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Article

A New Class of Dihaloquinolones Bearing *N'*-Aldehydoglycosylhydrazides, Mercapto-1,2,4-triazole, Oxadiazoline and α-Amino Ester Precursors: Synthesis and Antimicrobial Activity

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A reação das quinolonas **6-8** com hidrazina forneceu as hidrazidas **9-11** em rendimentos moderados. A condensação de **9** e **11** com CS_2/KOH rendeu os sais de potássio **13** e **14**, respectivamente, que espontaneamente forneceram as 3-(1,2,4-triazolil)-quinolonas **15** e **16**, respectivamente, quando tratadas com hidrazina. A reação de **9** com CS_2/KOH sob refluxo resultou na 3-(1,2,4-oxadiazolil)-quinolona **17**. Alternativamente, **15** foi preparado a partir de **17**. O derivado **12**, obtido a partir de **10**, forneceu o derivado α-amino ester **18** mediante reação com o éster etílico da glicina. O acoplamento de **10** com vários açúcares forneceu as *N'*-(aldeidoglicosil-quinolona-3-il)carbohidrazidas **19a-e**. Os novos compostos sintetizados foram avaliados quanto a sua atividade antibacteriana.

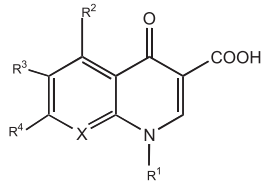
Reaction of the quinolones **6-8** with hydrazine afforded the hydrazide **9-11** in moderate yields. Condensation of **9** and **11** with CS_2 /KOH furnished the potassium salts **13** and **14**, respectively, which spontaneously afforded the 3-(1,2,4-triazolyl)-quinolones **15** and **16**, respectively, on treatment with hydrazine. Reaction of **9** in refluxing CS_2 /KOH gave the 3-(1,2,4-oxadiazolyl)-quinolone **17**. Alternatively, **15** was prepared from **17**. The azide derivative **12**, obtained from **10**, furnished the α-amino ester derivative **18**, on reaction with the glycine ethyl ester. Coupling of **10** with various sugars gave the *N'*-aldehydoglycosyl-quinolone-3-yl)carbohydrazides **19a-e**. The newly synthesized compounds were screened for their antibacterial activity.

Keywords: antimicrobial activity, hydrazides, quinolones

Introduction

The second generation of fluoroquinolones[1-3] such as norfloxacin[4] **2**, the modified analogue of nalidixic acid[5] **1**, ciprofloxacin[6] **3**, ofloxacin[7] **4**, and sparfloxacin[8] **5** are known as a major class of antibacterial agents and widely used to treat patient with infections. In recent years, and due to the increasing of resistance of many infections by gram negative and gram positive bacteria to these quinolones, several studies[9] described various modifications in the quinolone ring, for example: substitution with different groups at aromatic ring,[10-13] replacement of the same ring by thiophene moiety,[13,14] introduction of amido group[14,15] at C-3, as well as substitution at N-1 by sugar[16-19] or acyclic moieties.[20]

Nevertheless, some quinolones cause injury to the chromosome of eukaryotic cells.[21,22] These findings prompted us to optimize the substituent at C-3, by introduction of heterocyclic, α-amino acid ester precursors or *N'*-aldehydoglycosylcarbohydrazide moities to evaluate the effect of these groups on the antibacterial activity. It had been reported[23] that heterocycles such as oxadiazoles, thiadiazoles and mercaptotriazoles are themselves important chemotherapeutic agents and exhibit



	R^1	R^2	X	R^3	R^4
1. nalidixic acid	Et	N	N	H	Me
2. norfloxacin	Et	H	CH	F	HN⌒N
3. ciprofloxacin	▷—	H	CH	F	HN⌒N
4. ofloxacin	—$OCH_2CH(Me)$—		CH	H	MeN⌒N
5. sparfloxacin	▷—	NH_2	CF	F	Me, MeN⌒N, Me

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antitubercular, bacteriostatic, hypoglycemic, antiviral, antifungal, antithyroid, carcinostatic and strong herbicidal activity. Some reported mercaptotriazole derivatives showed potent activity[24] more than streptomycin against *Candida albicans*, whereas derivatives of 5-substituted 1,2,4-oxadiazole-2-thiones are known to possess interesting pharmacodynamic property and some have exhibited remarkable activity[25] against *Mycobacterium tuberculosis*. Recently, bactericidal and/or fungicidal or antimicrobial activity was reported for oxadiazolidinethiones.[26] Furthermore, a number of 1,2,4-triazole derivatives are angiotensin II receptor antagonists. To the best of our knowledge, only two examples of quinolone 3-hydrazides are reported: 1-phenyl-[27] and 1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrazides.[28]

Experimental

General procedures

Melting points are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on DRX 600, VRX 200 and UNITY 300 spectrometers with tetramethylsilane as an internal standard (δ scale in ppm and coupling constants in Hz). The signal assignments in the ^{1}H-NMR spectra were confirmed by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^{1}H-^{13}C COSY or HMQC experiments. EI and FAB mass were measured on an MAT 312 mass spectrometer using 3-nitrophenol (NBOH) or glycerol as matrix.

*Preparation of 6-chloro-1-ethyl- and 6,7-dihalo-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrazides (**9-11**)*

To a stirred suspension of **6-8** (10 mmol) in MeOH (50 mL) was added hydrated hydrazine (2.5 g, 50 mmol) at 23 °C. After stirring with EtOH (70 mL) for 72 h, the suspension was evaporated to dryness and the residue was washed with diethyl ether (50 mL), filtered and recrystallized from EtOH to give the desired products **9-11**, respectively, as yellow crystals.

