SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW 7-SUBSTITUTED FLUOROQUINOLONES

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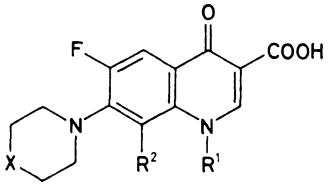
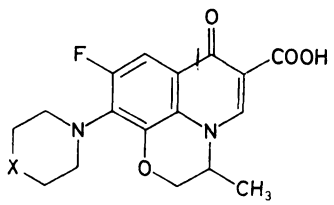
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Reaction of substituted 3-carboxyquinolone derivatives *IIIa*, *IIIb*, *IIIc*, and *IV* with 4-pyridone ethylene ketal in pyridine afforded corresponding 7-substituted derivatives *VIa*, *VIb*, *VIc*, and *VIIa*, respectively. Acidic deprotection of these compounds yielded respective oxo derivatives *VId*, *VIe*, *VIf*, and *VIIb* which were converted to their oximes *If*, *Ig*, *Ih*, and *IIb*.

Some antibacterial quinolones have been proven to be clinically important drugs[1,2]. It has been shown that C-7 substituent together with the presence of C-6 fluorine substituent has a major influence on the antibacterial activity. Most of the currently significant fluoroquinolones, as norfloxacin (*Ia*), pefloxacin (*Ib*), ciprofloxacin (*Ic*), and ofloxacin (*IIa*), contain 1-piperazinyl or 4-methyl-1-piperazinyl group at this position[2]. Recently 7-(4-hydroxy-1-piperazinyl) quinolone derivatives *Id* and *Ie* have been reported to be more potent than the corresponding 1-piperazinyl derivatives *Ia* and *Ic*. A QSAR study[3] revealed that good activity could be achieved for



Ia, $R^1 = C_2H_5$; $R^2 = H$; X = NH
Ib, $R^1 = C_2H_5$; $R^2 = H$; $X = NCH_3$
Ic, R^1 = cyclopropyl; $R^2 = H$; X = NH
Id, $R^1 = C_2H_5$; $R^2 = H$; X = NOH
Ie, R^1 = cyclopropyl; $R^2 = H$; X = NOH
If, $R^1 = C_2H_5$; $R^2 = H$; X = C=NOH
Ig, R^1 = cyclopropyl; $R^2 = H$; X = C=NOH
Ih, $R^1 = C_2H_5$; $R^2 = F$; X = C=NOH



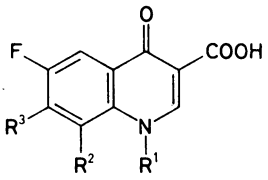
IIa, $X = NCH_3$
IIb, X = C=NOH

STERIMOL lengths of C-7 substituents in range of 0·5 to 0·9 nm. These facts inspired us to prepare compounds *If*, *Ig*, and *IIb* having at the position oximes of an 4-oxo-1-piperidino group. These compounds have also a N—OH fragment and STERIMOL length of the substituent is inside the optimal range. Since some 6,8--difluoro quinolones are more potent than corresponding 6-fluoro derivatives[2] we prepared also compound *Ih*. We report here the synthesis of these compounds and their antibacterial potency.

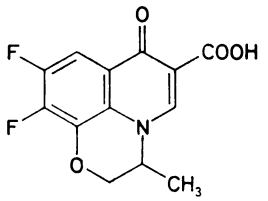
Desired quinolone intermediate compounds *IIIa* (ref.[4]), *IIIb* (ref.[5]), *IIIc* (ref.[6]), and *IV* (ref.[7]) were prepared according to the literature cited here. As a C-7 promoiety we chose *Vc*. Reaction of N-benzyl-4-piperidone (*Va*) with 1,2-dihydroxyethane was performed in usual way and provided corresponding ketal *Vb* in good yield. N-Debenzylation of *Vb* was performed by catalytic hydrogenation on 5% palladium on charcoal providing *Vc*.

