, H-4'); 3.79 (m, 1 H, H-5'); 3.50 (m, 1 H, H-5'').

Anal. Calc. for $C_{15}H_{12}ClFNO_7Na$ (395.70) : C, 45.53; H, 3.06; N, 3.54. Found : C, 45.33; H, 3.28; N, 3.45. m/z : (FAB>0) 396 $(M+H)^+$, 418 $(M+Na)^+$.

7-Chloro,6-fluoro-1,4-dihydro-4-oxoquinoline-1-β-D-ribofuranosyl-3-carboxamide **(19).** A solution of **14** (0.60 g, 0.84 mmol) in 16% methanolic ammonia (20 ml) was stirred at room temperature for 18 h. The solution was evaporated to dryness and the residue was partitioned between H_2O (35 ml) and ether (3 × 30 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 30 ml) to give crude product (0.29 g). Recrystallization from EtOH afforded **19** (0.21g, 65 %); R_f (CH_2Cl_2-MeOH 85 : 15) 0.57; m.p. 225-227 °C dec. ^{1}H-NMR (DMSO-d_6, 600 MHz) : δ 9.19 (s, 1 H, H-2); 9.02 (d, 1 H, J 4.0 Hz , NH); 8.26 (d, 1 H, $J_{8,F}$ 6.1 Hz, H-8);

8.14 (d, 1 H, $J_{5,F}$ 9.0 Hz, H-5); 7.56 (d, 1 H, J 4.0, NH); 6.11 (d, 1 H, $J_{1',2'}$ 4.2 Hz, H-1'); 5.81 (d, 1 H, J 5.9 Hz, $C_{5'}$-OH); 5.34 (d, 1 H, J 5.7 Hz, $C_{2'}$-OH); 5.12 (d, 1 H, J 4.8 Hz, $C_{3'}$-OH); 4.20 (dd, 1 H, $J_{2',3'}$ 5.3 Hz, H-2'); 4.10 (dd, 1 H, $J_{3',4'}$ 3.8 Hz, H-3'); 3.98 (dd, 1 H, $J_{4',5'}$ 5.5 Hz, H-4'); 3.75 (t, 1 H, $J_{4',5''}$ 10.5 Hz, H-5'); 3.66 (t, 1 H , $J_{5',5''}$ 12.0 Hz, H-5'').

Anal. Calc. for $C_{15}H_{14}ClFN_2O_6$.1/2 H_2O (381.74) : C, 47.19; H, 3.96; N, 7.34. Found : C, 47.42; H, 4.19; N, 7.24. m/z : (FAB>0) 373 $(M+H)^+$.

***6,7-Dichloro-1,4-dihydro-4-oxoquinoline-1-β-D-ribofuranosyl-3-carboxylic acid sodium salt* (20).** A solution of **16** (1.40 g, 1.99 mmol) in 0.3 M sodium methoxide (50 ml) was stirred at room temperature for 16 h. The reaction mixture was worked-up in the usual way to give crude product (0.70 g). Recrystallization from EtOH afforded **20** (0.65 g, 70 %) : R_f (CH_2Cl_2-MeOH 9:1) 0.25; m.p. 269-272 °C dec. ^{1}H-NMR (DMSO-d_6 ,600 MHz) : δ 9.0 (s, 1 H, H-2); 8.5 (s, 1 H, H-5); 8.0 (s, 1 H, H-8); 5.97 (d, 1 H, $J_{1',2'}$ 6.2 Hz, H-1'); 5.49 (m, 1 H, $C_{2'}$-OH); 5.01(m, 1 H, $C_{3'}$-OH); 4.89 (m, 1 H, $C_{5'}$-OH); 4.23 (q, 1 H , $J_{2',3'}$ 6.2 Hz, H-2'); 3.94-3.28 (m, 4 H, H-3`-H-5'').

Anal. Calc. for $C_{15}H_{12}Cl_2NO_7Na$ (412.15) : C, 43.71; H, 2.93; N, 3.40. Found : C, 43.52; H, 2.78; N, 3.65. m/z : (FAB) 412 / 414 $(M)^+$.

***1-(2-O-Acetyl-3-azido-3-deoxy-5-O-p-toluoyl-β-D-ribofuranosyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (22).** A suspension of 7 (0.41 g, 1.69 mmol) and hexamethyldisilizane (20 ml) containing few crystals of $(NH_4)_2SO_4$ was boiled for 5 h. After cooling, the solution was evaporated to dryness to give silylated product **11**. To a solution of **11** in dry 1,2-dichloroethane (20 ml) was added a solution of the acylated sugar **21** (0.62 g, 1.69 mmol) followed by dropwise addition of trimethylsilyl triflate catalyst (0.40 ml, 2.20 mmol). After stirring at room temperature for 9 h, the reaction mixture was worked-up as usual to give crude amorphous (0.87 g). This product was chromatographed on column of silica gel (40 g). Elution with $CHCl_3$-MeOH (99:1) afforded **22** (0.38 g, 40%) as amorphous; R_f (CH_2Cl_2-MeOH 99:1) 0.34; m.p. 192-197 °C dec. ^{1}H-NMR ($CDCl_3$) : δ 14.50 (s, 1 H, -CO_2H); 8.30 (d, 2 H, Ar); 8.28 (d, 1 H, $J_{5,F}$ 8.5 Hz, H-5); 7.97 (d, 2 H, $J_{8,F}$ 8.2 Hz, H-8); 7.67 (d, 2 H, Ar); 6.45 (d, 1 H, $J_{1',2'}$ 5.6 Hz H-1'); 4.85 (t, 1 H, $J_{2',3'}$ 3.8 Hz, H-2'); 4.62 (m, 1 H, $J_{4',5'}$ 4.2 Hz, H-4'); 4.46 (dd, 1 H, $J_{3',4'}$

3.0 Hz, H-3′); 4.21 (dd, 1 H, $J_{4',5''}$ 2.8 Hz, H-5′); 4.11(dd, 1 H, $J_{5',5''}$ 11.5 Hz, H-5″); 2.34 (s, 3 H, Ar-<u>CH₃</u>); 2.08 (s, 3 H, OAc). IR. (nujol) : 2113 cm $^{-1}$ (N_3).