*6,7-Dichloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrazide (**9**)*

From **6** (3.14 g). Yield: 2.01 g (67%); mp 204-206 °C; ^{1}H-NMR (DMSO-d_6) δ 11.64 (s,br, 3H, NH, NH_2); 8.99 (s, 1H, H-2); 8.38 (s, 1H, H-8); 8.38 (s, 1H, H-5); 4.45 (q, *J* 7.0 Hz, 2H, CH_2CH_3); 1.60 (t, 3H, CH_2CH_3). ^{13}C-NMR (DMSO-d_6) δ 175.0 (C-9); 164.8 (C-4); 149.8 (H-2); 140.4 (C-7); 137.8 (C-8a); 132.7 (C-6); 128.5 (C-5); 126.2 (4a); 118.8 (C-8); 108.8 (C-3); 50.8 (CH_2CH_3); 14.2 (CH_2CH_3); MS *m/z* (EI, relative abundance %) 300/302 ($M^{+\bullet}$, 38/24).

*6-Chloro-1-ethyl-7-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrazide (**10**)*

From **7** (2.98 g). Yield: 1.50 g (53%) as a yellow crystals; mp 263–264 °C; ^{1}H-NMR (DMSO-d_6) δ 10.43 (s, 1H, NH); 8.85 (s, 1H, H-2); 8.24 (d, 1H, $J_{H8\text{-}F}$ 5.5 Hz, H-8); 8.11 (d, 1H, $J_{H5\text{-}F}$ 8.3 Hz, H-5); 7.20 (s, br, 2H, NH_2); 4.52 (q, 2H, *J* 7.1 Hz, CH_2CH_3); 1.38 (t, 3H, *J* 7.1 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 173.5 (C-9); 163.1 (C-4); 154.2 (d, $J_{C6\text{-}F}$ 247.7 Hz, H-6); 147.6 (C-2); 135.6 (C-8a); 127.3 (d, $J_{C4a\text{-}F}$ 5.5 Hz, C-4a); 125.9 (d, $J_{C7\text{-}F}$ 20.4 Hz, C-7); 120.0 (C-8); 112.1 (d, $J_{C5\text{-}F}$ 22.6 Hz, C-5); 110.6 (C-3); 48.6 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{12}H_{11}FClN_3O_2$: C, 50.81; H, 3.91; N, 14.81. Found: C, 50.70; H, 3.87; N, 14.70; MS *m/z* (EI, relative abundance %) 283/285 ($M^{+\bullet}$, 50/19).

*6-Chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrazide (**11**)*

From **8** (2.80 g). Yield: 1.72 g (65%); mp 224-226 °C; ^{1}H-NMR (DMSO-d_6) δ 11.64 (s, br, 3H, NH, NH_2); 8.99 (s, 1H, H-2); 8.38 (dd, 1H, $J_{H7\text{-}8}$ 9.5 Hz, H-8); 8.28 (d, 1H, $J_{H5\text{-}7}$ 3.0 Hz, H-5); 7.92 (m, 1H, H-7); 4.45 (q, 2H, *J* 7.0 Hz, CH_2CH_3); 1.60 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 175.0 (C-9); 164.8 (C-4); 149.8 (H-2); 140.4 (C-7); 137.8 (C-8a); 132.7 (C-6); 128.5 (C-5); 126.2 (4a); 118.8 (C-8); 108.8 (C-3); 50.8 (CH_2CH_3); 14.2 (CH_2CH_3); Anal. calc. for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; N, 15.81. Found: C, 54.10; H, 4.49; N, 15.67; MS *m/z* (EI, relative abundance %) 264/266 ($M^{+\bullet}$, 45/24).

*3-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-6-chloro-1-ethyl-1,4-dihydro-4-oxoquinoline (**15**)*

Method A. A solution of KOH (0.38 g, 6.77 mmol) in EtOH (25 mL) was added stepwise to a mixture of CS_2 (0.52 g, 6.83 mmol) and hydrazide **9** (1.35 g, 4.50 mmol). The mixture was stirred at 23 °C for 72 h, then evaporated to dryness. The residue was washed with Et_2O (50 mL) to give the potassium salt **13**, which was used directly for the next step without purification. To a solution of 4.0 mmol of the salt in H_2O (25 mL) was added 95% hydrated hydrazine (0.26 g, 5.19 mmol) and the mixture was heated under reflux for 18 h. After cooling, the solution was acidified with concentrated HCl, and the precipitate was filtered . The product was washed with H_2O (100 mL), dried and recrystallized from MeOH-EtOH 1:1 to afford **15**

(0.96 g, 60%); mp 239-240 °C; ^{1}H-NMR (DMSO-d_6) δ 13.20 (s, 1H, NH); 8.54 (s, 1H, H-2); 8.22 (d, 1H, $J_{H5\text{-}8} < 1.0$ Hz, H-5); 7.98 (d, 1H, $J_{H8\text{-}5} < 1.0$ Hz, H-8); 6.67 (s, br, 2H, NH_2); 4.43 (q, 2H, *J* 7.1 Hz, 2H, CH_2CH_3); 1.40 (t, 3H, *J* 7.1 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 172.6 [C-12, (C=S)]; 163.7 (C-4); 146.6 (C-9); 145.9 (H-2); 137.6 (H-8a); 132.6 (C-6); 129.6 (C-5); 127.5 (C-4a); 124.9 (C-7); 119.8 (C-8); 107.4 (C-3); 48.00 (CH_2CH_3); 14.3 (CH_2CH_3); Anal. calc. for $C_{13}H_{11}Cl_2N_5SO$: C, 43.83; H, 3.11; N, 19.66. Found: C, 43.61; H, 3.02; N, 19.38; MS *m/z* (EI, relative abundance %) 355/357 ($M^{+\bullet}$, 35/30).

Method B. A solution of **17** (1.00 g, 3.42 mmol), H_2O (3 mL) and 95% N_2H_4 (1.60 g) was heated under reflux for 4 h. After cooling, the solution was diluted with cold H_2O (20 mL), acidified by dropwise addition of concentrated HCl, and filtered. The solid was washed with a minimium of cold H_2O, dried and recrystallized from 1:1 EtOH:H_2O to give **15** (0.70 g, 57%). The product had identical mp, mixed mp (238-240 °C) and other physical properties for those of the authentic sample prepared in method A.