Reaction of quinolone intermediates *IIIa* and *IIIb* with *Vc* was performed in pyridine at 110°C. Nucleophilic displacement reaction of pyrido[1,2,3-*de*][1,4]benzoxazine *IV* was much faster and could be performed at lower temperature. The most reactive 6,7,8-trifluoro derivative *IIIc* yielded smoothly compound *VIc* at temperature 50–60°C.

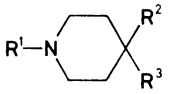
Compounds *VIa* – *VIc*, *VIIa* were converted to *VId* – *VIf*, *VIIb* under acidic condi-



IIIa, $R^1 = C_2H_5$; $R^2 = H$; $R^3 = Cl$
IIIb, R^1 = cyclopropyl; $R^2 = H$; $R^3 = Cl$
IIIc, $R^1 = C_2H_5$; $R^2 = F$; $R^3 = F$

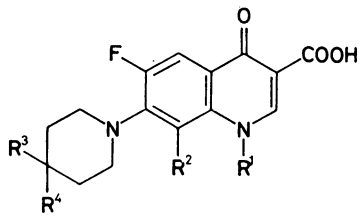


IV

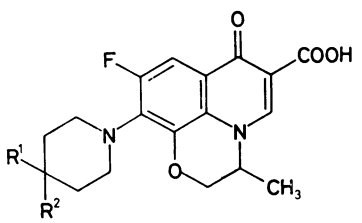


Va R^1 = benzyl; $R^2, R^3 = O$
Vb R^1 = benzyl; $R^2, R^3 = OCH_2CH_2O$
Vc $R^1 = H$; $R^2, R^3 = OCH_2CH_2O$

tions. The best results were obtained with the use of *p*-toluenesulfonic acid. Oxo derivatives *VId–VIf*, *VIIb* were treated with hydroxylamine in ethanol and provided corresponding oximes *If–Ih*, and *IIb*.



VI a, $R^1 = C_2H_5$; $R^2 = H$; $R^3, R^4 = OCH_2CH_2O$
VI b, R^1 = cyclopropyl; $R^2 = H$; $R^3, R^4 = OCH_2CH_2O$
VI c, $R^1 = C_2H_5$; $R^2 = F$; $R^3, R^4 = OCH_2CH_2O$
VI d, $R^1 = C_2H_5$; $R^2 = H$; $R^3, R^4 = O$
VI e, R^1 = cyclopropyl; $R^2 = H$; $R^3, R^4 = O$
VI f, $R^1 = C_2H_5$; $R^2 = F$; $R^3, R^4 = O$



VII a, $R^1, R^2 = OCH_2CH_2O$
VII b, $R^1, R^2 = O$

All the prepared compounds were tested for their antimicrobial activity in vitro at the Department of Microbiology of the Institute (Dr V. Holá, Head). Norfloxacin (*Ia*) was used as a standard. The minimum inhibitory concentrations in mg/l are given in Table I which summarizes the in vitro activity against Gram positive bacteria (*Staphylococcus aureus 1/45*, *Streptococcus pyogenes 4/49*, *Streptococcus faecalis D 16/66*) and Gram negative organisms (*Escherichia coli 326/61*, *Proteus vulgaris 2/35*, *Pseudomonas aeruginosa 26/56*). The organisms are from the State Collection of Strains, Prague. It is evident that all three types of compounds, i.e. 7-(4-oxopiperidine) derivatives, their ethylene ketals, and their oximes, have interesting antibacterial activities especially against Gram negative strains. More detailed results of their antibacterial activities will be published elsewhere.

EXPERIMENTAL

The melting points were determined on a Mettler FP 5 apparatus, and were not corrected. IR spectra were taken on a Unicam SP-2006 spectrometer in KBr pellets; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam PU 8800 spectrophotometer in ethanol, molar absorption coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. Mass spectra were measured on MCH 1320 and MAT 44 S spectrometers. ^1H NMR spectra (100 MHz) were measured on an apparatus BS-487 (Tesla Brno) 100 MHz in deuterated chloroform with tetramethylsilane as an internal standard, unless otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. The assignments indicated by an asterisk may be interchanged.

