SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF FURYL-SUBSTITUTED QUINOLONECARBOXYLIC ACIDS

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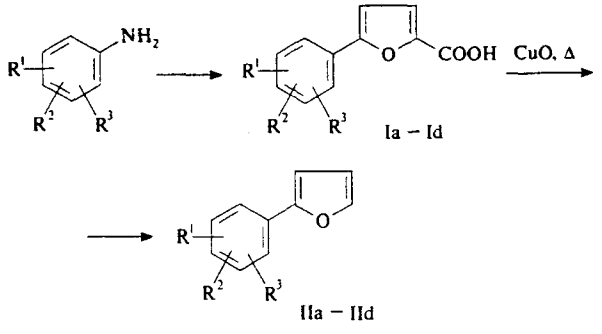
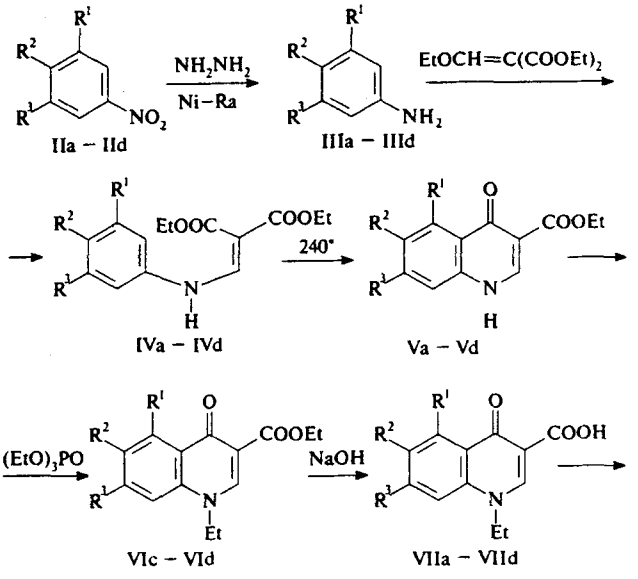
The results of our previous investigations of furyl-substituted quinolonecarboxylic acids [1, 2] revealed their high antibacterial activity depending on the character of the substituent in the quinolone cycle. Among the compounds studied, the maximum activity was observed for the quinolonecarboxylic acids containing nitrofuryl residues substituted in positions 6 and 7.

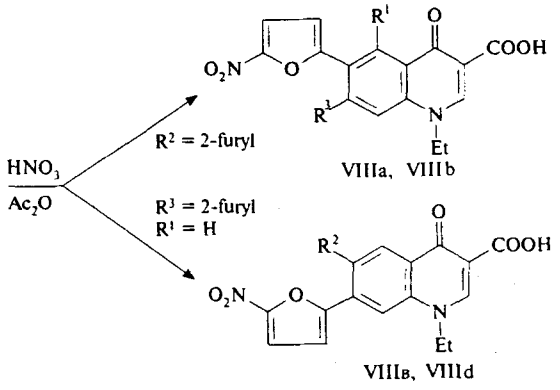
In continuation of the previous work, we have synthesized a series of quinolonecarboxylic acids with different substituents including, besides the nitrofuryl residue, halogen atoms (F, Cl) in various positions of the quinolone cycle. The initial compounds in the syntheses were represented by furylnitrobenzenes IIa – IId obtained by arylation of pyromucic acid with the corresponding nitroanilines followed by decarboxylation:



Ia, IIa: R^1 = 2-Cl; R^2 = 4-NO_2; R^3 = 6-Cl;
Ib, IIb: R^1 = 2-Cl; R^2 = 4-NO_2; R^3 = H;
Ic, IIc: R^1 = 2-Cl; R^2 = 5-NO_2; R^3 = H;
Id, IId: R^1 = 2-F; R^2 = 5-NO_2; R^3 = H.