*3-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-6,7-dichloro-1-ethyl-1,4-dihydro-4-oxoquinoline (**16**)*

This compound was prepared from **11** (1.20 g, 4.52 mmol) in a similar manner as desribed for the preparation of **15** (method A) *via* salt **14**. Yield: 1.20 g, (83%); mp 235-238 °C; ^{1}H-NMR (DMSO-d_6) δ 13.81 (s, 1H, NH); 8.55 (s, 1H, H-2); 8.7 (s, 1H, H-5); 8.20 (s, 1H, H-8); 5.68 (s, br, 2H, NH_2); 4.33 (q, 2H, *J* 7.0 Hz, CH_2CH_3); 1.40 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 172.9 [C-12, (C=S)]; 163.8 (C-4); 150.8 (C-2); 145.9 (C-9); 138.9 (C-7); 136.8 (H-8a); 128.6 (C-6); 127.8 (C-5); 126.6 (C-4a); 118.5 (C-8); 108.5 (C-3); 48.8 (CH_2CH_3); 15.0 (CH_2CH_3); Anal. calc. for $C_{13}H_{12}ClN_5SO$: C, 48.52; H, 3.76; N, 21.76. Found: C, 48.36; H, 3.67; N, 21.49; MS *m/z* (EI, relative abundance %) 321/323 ($M^{+\bullet}$, 100/45).

*6,7-Dichloro-1-ethyl-4-dihydro-3-(5-thioxo-1H-1,3,4-oxadiazol-3-yl)-4-oxoquinoline (**17**)*

To a solution containing EtOH (20 mL) and KOH (5.00 mmol) dissolved in H_2O (5 mL), the hydrazide **9** (1.50 g, 5.00 mmol) was added. After solution occurred, CS_2 (0.42 g, 5.51 mmol) was added and the mixture was heated under reflux for 3 h. After concentration of the solution to a small volume, the residue was dissolved in H_2O (10 mL). A precipitate was obtained by adding the solution to ice containing concentrated HCl. The solid was filtered off and dried. Recrystallization from EtOH gave the title compound **17** (1.00 g, 58%); mp 227-229 °C; ^{1}H-NMR (DMSO-d_6) δ 11.05 (s, 1H, NH); 9.045 (s, 1H, H-2); 8.47 (s, 1H, H-5); 7.88 (s, 1H, H-8); 4.50 (q, 2H, *J* 7.0 Hz, CH_2CH_3); 1.65 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 175.2 (C=S); 165.0 (C-4); 150.0 (C-2); 141.0 (C-9); 138.0 (C-7); 133.4 (H-8a); 128.6 (C-6); 126.2 (C-5); 121.6 (C-4a); 119.1 (C-8); 108.7 (C-3); 51.2 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{13}H_9Cl_2N_3SO_2$: C, 45.63; H, 2.65; N, 12.28. Found: C, 45.42; H, 2.56; N, 12.02; MS *m/z* (EI, relative abundance %) 341/343 ($M^{+\bullet}$, 20/14).

*7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid azide (**12**)*

To compound **10** (1.00 g, 2.84 mmol) was added a mixture of 2.0 mol L^{-1} HCl (12 mL, 40 mmol) and AcOH (2 mL, 80 mmol) at – 10 °C with stirring, followed by addition of $NaNO_2$ solution (0.40 g in 3 mL H_2O). After additional 15 min stirring between 0 °C and – 10 °C, the yellow azide product **12** was collected, washed with cold H_2O and used immediately for the preparation of **18**. The title azide **12** is rather unstable, and starts to decompose in the solid state at 23 °C within two days. However, this azide is stable when stored as solid at – 10 °C: IR ν_{max}/cm^{-1}: 2100 (azide group), (KBr); ^{1}H-NMR (DMSO-d_6) *d* 8.74 (s, 1H, H-2); 8.14 (d, 1H, $J_{8,F}$ 5.4 Hz, H-8); 8.02 (d, 1H, $J_{5,F}$ 8.1 Hz, H-5); 4.48 (q, 2H, *J* 7.0 Hz, CH_2CH_3); 1.32 (t, 3H, *J* 7.0 Hz, CH_2CH_3); MS *m/z* (FAB, relative abundance %) 293/295 ($MNa^{+\bullet}$, 87/25).

*(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolino-3-yl)-α-amino acetic acid ethyl ester (**18**)*

To a solution of **12** (1.20 g, 4.07 mmol) in DMF (40 mL) was added glycine ethyl ester (0.70 g, 6.79 mmol) at – 10 °C, followed by slow addition of Et_3N (0.60 g, 5.93 mmol). After stirring at 0 to 5 °C for 1 h, the mixture was added to an ice-cold water (150 ml) and the precipitate was filtered, dried and recrystallized from $CHCl_3$ to give **18** (0.72 g, 50%); mp 258-260 °C; ^{1}H-NMR ($CDCl_3$) δ 10.10 (s, 1H, NH); 8.80 (s, 1H, H-2); 8.20 (d, 1H, $J_{5,F}$ 8.5 Hz, H-5); 7.51 (d, $J_{8,F}$ 5.8 Hz, 1H, H-8); 4.19 (m, 6H, 3xCH_2); 1.58, 1.22 (m, 6H, 2xCH_2CH_3); δ_C (DMSO-d_6): 175.1, 175.0, 169.8 (C=O); 164.8 (C-4); 155.4 (d, $J_{5,F}$ 251.1; C-5); 147.6 (C-2); 135.5 (d, $J_{8a,F}$ 1.6 Hz, C-8a); 128.2 (d, $J_{4a,F}$ 6.3 Hz, C-4a); 127.7 (d, $J_{7,F}$ 21.6 Hz, C-7); 118.3 C-8); 113.7 (d, $J_{5,F}$ 23.6 Hz, C-5); 111.5 (C-3); 61.3 (C-10); 49.5 (NCH_2CH_3); 41.5 (OCH_2CH_3); 14.5 (OCH_2CH_3); 14.2 (NCH_2CH_3); Anal. calc. for $C_{16}H_{16}FClN_2O_4$: C, 54.17; H, 4.55; N, 7.90. Found: C, 53.95; H, 4.50; N, 7.78; MS *m/z* (EI, relative abundance %) 354/356 ($M^{+\bullet}$, 25/10).