1-Benzyl-4-piperidone Ethylene Ketal (*Vb*)

A mixture of 1-benzyl-4-piperidone (1·9 g, 10 mmol), 4-toluenesulfonic acid monohydrate (3 g, 15·8 mmol), ethylene glycol (5 g, 80 mmol), and toluene (70 ml) was refluxed using Dean-Stark apparatus for 10 h. The mixture was neutralized with saturated aqueous solution of sodium hydrogen carbonate, then washed with water and the toluene solution was dried with magnesium sulfate. Vacuum disillation provided 2 g (87%) of colourless oil, b.p. 142–144°C/265–330 Pa. For $C_{14}H_{19}NO_2$ (233·3) calculated: 72·07% C, 8·21% H, 6·00% N; found: 72·39% C, 8·35% H, 5·96% N. ^{1}H NMR spectrum ($CDCl_3$): 1·70 bt*, 4 H (H-2, H-6); 2·49 bt*, 4 H (H-3, H-5); 3·48 s, 2 H (N—CH_2); 3·88 s, 4 H (O—CH_2); 7·24 m, 5 H (phenyl).

4-Piperidone Ethylene Ketal (*Vc*)

A solution of *Vb* (23·3 g, 0·1 mol) in methanol (230 ml) was hydrogenated on 5% palladium on charcoal (3 g) at room temperature until the required volume of hydrogen had been taken up (6 h), the catalyst was removed by filtration, methanol distilled off and vacuum distillation of the residue yielded 10·5 g (85%) of *Vc*, b.p. 70°C/160 Pa. For $C_7H_{13}NO_2$ (143·2) calculated: 58·72% C, 9·15% H, 9·78% N; found: 58·36% C, 9·34% H, 9·40% N. ^{1}H NMR spectrum ($CDCl_3$): 1·68 bt*, 4 H (H-2, H-6); 1·85 s, 1 H (N—H); 2·97 bt*, 4 H (H-3, H-5); 4·00 s, 4 H (O—CH_2).

TABLE I

In vitro antibacterial activity (MIC given in mg/l)

Compound	Organisms[a]					
	1	2	3	4	5	6
Ia	2	16	2	1	1	1
If	8	8	2	2	1	1
Ig	8	2	1	1	1	1
Ih	16	4	2	1	1	1
IIb	8	2	1	1	1	1
VIa	16	16	4	2	1	1
VIb	32	4	2	1	1	1
VIc	16	8	2	1	1	1
VId	4	16	4	2	1	1
VIe	32	4	2	1	1	1
VIf	4	4	1	1	1	1
VIIa	32	4	2	1	1	1
VIIb	4	2	1	1	1	1

[a] 1 — *Staphylococcus aureus*; 2 — *Streptococcus pyogenes*; 3 — *Streptococcus faecalis*; 4 — *Escherichia coli*; 5 — *Proteus vulgaris*; 6 — *Pseudomonas aeruginosa*.

TABLE II

Physico-chemical properties of compounds *If*—*Ih*, *IIb*, *VId*—*VIf*

Product m.p., °C	Starting compound	Yield, % time, h	Formula (M.w.)	Calculated/Found			
				% C	% H	% F	% N
If	*VId*	85	$C_{17}H_{18}FN_3O_4$	58·78	5·22	5·47	12·10
261—262		4	(347·4)	58·39	4·88	5·51	11·81
Ig	*VIe*	85	$C_{18}H_{18}FN_3O_4$	60·16	5·05	5·29	11·69
263—263·5		4	(359·4)	59·82	5·32	5·19	11·41
Ih	*VIf*	87	$C_{17}H_{17}F_2N_3O_4$	55·89	4·69	10·40	11·50
237·5—238		2	(365·3)	55·55	4·78	10·14	11·34
IIb[a]	*VIIb*	85	$C_{18}H_{18}FN_3O_5$	57·60	4·83	5·06	11·19
251·5—252		4	(375·4)	57·46	4·87	5·00	11·32
VId	*VIa*	90	$C_{17}H_{17}FN_2O_4$	61·44	5·16	5·72	8·43
233—235		16	(332·3)	61·07	5·26	5·67	8·47
VIe[b]	*VIb*	90	$C_{18}H_{17}FN_2O_4$	62·78	4·98	5·52	8·14
255—274[c]		8	(344·3)	62·90	5·28	5·35	8·56
VIf	*VIc*	90	$C_{17}H_{16}F_2N_2O_4$	58·29	4·60	10·85	8·00
286—287		8	(350·3)	58·40	4·80	10·92	7·84
VIIb	*VIIa*	90	$C_{18}H_{17}FN_2O_5$	60·00	4·76	5·27	7·77
259[c]		12	(360·3)	59·58	4·85	5·13	7·57