The target quinolonecarboxylic acids VIIIa – VIIId were synthesized by the scheme developed previously [1, 2]:





IIa – VIIa: R^1 = Cl; R^2 = 2-furyl; R^3 = Cl;
IIb – VIIb: R^1 = H; R^2 = 2-furyl; R^3 = Cl;
IIc – VIIc: R^1 = H; R^2 = Cl; R^3 = 2-furyl;
IId – VIId: R^1 = H; R^2 = F; R^3 = 2-furyl;
VIIIa: R^1 = R^3 = Cl;
b: R^1 = H; R^3 = Cl;
c: R^2 = Cl;
d: R^2 = F.

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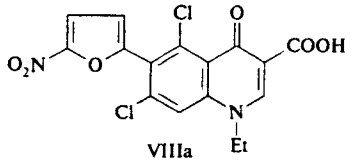
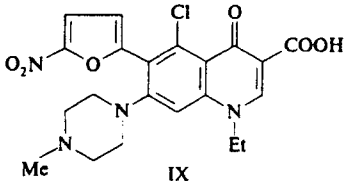
A number of quinolonecarboxylic acids available as drugs (perfloxacin, ofloxacin, etc.) are known to contain piperazinyl groups in position 7 of the quinolone cycle. Therefore, it was of interest to synthesize compound IX containing, besides the nitrofuryl group and a chlorine atom, an N-methylpiperazinyl substituent in position 7:



VIIIa



IX

EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were measured on the XL-200 and Unity+400 spectrometer (Varian, USA) spectrometers using TMS as an internal standard. The mass spectra were obtained with an SSQ-710 spectrometer (Finnegan, USA) with direct introduction of the samples into the ion source operated at an electron impact energy of 70 eV and an ionization chamber temperature of 150°C. The data of elemental analysis agree with the results of analytical calculations according to empirical formulas. The purity of synthesized compounds was checked by TLC on Silufol UV-254 plates eluted with the following solvent systems: benzene – dioxane – acetic acid (95 : 25 : 4) for compounds II, VII, VIII; petroleum ether – ethyl acetate (10 : 3) for compounds I, III, V; and chloroform – methanol (9 : 1) for compounds IV and VI.

5-(4-Nitro-2,6-dichloro)pyromucic acid (Ia). To a solution of 17.7 g (85 mmole) of 2,6-dichloro-4-nitroaniline in 270 ml of 75% aqueous sulfuric acid cooled to 0°C was added dropwise 68 ml of 33% sodium nitrite solution, and the mixture was kept for 30 min at 0 – 4°C. Then was added 330 ml of 20% hydrochloric acid solution, while the temperature was controlled so as not to exceed 10°C. Finally, urine was added until no iodine – starch paper indicator reaction was observed, and the reaction mixture was filtered. To the filtrate was added 7.0 g (73 mmole) of a pyromucic acid solution in 90 ml of acetone, and the mixture was heated to 15°C. Then was added a solution of 1.8 g copper(II) chloride in 25 ml water, and the mixture was kept for 12 h at room temperature. The precipitate was separated by filtration, washed with water (to pH 5 – 6) and benzene, and recrystallized to obtain 9.1 g of compound Ia. Similar procedures were used for the synthesis of compounds Ib – Id (Table 1).

5-(4-Nitro-2,6-dichloro)furan (IIa). To a solution of 7.9 g (26 mmole) of compound Ia in 200 ml of dimethylformamide was added 1.1 g of copper(II) oxide. The mixture was boiled with stirring for 6 h and cooled down to room temperature. The catalyst was separated by filtration and the filtrate was diluted with water. The precipitate was filtered and recrystallized to obtain 5.5 g of compound IIa. Similar procedures were used for the synthesis of compounds IIb – IId.