Anal. Calc. for $C_{25}H_{20}ClFN_4O_8$ (558.90) : C, 53.73; H, 3.61; N, 10.02. Found : C, 53.91; H, 3.73; N, 9.81. m/z : (FAB>0) 559 $(M+H)^+$.

***1-(3-Azido-3-deoxy-β-D-ribofuranosyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid* (23).** A solution of **22** (0.34 g, 0.61 mmol) in 16% methanolic ammonia solution (20 ml) was stirred at room temperature for 15 h. The solution was evaporated to dryness and the residue was partitioned between H_2O (15 ml) and ether (3 × 15 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 15 ml) to give a crude product (0.24 g). This was chromatographed on column of silica gel (10 g). Elution with a gradient of MeOH (0 - 20%) in $CHCl_3$ afforded **23** (0.17 g, 71%); R_f ($CHCl_3$-MeOH 4:1) 0.37; m.p. 188-192 °C dec. ^{1}H-NMR (DMSO-d_6, 600 MHz) : δ 8.81 (s, 1 H, H-2); 8.13 (bs, 1 H, H-5); 8.07(d, 1 H, $J_{8,F}$ 8.2 Hz, H-8); 6.48 (d, 1 H, $J_{1',2'}$ < 1.0 Hz, H-1′); 6.14 (m, 1 H, $C_{5'}$-OH); 5.23 (m, 1 H, $C_{2'}$-OH); 4.85 (dd, 1 H, $J_{2',3'}$ 5.5 Hz, H-2′); 4.40 (dt, 1 H, $J_{4',5'}$ 6.7 Hz, H-4′); 4.08 (t, 1 H, $J_{3',4'}$ 5.6 Hz, H-3′); 3.75 (dd, 1 H, $J_{4',5''}$ 3.0 Hz, H-5′).

Anal. Calc. for $C_{15}H_{12}ClFN_4O_6$ (398.73) : C, 45.18; H, 3.03; N, 14.05. Found : C, 45.39; H, 3.16; N,13.87. m/z : (FAB>0) 399 / 401 $(M+H)^+$.

***6-Chloro-1-(2-deoxy-3,5-di-O-p-toluoyl-α- and β-D-erythropentofuranosyl)-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (25).** A mixture of **7** (1.96 g , 8.11 mmol) and few crystals of $(NH_4)_2SO_4$ was heated in hexamethyldisilizane (30 ml) under reflux for 5 h. After cooling, the solution was evaporated to dryness under dry condition to yield **11**. Compound **11** was dissolved in dry $CHCl_3$ (50 ml) and then a solution of 1-chloro-2-deoxy-3,4-di-O-p-toluoyl-D-*erythro*pentofuranose (**24**) (3.48 g, 8.11 mmol) in dry $CHCl_3$ (50 ml) and copper iodide (1.53 g, 8.11 mmol) were added . After stirring for 4 h at room temperature, the mixture was partitioned with sodium thiosulfate solution (40 ml) and filtered through celite. The aqueous layer was washed with $CHCl_3$ (2 × 20 ml), the combined organic extracts were dried (Na_2SO_4) and filtered. The filtrate was treated with charcoal, filtered and evaporated to yield (3.7 g) of crude product. Recrystallization from EtOH afforded the pure mixture of α- and β- anomers **25** (2.8 g , 58%) in the ratio 2 : 1.

***6-Chloro-1-(2-deoxy-α-D-erythropentofuranosyl)-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (26).** Compound **25** (2.0 g, 3.36 mmol) was treated with 16 % methanolic ammonia solution (50 ml) by stirring at room temperature for 15 h. The solution was evaporated to dryness and the residue was partitioned between H_2O (50 ml) and ether (3 × 40 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 40 ml) to give a mixture of α- and β- nucleosides (0.90 g, 75 %). Recrystallization from EtOH afforded pure α-anomer **26** (0.54 g, 45%); m.p. 277-280 °C dec. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 9.06 (s, 1 H, H-2); 8.36 (d, 1 H, $J_{8,F}$ 7.9 Hz, H-8); 8.33 (d, 1 H, $J_{5,F}$ 9.1 Hz , H-5); 6.63 (d, 1 H, $J_{1',2'}$ 6.5 Hz, H-1'); 5.16 (d, 1H, J 1.5 Hz, $C_{3'}$-OH); 5.00 (t, 1 H, J 3.5 Hz, $C_{5'}$-OH); 4.56 (t, 1 H, $J_{4',5'}$ 4.8 Hz, H-4'); 4.30 (m, 1 H, H-3'); 3.53-3.49 (m, 2 H, H-5', H-5''); 2.85 (dt, 1 H, J 6.3 Hz, 14.2 Hz, H-2'); 2.11 (dd, 1 H, J 14.2 Hz, H-2'').

Anal. Calc. for $C_{15}H_{13}ClFNO_6$ (357.72): C, 50.36; H, 3.66; N, 3.92. Found: C, 50.11; H, 3.56; N, 4.12. m/z (FAB > 0) 380 / 382 $(M+Na)^+$; 357 / 359 $(M+H)^+$.

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