[a] Mass spectrum m/z = 375 (M^+); [b] mass spectrum m/z = 344 (M^+); [c] decomposition.

TABLE III

IR spectra of fluoroquinolone derivatives

Compound	C=O[a]	C=O[b]	COO	COOH	C=N	N—OH
If	1 630	—	1 735	945	1 612	3 310
Ig	1 625	—	1 720	970	1 610	3 250
Ih	1 620	—	1 735	943	1 610	3 300
IIb	1 619	—	1 701	917	1 610	3 300
VId	1 628	1 705[c]	1 710	998	—	—
VIe	1 628	1 718[c]	1 727	987	—	—
VIf	1 628	1 710	1 730	965	—	—
VIIb	1 620	1 710[c]	1 715	977	—	—

[a] C=O of quinolone; [b] C=O of piperidone; [c] weak signal.

1-Ethyl-6-fluoro-1,4-dihydro-7-(1,4-dioxa-8-azaspiro-[4,5]decan-8-yl)-4-oxoquinoline-3-carboxylic Acid (*VIa*)

A mixture of *IIIa* (2·7 g, 10 mmol), *Vc* (4·3 g, 30 mmol) and pyridine (30 ml) was stirred at 110°C for 40 h. Then pyridine was evaporated under reduced pressure and the oily residue was dissooved in ethanol and precipitated with dry ether. The formed precipitate was filtered off, washed with ethanol and ether. Crystallization from ethanol using charcoal yielded 2·4 g (64%) of white crystals; m.p. 214·5–216°C. For $C_{19}H_{21}FN_2O_5$ (376·4) calculated: 60·63% C, 5·62% H, 5·05% F, 7·44% N; found: 60·65% C, 5·72% H, 5·06% F, 7·18% N. ^{1}H NMR spectrum (perdeuterated dimethylsulfoxide, 3-trimethylsilylpropionic acid): 1·44 t, 3 H (CH_3, $J = 7$); 1·85 bt, 4 H (H-3′, H-5′); 3·20 bt, 4 H (H-2′, H-6′); 3·96 s, 4 H (O—CH_2); 4·60 q, 2 H (N—CH_2, $J = 7$); 7·20 d, 1 H (H-8, $J_{H,F} = 7$); 7·85 d, 1 H (H-5, $J_{H,F} = 12$); 8·95 s, 1 H (H-2). IR spectrum: 1 708 (COO), 1 625 (C=O), 1 518, 1 485, 1 450 (aromat. syst.), 1 248, 1 090 (C—O—C), 978 (COOH). UV spectrum, λ_{max} (log ε): 282 (3·37), 226 (2·76), 207 (2·93).

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1,4-dioxa-8-azaspiro-[4,5]decan-8-yl)-4-oxoquinoline-3-carboxylic Acid (*VIb*)

Using procedure described for *VIa* (reaction time 48 h) compound *VIb* was prepared in 67% yield; m.p. 200·5–203°C. For $C_{20}H_{21}FN_2O_5$ (388·4) calculated: 61·85% C, 5·45% H, 4·89% F, 7·21% N; found: 61·45% C, 5·60% H, 4·69% F, 7·61% N. IR spectrum: 1 723 (COO), 1 625 (C=O), 1 548, 1 490 (aromat. syst.), 1 040 (C—O—C), 948 (COOH). UV spectrum, λ_{max} (log ε): 320 (3·08), 281 (3·64), 224 (3·07), 206 (3·26).