5-(4-Amino-2,6-dichloro)furan (IIIa). To a solution of 2.8 g (11 mmole) of compound IIa in 200 ml of absolute ethyl alcohol was added 3 ml of hydrazine hydrate and 0.6 g of Raney nickel. The reaction mixture was boiled for 1 h and the catalyst was separated by filtration. The filtrate was evaporated in vacuum and the residue recrystallized to obtain 2.1 g of compound IIIa. Similar procedures were used for the synthesis of compounds IIIb – IIId.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	M.p., °C (solvent)	Yield, %
Ia	$C_{11}H_5Cl_2NO_5$	251 – 253 (ethanol)	48
Ib	$C_{11}H_6ClNO_5$	252 – 254 (ethanol)	68
Ic	$C_{11}H_6ClNO_5$	244 – 245 (benzene)	63
Id	$C_{11}H_6FNO_5$	238 – 240 (acetonitrile)	53
IIa	$C_{10}H_5Cl_2NO_3$	97 – 98 (hexane)	81
IIb	$C_{10}H_6ClNO_3$	91 – 92 (hexane)	93
IIc	$C_{10}H_6ClNO_3$	117 – 119 (hexane)	63
IId	$C_{10}H_6FNO_3$	106 – 107 (petroleum ether)	58
IIIa	$C_{10}H_7Cl_2NO$	89 – 91 (benzene)	85
IIIb	$C_{10}H_8ClNO$	44 – 46 (petroleum ether)	72
IIIc	$C_{10}H_8ClNO$	38 – 40 (heptane)	49
IIId	$C_{10}H_8FNO$	36 – 38 (hexane)	54
IVa	$C_{18}H_{17}Cl_2NO_5$	93 – 94 (ethanol)	82
IVb	$C_{18}H_{18}ClNO_5$	68 – 69 (ethanol)	95
IVc	$C_{18}H_{18}ClNO_5$	90 – 91 (ethanol)	81
IVd	$C_{18}H_{18}FNO_5$	94 – 95 (ethanol)	82
Va	$C_{16}H_{11}Cl_2NO_4$	331 – 333 (DMF)	87
Vb	$C_{16}H_{12}ClNO_4$	> 280 (decomp.; DMF)	97
Vc	$C_{16}H_{12}ClNO_4$	> 280 (decomp.; DMF)	95
Vd	$C_{16}H_{12}FNO_4$	> 280 (decomp.; DMF)	96
VIa	$C_{18}H_{15}Cl_2NO_4$	189 – 190 (ethanol)	80
VIb	$C_{18}H_{16}ClNO_4$	188 – 189 (ethanol)	77
VIc	$C_{18}H_{16}ClNO_4$	230 – 232 (ethanol)	86
VId	$C_{18}H_{16}FNO_4$	215 – 216 (ethanol)	68
VIIa	$C_{16}H_{11}Cl_2NO_4$	261 – 263 (DMF)	89
VIIb	$C_{16}H_{12}ClNO_4$	263 – 265 (DMF)	92
VIIc	$C_{16}H_{12}ClNO_4$	265 – 267 (DMF)	90
VIId	$C_{16}H_{12}FNO_4$	254 – 256 (DMF)	85
VIIIa	$C_{16}H_{10}Cl_2N_2O_6$	303 – 304 (DMF)	72
VIIIb	$C_{16}H_{11}ClN_2O_6$	296 – 298 (DMF)	70
VIIIc	$C_{16}H_{11}ClN_2O_6$	288 – 290 (DMF)	69
VIIId	$C_{16}H_{11}FN_2O_6$	285 – 287 (DMF)	65
IX	$C_{21}H_{21}ClN_4O_6$	233 – 235 (heptane)	30

N-[4-(2-Furyl)-3, 5-dichlorophenyl]aminomethylenemalonic acid diethyl ester (IVa). A mixture of 4.5 g (20 mmole) of compound IIIa and 4.3 g (20 mmole) of ethoxymethylenemalonic acid ester was heated to 100 – 110°C with stirring for 2 h and then cooled. The precipitate was filtered and recrystallized to obtain 6.4 g of compound IVa. Similar procedures were used for the synthesis of compounds IVb – IVd.

1,4-Dihydro-4-oxo-6-(2-furyl)-5,7-dichloroquinoline-3-carboxylic acid ethyl ester (Va). A mixture of 2.7 g (7 mmole) of compound IVa with 55 ml of diphenyl ether was heated to 240 – 250°C and cooled. The precipitate was separated by filtration, washed with benzene, and recrystallized to obtain 1.8 g of compound Va. Similar procedures were used for the synthesis of compounds Vb – Vd.