*N'-D-Aldehydoglycosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbohydrazide (**19a-e**)*

A suspension of **10** (1.40 g, 4.93 mmol) in EtOH (50 mL) and the sugar moiety (5.20 mmol) was heated under reflux for 4-6 h. After cooling, the product was collected and recrystallized from EtOH to afford the desired product **19**.

*N'-D-Aldehydoarabinosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbohydrazide (**19a**)*

From D-arabinose (0.78 g). Yield: 2.01 g (98%); mp 225 °C; ^{1}H-NMR (600 MHz, HMQC, DMSO-d_6) δ 12.69 (s,1H, NH); 8.99 (s,1H, H-2); 8.32 (d, 1H, $J_{H8\text{-}F}$ 5.4 Hz, H-8); 8.15 (d, 1H, $J_{H5\text{-}F}$ 8.4 Hz, H-5); 7.65 (d, 1H, *J* 5.5 Hz, OH, exchangable with D_2O); 4.99 (d, 1H, *J* 5.5 Hz, OH); 4.64 (m, 5H, H-1', CH_2CH_3, 2xOH, exchangable with D_2O); 4.38 (dd, 1H, *J* 8.0 Hz, *J* 3.2 Hz, H-2'); 4.30 (dd, 1H, *J* 3.2 Hz, *J* 8.3 Hz, H-3'); 3.60 (m, 2H, H-4', H-5'); 3.46 (dd, 1H, $J_{H5',H5"}$ 12.0 Hz, H-5"); 1.42 (t, 3H, *J* 7.1 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 173.9 (C-9); 160.3 (C-4); 155.9 (d, $J_{C6\text{-}F}$ 180.3 Hz, C-6); 151.9 (N=*C*H-1'); 148.7 (C-2); 135.7(C-8a); 127.3 (d, $J_{C4a\text{-}F}$ 5.4 Hz, C-4a); 126.2 (d, $J_{C7\text{-}F}$ 20.3 Hz, C-7); 120.2 (C-8); 112.2 (d, $J_{C5\text{-}F}$ 22.3 Hz, C-5); 110.3 (C-3); 73.3 (C-3'); 70.9 (C-4'); 70.3 (C-2'); 63.3 (C-5'); 48.8 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{17}H_{19}FClN_3O_6$: C, 49.11; H, 4.61; N, 10.11. Found: C, 49.00; H, 4.50; N, 9.85; MS *m/z* (FAB, relative abundance %) 438/440 ($MNa^{+\bullet}$, 100/36).

*N'-D-Aldehydoxylosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbohydrazide (**19b**)*

From D-xylose (0.78 g). Yield: 1.90 g (93%); mp 131 °C, decomposed; ^{1}H-NMR (DMSO-d_6) δ 10.92 (s, 1H, NH); 8.90 (s,1H, H-2); 8.28 (d, 1H, $J_{H8\text{-}F}$ 5.3 Hz, H-8); 8.15 (d, 1H, $J_{H5\text{-}F}$ 8.5 Hz, H-5); 6.00 (t, 1H, $J_{OH\text{-}H5',H5"}$ 5.5 Hz, $C_{5'}$-OH, exchangable with D_2O); 5.05 (s, br, 1H, OH, exchangable with D_2O); 4.92 (m, 2H, 2xOH, exchangable with D_2O); 4.54 (m, 4H, H-1', H-2', CH_2CH_3); 4.34 (m, 1H, H-3'); 3.84 (m, 1H, H-4'); 3.55 (m, 1H, H-5'); 3.42 (m, 1H, H-5"); 1.40 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 173.6 (C-9); 163.5 (C-4); 154.5 (d, $J_{C6\text{-}F}$ 195.2 Hz, H-6); 149.0 (N=*C*H-1'); 148.1 (C-2); 135.7(C-8a); 127.3 (d, $J_{C4a\text{-}F}$ 6.1 Hz, C-4a); 125.8 (d, $J_{C7\text{-}F}$ 20.0 Hz, C-7); 120.1 (C-8); 112.2 (d, $J_{C5\text{-}F}$ 23.0 Hz, C-5); 110.0 (C-3); 76.5 (C-3'); 70.7 (C-4'); 69.7 (C-2'); 67.1 (C-5'); 48.7 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{17}H_{19}FClN_3O_6$: C, 49.11; H, 4.61; N, 10.11. Found: C, 48.82; H, 4.52; N, 9.89; MS *m/z* (FAB, relative abundance %) 438/440 ($MNa^{+\bullet}$, 86/38).

*N'-D-Aldehydoribosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbohydrazide (**19c**)*

From D-ribose (0.78 g). Yield: 1.80 g (88%); mp 168-171 °C; ^{1}H-NMR (DMSO-d_6) δ 12.58 (s, 1H, NH); 8.97 (s,1H, H-2); 8.32 (d, 1H, $J_{H8\text{-}F}$ 6.0 Hz, H-8); 8.17 (d, 1H, $J_{C5\text{-}F}$ 9.4 Hz, H-5); 6.15 (t, 1H, $J_{OH\text{-}H5',H5"}$ 5.3 Hz, $C_{5'}$-OH, exchangable with D_2O); 5.50-4.65 (m, 3H, 3xOH, exchangable with D_2O); 4.56 (m, 4H, H-1', H-2', CH_2CH_3); 3.40-3.33 (m, 3H, H-3', H-4', H-5'); 3.37 (dd, 1H, *J* 12.1 Hz, *J* 4.4 Hz, H-5"); 1.42 (t, 3H, *J* 7.1 Hz, CH_2CH_3); Anal. calc. for $C_{17}H_{19}FClN_3O_6$: C, 49.11; H, 4.61; N, 10.11. Found: C, 48.87; H, 4.52; N, 9.87; MS *m/z* (FAB, relative abundance %) 438/440 ($MNa^{+\bullet}$, 100/36).