1-Ethyl-6,8-difluoro-1,4-dihydro-7-(1,4-dioxa-8-azaspiro-[4,5]decan-8-yl)-4-oxo-quinoline-3-carboxylic Acid (*VIc*)

A mixture of *IIIc* (0·54 g, 2 mmol), *Vc* (0·86 g, 6 mmol), and pyridine (10 ml) was stirred at 50–60°C for 3 h. Crystals formed after cooling were collected by filtration and recrystallized from ethanol; yields 0·6 g (76%), m.p. 247·5–252°C. For $C_{19}H_{20}F_2N_2O_5$ (394·4) calculated:

TABLE IV

UV spectra of fluoroquinolone derivatives

Compound	λ_{max} (log ε)
If	330 (3·06), 314 (3·11), 282 (3·67), 225 (3·14), 205 (3·29)
Ig	315 (3·12), 282 (3·67), 224 (3·09), 205 (3·30)
Ih	330 (3·57), 318 (3·21), 208 (3·35)
IIb	323 (3·17), 297 (3·58), 225 (3·29)
VId	281 (3·64), 226 (3·08), 206 (2·95)
VIe	320[a] (3·01), 281 (3·59), 223[a] (2·97)
VIf	290 (3·56), 222 (3·19), 208 (3·28)
VIIb	298 (3·55), 225 (3·27)

[a] Shoulder.

57·87% C, 5·11% H, 9·63% F, 7·10% N; found: 57·58% C, 4·81% H, 9·65% F, 6·79% N. IR spectrum: 1 720 (COO), 1 620 (C=O), 1 530, 1 475, 1 460 (aromat. syst.), 1 080 (C—O—C), 945 (COOH). UV spectrum, λ_{max} (log ε): 290 (3·54), 223 (3·18), 207 (3·26).

9-Fluoro-2,3-dihydro-10-(1,4-dioxa-8-azaspiro[4,5]decan-8-yl)-
-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (*VIIa*)

Using procedure described for *VIc* (reaction time 24 h) compound *VIIa* was prepared in 96% yield, m.p. 253—256°C. For $C_{20}H_{21}FN_2O_6$ (404·4) calculated: 59·40% C, 5·24% H, 4·70% F, 6·93% N; found: 58·74% C, 5·50% H, 4·71% F, 6·64% N. IR spectrum: 1 725 (COO), 1 623 (C=O), 1 530, 1 492, 1 482, 1 460 (aromat. syst.), 1 092 (C—O—C), 960 (COOH). UVspectrum, λ_{max} (log ε): 298 (3·49), 225 (3·19); λ_{infl} 325 (3·09).

General Procedure for Preparation of *VId*, *VIe*, *VIf*, and *VIIb*

A mixture of 1 mmol of the respective ketal (*VIa*, *VIb*, *VIc*, *VIIa*), ethanol (10 ml), water (20 ml), and a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed until the starting material was present (Merck pre-coated TLC plates silica gel 60 F-254, dichloromethane–methanol–acetic acid 95 : 2·5 : 2·5). Then the mixture was cooled down, the insoluble portion was filtered off and crystallized from ethanol. Reaction time, yields and elemental data are in Table II. Results of IR (Table III), and UV spectra (Table IV) were in accordance with the proposed structures.

General Procedure for Preparation of oximes *If*, *Ig*, *Ih*, and *IIb*

To a solution of 1 mmol of the respective oxo derivative (*VId*, *VIe*, *VIf*, *VIIb*) in ethanol (300 ml) was at 60°C added a solution of 1 mmol of hydroxylamine in 50 ml of ethanol. The hydroxylamine solution was prepared in usual way from hydroxylamine hydrochloride and sodium ethanolate. The reaction mixture was stirred at room temperature until the starting material was present (Merck pre-coated TLC plates silica gel 60 F-254, dichloromethane–methanol–acetic acid 95 : 2·5 : 2·5) and evaporated to dryness. The residue was triturated with water, insoluble portion was filtered off and washed with water and ethanol. Recrystallization from ethanol yielded white crystals. M.p., yields, and elemental data are in Table II. Results of IR (Table III) and UV spectra (Table IV) were in accordance with the proposed structures.

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