1,4-Dihydro-4-oxo-6-(2-furyl)-5,7-dichloro-1-ethylquinoline-3-carboxylic acid ethyl ester (VIa). A mixture of 3.7 g (10 mmole) of compound Va and 1.7 g potassium carbonate in 6 ml of triethyl phosphate ether was heated to 200 – 210°C for 1 h and cooled. The precipitate was separated by filtration, washed with water, and recrystallized to obtain 3.1 g of compound VIa. Similar procedures were used for the synthesis of compounds VIb – VId.

1,4-Dihydro-4-oxo-6-(2-furyl)-5,7-dichloro-1-ethylquinoline-3-carboxylic acid (VIIa). A mixture of 1.0 g (3 mmole) of compound VIa in 90 ml of 10% KOH was boiled for 1 h. Then the solution was filtered and acidified with 2 N hydrochloric acid to pH 1.0. The precipitate was separated by filtration and washed with water to pH 6.0 – 7.0 to obtain 0.9 g of compound VIIa. Similar procedures were used for the synthesis of compounds VIIb – VIId (see Tables 1 and 2).

1,4-Dihydro-6-(5-nitro-2-furyl)-4-oxo-5,7-dichloro-1-ethylquinoline-3-carboxylic acid (VIIIa). To 3 ml of acetic anhydride cooled to – 5°C was added dropwise with stirring 0.9 ml of nitric acid (d = 1.4). To the resulting solution was added by portions 0.6 g (2 mmole) of compound VIIa and the mixture was stirred for 20 min at 20°C. Then the reaction mixture was poured into 50 ml of ice-cold water and the precipitate was filtered and recrystallized to obtain 0.5 g of compound VIIIa. Similar procedures were used for the synthesis of compounds VIIIb – VIIId.

1,4-Dihydro-7-(4-methyl-1-piperazinyl)-6-(5-nitro-2-furyl)-4-oxo-5-chloro-1-ethylquinoline-3-carboxylic acid (IX). A mixture of 0.40 g (1 mmole) of compound VIIIa and 0.44 g (2 mmole) of N-methylpiperazine in 1.8 ml of dry dimethyl sulfoxide was heated for 15 min at 120°C. Then the reaction mixture was poured into water and the product was extracted with ethyl acetate. The extract was dried over Na_2SO_4, after which the solvent was distilled off and the residue recrystallized to obtain 0.15 g of compound IX (Table 1).

EXPERIMENTAL BIOLOGICAL PART

The *in vitro* antimicrobial activity of the synthesized compounds was studied with respect to aerobic bacteria (*S. aureus* ATCC 6538-P; *S. aureus* 178; *S. aureus* Gure; *S. aureus* Smith, *B. subtilis* ATCC 6633; *E. coli* ATCC 25922; *Ps. aeruginosa* ATCC 27853; *Pr. vulgaris* ATCC 6896) and obligate anaerobes (*Bacteroides fragilis* 323; *Bacteroides distasonis* 255/82; *Peptostreptococcus anaerobius*

TABLE 2. Parameters of the ^{1}H NMR Spectra of Compounds VIIa – VIId and VIIIa – VIIId