*N'-D-Aldehydomannosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbo-hydrazide (**19d**)*

From D-mannose (0.94 g).Yield: 2.1 g (95%); mp 88-90 °C; ^{1}H-NMR (DMSO-d_6) δ 10.92 (d, 1H, $J_{NH,1'}$ 1.2 Hz, NH); 8.88 (s,1H, H-2); 8.28 (d, 1H, $J_{H8\text{-}F}$ 5.2 Hz, H-8); 8.12 (d, 1H, $J_{H5\text{-}F}$ 8.3 Hz, H-5); 4.76-4.51 (m, 3H, 3xOH, exchangable with D_2O); 4.59 (m, 5H, H-1', H-2', CH_2CH_3, OH); 4.54 (s, br, 1H, OH, exchangable with D_2O); 4.20 (dd, 1H, $J_{H2'\text{-}H3'}$ 9.2 Hz, $J_{H3'\text{-}H4'}$ 1.2 Hz, H-3'); 3.76 (dd, 1H, $J_{H3'\text{-}H4'}$ 1.2 Hz $J_{H4'\text{-}H5'}$ 9.1 Hz, H-4'); 3.64 (dd, 1H, $J_{H5'\text{-}H6'}$ 5.3 Hz, $J_{H6'\text{-}H6"}$ 12.0 Hz H-6'); 3.50 (dt, 1H, $J_{H5'\text{-}H.6'}$ 5.3 Hz, $J_{H5'\text{-}H.6"}$ 3.0 Hz, H-5'); 3.36 (d, 1H, $J_{H6'\text{-}H6"}$ 12.0 Hz, H-6"); 1.38 (t, 3H, *J* 7.1 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 173.5 (C-9); 161.8 (C-4); 154.5 (d, $J_{C6\text{-}F}$ 210.2 Hz, H-6); 152.6 (N=*C*H-1'); 147.9 (C-2); 135.6 (C-8a); 127.3 (d, $J_{C4a\text{-}F}$ 6.1 Hz, C-4a); 125.0 (d, $J_{C7\text{-}F}$ 20.4 Hz, C-7); 120.1 (C-8); 112.1 (d, $J_{C5\text{-}F}$ 23.5 Hz, C-5); 110.8 (C-3); 78.2 (C-3'); 74.2 (C-5'); 69.9 (C-4'); 67.2 (C-2'); 61.4 (C-6'); 48.6 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{18}H_{21}FClN_3O_7$: C, 48.49; H, 4.75; N, 9.43. Found: C, 48.31; H, 4.64; N, 9.21; MS *m/z* (FAB, relative abundance %) 468/470 ($MNa^{+\bullet}$, 100/38).

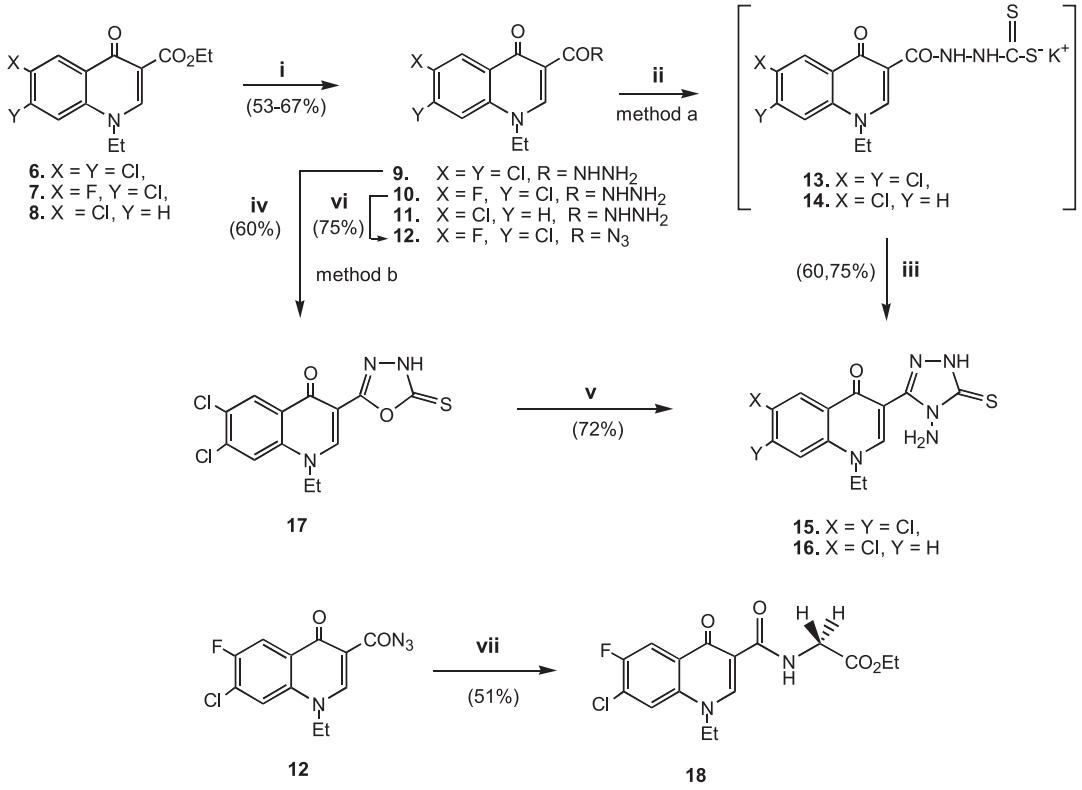
*N'-D-Aldehydogalactosyl-(7-chloro-l-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-3-yl)carbohydrazide (**19e**)*