Compound	Solvent*	Chemical shift, δ, ppm							
		H-C^2	H-C^5	H-C^8	H-$C^{3'}$**	H-$C^{4'}$**	H-$C^{5'}$**	N-C_2H_5	COOH
VIIa	DMSO-d_6	9.06 (s, 1H)	–	8.25 (s, 1H)	6.68*** (nm, 2H)		7.89 (t, 1H)	1.36 (t, 3H, CH_3), 4.61 (q, 2H, CH_2)	14.9 (s, 1H)
VIIb	DMF-d_7	9.06 (s, 1H)	8.76 (s, 1H)	8.37 (s, 1H)	7.35 (q, 1H, $^3J_{3',4'}$ 3.55 Hz, $^4J_{3',4'}$ 0.4 Hz)	6.76 (q, 1H, $^3J_{4',5'}$ 1.8 Hz)	7.99 (q, 1H)	1.59 (t, 3H, CH_3), 4.70 (q, 2H, CH_2)	14.84 (s, 1H)
VIIc	DMSO-d_6	9.07 (s, 1H)	8.30 (s, 1H)	8.18 (s, 1H)	7.45 (d, 1H, $^3J_{3',4'}$ 3.3 Hz)	6.79 (q, 1H, $^3J_{4',5'}$ 1.8 Hz)	8.03 (d, 1H)	1.45 (t, 3H, CH_3), 4.63 (q, 2H, CH_2)	14.79 (s, 1H)
VIId	DMSO-d_6	9.01 (s, 1H)	8.12 (d, 1H, ^{3}J5,F 11.4 Hz)	8.19 (d, 1H, 4J8, F 6.3 Hz)	7.20 (t, 1H, $^3J_{3',4'}$ 3.5 Hz)	6.76 (q, 1H, $^3J_{4',5'}$ 1.85 Hz)	7.99 (d, 1H)	1.48 (t, 3H, CH_3), 4.65 (q, 2H, CH_2)	14.81 (s, 1H)
VIIIa	DMSO-d_6	9.10 (s, 1H)	–	8.35 (s, 1H)	7.17 (d, 1H, $^3J_{3',4'}$ 3.8 Hz)	7.89 (d, 1H)	–	1.39 (t, 3H, CH_3) 4.58 (q, 2H, CH_2)	14.70 (s, 1H)
VIIIb	DMSO-d_6	9.09 (s, 1H)	8.73 (s, 1H)	8.38 (s, 1H)	7.59 (d, 1H, $^3J_{3',4'}$ 4.0 Hz)	7.88 (d, 1H)	–	1.37 (t, 3H, CH_3), 4.55 (q, 2H, CH_2)	14.61 (s, 1H)
VIIIc	DMSO-d_6	9.07 (s, 1H)	8.47 (s, 1H)	8.33 (bs, 1H)	7.62 (d, 1H, $^3J_{3',4'}$ 3.2 Hz)	7.85 (d, 1H)	–	1.46(t, 3H, CH_3), 4.64 (q, 2H, CH_2)	14.67 (s, 1H)
VIIId	DMSO-d_6	9.06 (s, 1H)	8.21 (d, 1H, ^{3}J5,F 11.2 Hz)	8.21 (d, 1H, 4J8, F 5.8 Hz)	7.53 (q, 1H, $^3J_{3',4'}$ 3.8 Hz)	7.86 (d, 1H)	–	1.50 (t, 3H, CH_3), 4.67 (q, 2H, CH_2)	14.48 (s, 1H)

* The NMR measurements performed at 23°C for VIIa – VIIc, VIIIb and 80°C for VIId, VIIIa, VIIIc, VIIId.
** Furyl group protons H-$C^{3'}$, H-$C^{4'}$, and H-$C^{5'}$.
*** Protons of the furan cycle form a system of the AA'M type.

891; *Clostridium septicum* 286; *Clostridium novji* t. A 302 NCTC 2908). The bacterial strains were obtained from the Tarasevich Institute for Standardization and Control of Medical and Biological Preparations.

The activity of compounds tested with respect to bacteria was determined by the method of serial double dilutions in a liquid nutrient medium [3]. Experiments with aerobic bacteria were performed in the Hottinger medium, and the obligate anaerobes were studied in the Schaedler anaerobe broth (Oxoid). The microbial load was 1×10^6 and 1×10^8 CFU / ml for aerobic and anaerobic bacteria, respectively [4].

The cultures were incubated for 24 h at 37°C. The anaerobic conditions were created by placing objects into a Jouan anaerobic station filled with a gas mixture composed of 10% CO_2, 10% H_2, and 80% N_2. The results were evaluated after a 24-h exposure.