From D-galactose (0.94 g). Yield: 1.90 g (86%); mp 114-117 °C; ^{1}H-NMR (DMSO-d_6) δ 10.78 (d, 1H, $J_{NH,1'}$ 2.0 Hz, NH); 8.78 (s,1H, H-2); 8.28 (d, 1H, $J_{H8\text{-}F}$ 5.1 Hz, H-8); 8.13 (d, 1H, $J_{H5\text{-}F}$ 8.4 Hz, H-5); 5.98 (t, 1H, $J_{OH\text{-}H6',H6"}$ 2.0 Hz, $C_{6'}$-OH, exchangable with D_2O); 4.88-4.72 (m, 3H, 3xOH, exchangable with D_2O); 4.66 (s, br, 1H, H-1'); 4.57 (m, 4H, H-2', CH_2CH_3, OH, exchangable with D_2O); 3.82 (dd, 1H, $J_{H2'\text{-}H3'}$ 1.3 Hz $J_{H3'\text{-}H4'}$ 8.5 Hz, H-3'); 3.69 (dd, 1H, $J_{H3'\text{-}H4'}$ 8.5 Hz; $J_{H4'\text{-}H5'}$ 2.5 Hz, H-4'); 3.55 (dd, 1H, $J_{H5'\text{-}H6'}$ 5.6 Hz,

$J_{H6'-H6''}$ 12.2 Hz, H-6'); 3.45 (dt, 1H, $J_{H5'-H6'}$ 5.6 Hz, $J_{H5'-H6''}$ 3.5 Hz, H-5'); 3.38 (d, 1H, $J_{H6'-H6''}$ 12.2 Hz, H-6''); 1.39 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C-NMR (DMSO-d_6) δ 173.6 (C-9); 163.8 (C-4); 155.0 (d, J_{C6-F} 212.8 Hz, H-6); 151.8 (N=*C*H-1'); 148.2 (C-2); 135.7 (C-8a); 127.3 (d, J_{C4a-F} 6.1 Hz, C-4a); 126.1 (d, J_{C7-F} 20.3 Hz, C-7); 120.1 (C-8); 112.2 (d, J_{C5-F} 22.3 Hz, C-5); 110.0 (C-3); 76.7 (C-3'); 73.3 (C-5'); 68.3 (C-4'); 68.0 (C-2'); 60.5 (C-6'); 48.7 (CH_2CH_3); 14.4 (CH_2CH_3); Anal. calc. for $C_{18}H_{21}FClN_3O_7$: C, 48.49; H, 4.75; N, 9.43. Found: C, 48.29; H, 4.61; N, 9.32; MS *m/z* (FAB, relative abundance %) 468/470 ($MNa^{+\bullet}$, 100/40).

Results and Discussion

Hydrazides **9-11** were prepared in 67, 53 and 65% yield, respectively, as key intermediates for the synthesis of the target molecules from reaction of the quinolones **6-8** with the hydrated hydrazine at 23 °C for 72 h (Scheme 1). Condensation of the carboxylic acid hydrazides **9** and **11** with CS_2 in ethanolic KOH afforded the unseparable potassium 3-quinolonodithio-carbazates **13** and **14**, respectively. These salts were cyclized, at refluxing temperature, with hydrazine followed by acidification with conc. HCl to furnish triazoles **15** and **16** in 60 and 83% yield, respectively. The 1,3,4-oxadiazole-2-thione derivative **17** was prepared from **9**, following Young and Wood[29] in 58% yield. Alternatively, **17** could be converted with hydrazine into the triazole **15** in 57% yield. Treatment of **10** with with $NaNO_2$ in the presence of 2 mol L^{-1} HCl and AcOH mixture at – 10 °C afforded the unstable carboxylic acid azide derivative **12**, which was used immediately for the next step. Condensation of the azide derivative **12** with glycine ethyl ester in the presence of base at – 10 °C for 1 h afforded the ethyl ester derivative **18** in 50% yield (Scheme 1). The structures of the newly compounds were confirmed by homo- and heteronuclear NMR spectroscopy methods and mass spectrometry. The proton spin systems of compounds **13-16** were elucidated from their DQF-COSY[30] spectra (chemical shifts are listed in experimental section). Compound **18** was selected for further NMR studies *via* gradient selected HMBC[31] spectrum: the carbonyl group (C-9) at δ_C 169.8 shows a $^3J_{C,H}$ correlation to CH_2-11 at δ_H 4.19, meanwhile C-2 at δ_C 147.6 shows the same correlation to N^1-CH_2CH_3 at δ_H 4.19.



(i) $N_2H_4.H_2O$/EtOH, 23 °C, 72 h; (ii) CS_2/KOH, EtOH, 23 °C, 72 h; (iii) $N_2H_4.H_2O$, reflux, 18 h; (iv) aq. KOH/EtOH, CS_2, reflux, 3 h; (v) 95% N_2H_4, H_2O, reflux, 4 h; (vi) 2 mol L^{-1} HCl/AcOH, - 10 °C, $NaNO_2$, 15 min; (vii) $NH_2CH_2CO_2Et$, Et_3N, 0-5 °C, 1 h

Scheme 1. Multistep synthesis of the hydrazides **9**-**11**, acid azide **12**, oxadiazoline **17**, mercapto-1,2,4-triazole **15**,**16** and α-amino ester **18** from the quinolones **6**-**8**.