The *in vivo* experiments were performed on a group of white inbred mice weighing 15 – 16 g. The test animals were intraperitoneally infected with a septicopyemia model at a dose (ID) corresponding to 1 LD_{100} (lethal challenge). The bacterial culture was injected as a suspension in an isotonic sodium chloride solution mixed with an 0.4% aqueous agar-agar as described in [5]. The infection doses (ID) employed led to a 95 – 100% loss of untreated animals in the control groups within 24 – 48 h after infection. The ID value corresponding to 1 LD_{100} was 8×10^8 CFU for the *S. aureus* Gure strain. The treatment of animals was initiated 30 – 40 min after infection by single peroral introduction of the drugs studied. The antibacterial activity was characterized by the percentage survival, ED_{50} value, and the total survival lifetime (% of the maximum possible lifetime) determined from the results of 10-day observation.

RESULTS

The results of our previous work showed that furyl-containing quinolonecarboxylic acids possessed antibacterial properties [1], the 7-furyl-substituted acid (VII, R^1 = H; R^2 = H; R^3 = 2-furyl) being more active with respect to Gram-positive bacteria (MPC = 0.06 μg / ml) and *E. coli* (MPC = 1 μg / ml) as compared to the 6-furyl-substituted derivative (VII, R^1 = H; R^2 = 2-furyl; R^3 = H) having the corresponding values of MPC = 0.5 – 1 and 2 μg / ml, respectively. Study of the antibacterial activity of the nitrofuryl-containing quinolonecarboxylic acids synthesized previously also demonstrated that their effect markedly exceeded that of the furylquinolonecarboxylic acids not substituted at the furan cycle, while retaining the same feature: the 7-nitrofuryl-substituted acid (VIII, R^1 = H; R^2 = H; R^3 = 5-nitro-2-furyl) was more active with respect to Gram-positive bacteria (MPC = 0.06 μg / ml) and *E. coli* (MPC = 1 μg / ml) as compared to the 6-nitrofuryl-substituted derivative (VIII, R^1 = H; R^2 = 5-nitro-2-furyl; R^3 = H) having the corresponding values of MPC = 1 μg / ml for *S. aureus* and MPC = 2 μg / ml for *E. coli*.

Table 3 presents the results of our investigation of the antibacterial activity of the newly synthesized compounds with respect to the aerobic bacteria. As is seen, the appearance of a chlorine atom in position 7 of the 6-nitrofurylquinolonecarboxylic acid VIIIb increases the antibacterial activity by two orders of magnitude as compared to that of the quinolonecarboxylic acid not substituted at this position. At the same time, the introduction of chlorine at position 6 (compound VIIIc) does not significantly affect the antibacterial activity: compounds VIIIb and VIIIc containing the nitrofuryl group in positions 6 and 7, respectively, have virtually equal activities. Thus, the influence of the position of nitrofuryl group on the antibacterial activity reported previously is not observed in the quinolonecarboxylic acids containing halogen atoms in addition to the nitrofuryl groups.

The presence of chlorine atoms in position 5 of the quinolone cycle sharply decreases the antibacterial activity of compounds VIIa and VIIIa.

Compound VIIId, containing a nitrofuryl group in position 7 and a fluorine atom in position 6 of the quinolone cycle, exhibits high activity with respect to Gram-positive bacteria (MPC = 0.003 – 0.0006 μg / ml) and medium activity with respect to *E. coli* (MPC = 0.5 μg / ml). Compound VIId, a fluorinated quinolone containing a furyl group in position 7,

TABLE 3. Antibacterial Activity of Quinolone-3-carboxylic Acids with Respect to Aerobic Bacteria

Compound	MPC, μg / ml				
	S. aureus	*B. subtil.*	*E. coli*	*Ps. aerug.*	*Pr. vulg.*
VIIa	31.2	31.2	> 250	> 250	> 250
VIIb	3.9	3.9	> 250	> 250	> 250
VIIc	125	125	> 250	125	125
VIId	0.25 – 0.5	0.12	15.6	3.9	> 250
VIIIa	31.2	31.2	> 250	> 250	> 250
VIIIb	0.06 – 0.12	0.25	3.9	62.5	> 250
VIIIc	0.03 – 0.06	0.25	31.2	> 250	> 250
VIIId	0.003 – 0.0006	0.06 – 0.01	0.5	62.5	> 250
IX	62.5	31.2	> 250	> 250	> 250

TABLE 4. Antibacterial Activity of Quinolone-3-carboxylic Acids with Respect to Anaerobic Bacteria

Compound	MPC, μg / ml				
	B. frag.	*B. dis.*	*Peptostr.*	*Cl. sep.*	*Cl. nov.*
VIIa	64	32	64	64	64
VIIb	16	16	32	32	16
VIIc	> 500	> 500	> 500	> 500	> 500
VIId	0.5 – 1	2	4	4 – 8	4 – 8
VIIIa	64	64	64	32	64
VIIIb	64	32	8	4	8
VIIIc	4	8	8	16	4
VIIId	0.25	0.25 – 0.5	2 – 4	4 – 8	4 – 8
IX	125	250	> 500	> 500	250

is less active compared to VIIId, although the activity of VIId with respect to Gram-positive bacteria is comparable with that of ciprofloxacin and maxaquin (MPC = 0.25 – 2.0 μg / ml).

Upon substituting fluorine for chlorine, while retaining the nitrofuryl group in position 7 (compound VIIc), the activity decreases to almost one-tenth of the initial level and amounts to MPC = 0.03 – 0.06 μg / ml for the Gram-positive bacteria and to MPC = 31.2 μg / ml for *E. coli*.

The absence of a nitro group in the furan cycle of furylquinolonecarboxylic acids considerably decreases their antibacterial activity (compounds VIIb – VIId).

Thus, we have established that the newly synthesized 7-nitrofuryl-substituted quinolonecarboxylic acids exhibit high antistaphylococcal activity. Our data confirm an important role for fluorine (enhancing the antibacterial activity) and the effect of chlorine in position 5 of the quinolone cycle (decreasing the antimicrobial action with respect to Gram-positive bacteria). Of the group of 9 quinolonecarboxylic acids studied, the maximum activity with respect to anaerobes was observed for two compounds containing fluorine in position 6 of the quinolone cycle. Compound VIIId with a nitrofuryl radical in position 7 is most active toward bacteroids (MPC = 0.25 – 0.5 μg / ml) and sufficiently active with respect to Gram-positive anaerobes (MPC = 2 – 8 μg / ml). The absence of the nitro group in the furan cycle (compound VIId) somewhat decreases the activity: the MPC values vary within 0.5 – 2 μg / ml for bacteroids and 4 – 8 μg / ml for peptostreptococci and clostridia.

Among the other compounds not containing fluorine, significant antibacterial activity was observed only for VIIIc (MPC = 4 – 8 μg / ml for bacteroids and clostridia).

Therefore, similarly to the case of aerobic bacteria, the major factor determining high antimicrobial effect with respect to anaerobes is the presence of a fluorine atom in position 6 of the quinolone cycle.

Because compound VIIId showed high activity *in vitro* with respect to Gram-positive aerobic bacteria (including four strains of *S. aureus*), it was of interest to assess the chemotherapeutic efficacy of this compound on the staphylococcal septicemia model in mice. For this purpose we have studied the chemotherapeutic activity of compound VIIId with respect to *S. aureus* Gure *in vivo* upon peroral administration in comparison to that of the reference drug lomefloxacin.

It was found that compound VIIId produces a chemotherapeutic effect equal to that of lomefloxacin, providing survival of about 70 – 80% of infected animals in the test group. The ED_{50} values of compound VIIId and lomefloxacin were 34.6 (24 – 49.9) and 42.01 (24.2 – 65.8) mg / kg, respectively. It should be noted that the *S. aureus* Gure strain is sensitive toward methicillin / oxacillin, and the published data are indicative of higher activity of fluoroquinolones with respect to this strain. Our experiments have confirmed the increased activity of a fluorine-substituted quinolonecarboxylic acid with respect to the methicillin / oxacillin-sensitive strain. In addition, we should like to point out a correlation between the results of *in vitro* and *in vivo* experiments on this strain.

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