Derivatization of the carboxylic group of the quinolone bases was extended next. The hydrazide key intermediate was used here for the synthesis of the 3-carbohydrazide-sugar compounds as promising antibacterial agents. Thus, boiling of **10** with five aldehydosugars (D-arabinose, D- xylose, D-ribose, D-mannose and D-galactose) for 2-4 h afforded, after purification, the yellowish 3-carbohydrazide derivatives **19a-e** in 86-98% yield (Scheme 2). The structures of these compounds were confirmed on the basis of their NMR spectra, which were characterized by the presence of a singlet in the region δ_H 8.99 – 8.78 (H-2) and two doublets at δ_H 8.32 – 8.24 with large coupling constant ($J_{H8\text{-}F}$ ~ 8.5 Hz), and at δ_H 8.15 – 8.11 with small coupling constant ($J_{H5\text{-}F}$ ~ 5.5 Hz), assigned to H-8 and H-5, respectively. The protons of the carbohydrate moiety were resolved, after exchanging the hydroxyl groups with D_2O, and comparison of their coupling constants with those of the corresponding free sugars. The proton spin system of **19a,c** was further confirmed from DFQ-COSY spectrum: H-1' of **19a** appeared as doublet at δ_H 4.99, while H-2' – H-5' in the region δ_H 4.64 – 3.46, and these protons correlated to the signals at δ_C 151.9, 70.3, 73.3, 70.9 and 63.3 for C-1' – C-5', respectively. Similarly, both protons and carbons of **19b-d** were identified, whereas the ^{13}C-NMR signals of the quinolone residue in **19a-e** were analysed by comparison to those of the previously reported quinolone nucleosides.[32]

Bioassay

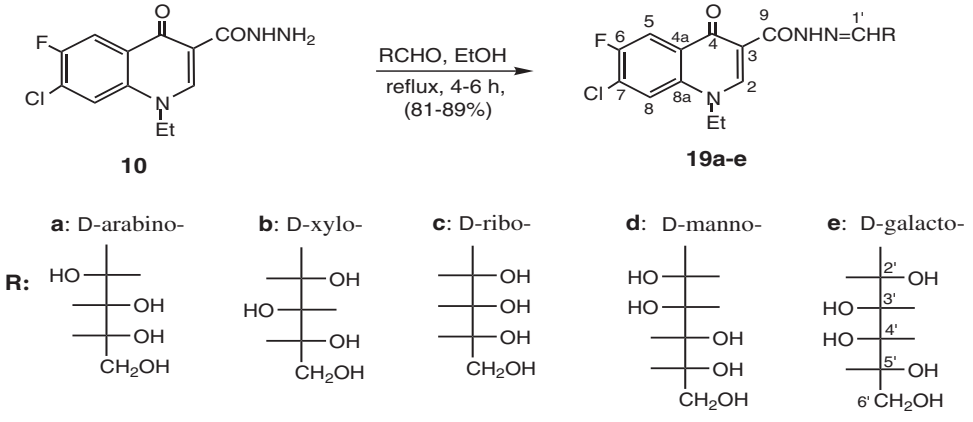
Two factors influence the Minimal Inhibitory Concentration (MIC) of fluoroquinolones: the rate of penetration into bacterial cell and its inhibitory activity of DNA gyrase.[33] Although, most of the studies proposed that a substituent at 7-position of the quinoline ring is related to the binding site with enzyme through electrostatic interactions,[34,35] our aim here was to study the influence of the structural change of the carboxylic group of the quinolone ring by *N'*-aldehydoglycosyl-carbohydrazides as well as a new heterocycle and a-amino acid ester groups on the antibacterial activity. The *in vitro* antimicrobial activity of compounds **15-18** and **19a-e** was tested by using the *Escherichia coli* K 12 wild-type strain D10, a gram negative bacterium, and wild-type *Bacillius subtilius*, a gram-positive bacterium, as well as *Staphylococcus aureus*. 10^4 Cells x mL^{-1} were incubated into LB medium containing the indicated amount of a given compond. After growth overnight at 37 °C, the optical density of the culture was determined. The minimal inhibitory concentrations (MIC) of **13-19** were determined by assaying the effect of each compound at concentrations of 0.1, 0.5, 1, 10, 50, 100, 200 and 500 mg x mL^{-1}, and none of them showed significant activity. The screening results of compounds **19a-e** are summarized in Table 1, using ciprofloxacine (CPR), as standard, for comparison.

Table 1. *In vitro* antibacterial screening[a]

Compd.	*E. coli*	*B.subtilis*	*S. aureus*
19a	5	10	100
19b	50	100	200
19c	10	200	100
19d	>500	200	200
19e	400	>500	200
CPR	0.03	-	0.25

[a] Numbers indicates the MIC in μg x mL^{-1} of the cell cultures.

The above data showed that the newly prepared compounds have slightly or no activity against the mentioned organisms, except **19a** which exhibited slight activity against *E. coli.* In conclusion, the substitution of the carboxylic group of the quinolones by 1,2,4-triazolyl,



Scheme 2. Synthesis of N'-aldehydoglycosyl-dihaloquinolone-carbohydrazides **19a-e** from the dihaloquinolone-carbohydrazide **10**.

1,3,4-oxadiazolyl, α-amino ester or hydrazide derivatives of aldehydosugars does not influence the antibacterial activity, since the new compounds are nearly inactive.

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References

1. For some recent reviews see: Chu, T. D. W.; Fernandez, P. B.; *Adv. Drug Res.* **1991**, *21*, 39; Wentland, M. P. In *The New Generation of Quinolones*; Siporin, C.; Heifetz, C. L.; Domagala, J. M., eds.; Maecel Dekker Inc.: New York, 1990, p. 1; Andriole, V. T.; *The Quinolones*; Academic Press: New York, 1988.
2. Chu, D. T. W.; Fernandez, P. B.; *Antimicrob. Agents Chemother.* **1989**, *33*, 131.
3. Smith, T. J.; Lewin, C. S. In *The Quinolones*; Anderiole, V. T., ed.; Academic Press: London, 1988, ch. 2.
4. Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Ivikura, T.; *J. Med. Chem.* **1980**, *23*, 1358.
5. Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailey, J. H.; Brundage, P. R.; *J. Med. Chem.* **1962**, *5*, 1963.
6. Wise, R; Andrews, J. M.; Edwards, L. J.; *Antimicrob. Agents Chemother.* **1983**, *23*, 559.
7. Hayakawa, I.; Hiramitsu, T.; Tanaka, Y.; *Chem. Pharm. Bull.* **1984**, *32*, 4907.
8. Miyamoto, T.; Matsumoto, J.; Chiba, K.; Egawa, H.; Shibamori, K.; Minamida, A.; Nishimura, Y.; Okada, H.; Fuzita, M.; Hirose, T.; Nakano, J.; *J. Med. Chem*. **1990**, *33*, 1645.
9. Ueda, Y.; Shimizu, K.; Konno, M.; Matsumoto, F. ,eds.; *The Quinolones*; Life Sciences Publisher: Tokyo, 1991, p. 315.
10. El-Subbagh, H. I.; Abadi, A. H.; Al-Khawad, I. E.; Al-Rashood, K. A.; *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 19.
11. Yoshida, T.; Yamamatoo, Y.; Orita, H.; Kakiuchi, M.; Takahashi, Y.; Itakura, M.; Kado, N.; Mitani, K.; Yasuda, S.; Kato, H.; Itoh, Y.; *Chem. Pharm. Bull.* **1996**, *44*, 1074.
12. Nieto, M. J.; Alovero, F. d. L.; Manzo, R. H.; Mazzieri, M. R.; *Eur. J. Med. Chem.* **1999**, *34*, 209.
13. El-Abadelah, M. M.; Sabri, S. S.; Al-Ashqar, H. A.; *Heterocycles* **1997**, *45*, 255.
14. El-Abadelah, M. M.; Nazer, M. Z.; Sabri, S.; Khalid, S. M.; Voelter, N.; Geiger, M.; Z. *Naturforschung* **1997**, *52b*, 419.
15. El-Abadelah, M. M.; Nazer, M. Z.; El-Abadelah, N. S.; Meier, H.; *Heterocycles* **1995**, *41*, 2203.
16. Al-Masoudi, N. A.; Al-Soud, Y. A..; Eherman, M.; De Clercq, E.; *Nucleos. Nucleot.* **1998**, *17*, 2255.
17. de la Cruz, A; Elguero, J.; Goya, P.; Matinez, A.; De Clercq, E.; *J. Chem. Soc. Perkin Trans. 1* **1993**, 845.
18. da Matta, A. D.; Bernardino, A. M. R.; Romeiro, G. A.; de Oliveira, M. R. P.; de Souza, M. C. B. V.; Ferreira, V. F.; *Nucleos. Nucleot.* **1996**, *15*, 889.
19. Al-Masoudi, N. A.; Al-Soud, Y. A.; Al-Masoudi, I. A.; *Sulfur Lett.* **2000**, *24*, 13.
20. Al-Masoudi, N. A.; Al-Soud, Y. A.; Eherman, M.; De Clercq, E.; *Bioorg. Med. Chem*. **2000**, *8*, 1407.
21. Gootz, T. D.; Barrett, J. F.; Sutcliffe, J. A.; *Antimicrob. Agents Chemother.* **1990**, *34*, 8.
22. Shimada, H.; Itoh, S.; *Program and Abstracts of 31th. ICAAC*, *American Soc. for Microbiology*, Washington D. C., 1991.
23. For references see: Ram, V. J.; Pandey, H. N.; *Chem. Pharm. Bull.* **1974**, *22*, 2778; Ram, V. J.; Pandey, H. N.; *Agr. Biol. Chem.* **1973**, *37*, 1465 and 2191.
24. El-Khawass, S. M.; Habib, N. S.; *J. Heterocyclic Chem.* **1989**, *26*, 177.
25. Mir, I.; Siddiqui, M. T.; Comrie, A. M.; *J. Chem. Soc. (Org.)* **1971**, 2798.
26. For biological activity of 1,3,4-oxadiazoles, see: Hill J. In *The Comprehensive Heterocyclic Chem. II*; Storr, R. C., ed.; Pergamon, Elsevier Science Ltd.: Oxford, 1996, ch. 4.06, p. 285; For biological activity of 1,2,4-triazoles, see: ch. 4.02, pp. 162, 163.
27. Oldfield, W.; *GB pat. 1, 147, 336* **1965** (*CA 71: P49795t*).
28. Kozello, I. A.; Khmelevskii, V. I.; Gasneva, A. Ya.; *PCJOAU*, *Pharma. Chem. J. (Engl. Transl.)* **1971**, *5*, 21 (*CA 74: P99832k*).
29. Young, R. W.; Wood, K. H.; *J. Am. Chem. Soc.* **1955**, *77*, 400.
30. Paintini, U.; Sørensen, O. W.; Ernst, R.; *J. Am. Chem. Soc.* **1982**, *104*, 6800.
31. Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W.; *Mag. Res. Chem.* **1993**, *31*, 287.
32. Al-Masoudi, N. A.; Al-Soud, Y. A.; Geyer, A.; *Spectroscopy Lett.* **1998**, *31*, 287.
33. Bazile, S.; Moreau, N.; Bouzard, D.; Essiz, M.; *Antimicrob. Agent Chemother.* **1992**, *36*, 2622.
34. Hooper, D. C.; Wolfson, J. S. eds; *Quinolone Antibacterial Agents*, 2nd ed., American Society for Microbiology: Washington DC., 1993, p. 489.
35. Shen, L. L.; Mitcher, L. A.; Sharma, P. N.; O'Donnell, T. J.; Chu, D. W. T.; Cooper, C. S.; Pernet, T. A. G.; *Biochemistry* **1989**, *28*, 3886.

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