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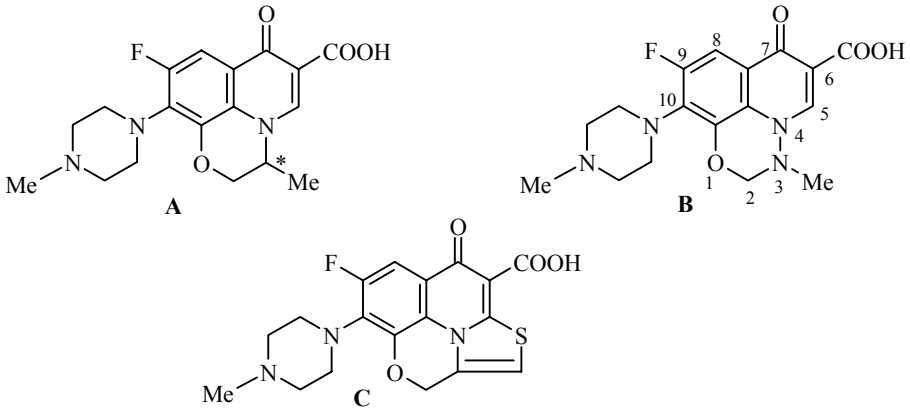
SYNTHESIS OF FLUORINATED 1,3,4-OXADIAZINO[6,5,4-*i*,*j*]QUINOLINES

G. N. Lipunova, E. V. Nosova, V. N. Charushin, and O. M. Chasovskikh

3-(2-Acylhydrazino)-2-tetra(penta)fluorobenzoylacrylates are readily converted to acylamino-substituted quinolones and, under more forcing conditions, annelation of oxadiazine ring occurs. We have identified the possible cyclization of the mentioned acrylates to 4,5-substituted pyrazoles.

Keywords: hydrazides of aromatic and pyridinecarboxylic acids, 1,3,4-oxadiazino[6,5,4-*i*,*j*]quinolines, reactivity, spectral characteristics.

Derivatives of 6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acids (fluoroquinolones) have presented themselves as efficient antibacterial agents [1-3]. Tri- and tetracyclic fluoroquinolones are particularly promising in this series and, along with their antibacterial activity, they possess antiviral and antitumor activity. The most important representatives of these polycyclic fluoroquinolones, having use in clinical practice, are the preparations ofloxacin (**A**), levofloxacin (the optically active S-isomer of ofloxacin), and marbofloxacin (**B**), and also the compound KB-5246 (**C**) which is under development [4-6].



In compounds **A** and **C** the quinolone residue is annelated at the [*i*,*j*] edge by the oxazine and in compound **B** by the 1,3,4-oxadiazine ring. Construction of the oxadiazine ring in compound **B** is carried out as in Scheme 1, but the given method allows one to obtain only derivatives which do not have a substituent at the position 2 [7].

Ural State Technical University, Yekaterinburg 620002, Russia; e-mail: charushin@prm.uran.ru, azine@htf.rcupi.e-burg.su. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1396-1406, October, 2001. Original article submitted July 20, 1999; revision submitted June 5, 2000.

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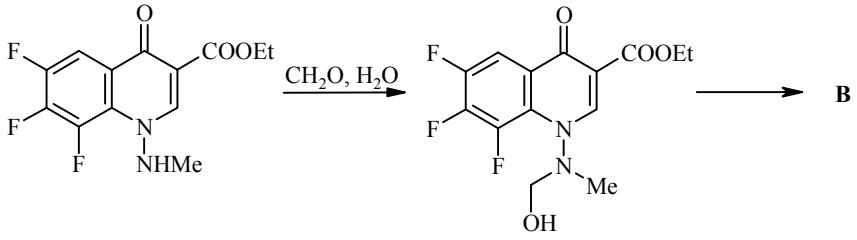
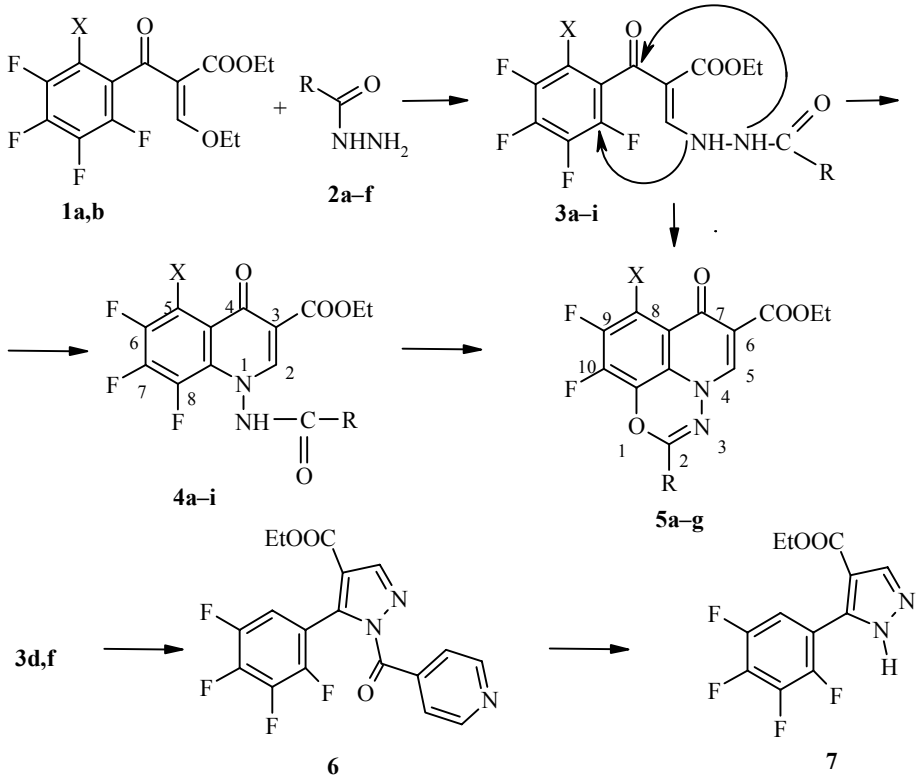
Scheme 1



Synthesis of [*i,j*]-annelated quinolones can be brought about if there are substituents at the quinoline nitrogen atom which contain a nucleophilic center in the γ-position [8, 9]. Hence cyclization of quinolones containing thiosemicarbazide fragment permits the preparation of 1,3,4-thiadiazino[*i,j*]-annelated systems [9].

By the reaction of ethyl 3-ethoxy-2-polyfluorobenzoylacrylates **1a,b** with the hydrazides of benzoic, *m*-nitrobenzoic, and acetic acids **2a,b,e** in ethanol or pyridinecarboxylic acids **2e,d** in toluene at room temperature, we have synthesized 3-(2-acylhydrazino)-2-tetra(penta)fluorobenzoylacrylates **3a-h** (Scheme 2) in 71-97% yields and have studied their cyclization. Like the starting acrylates **1a,b**, compounds **3a-c,h** exist in solution as a mixture of two isomers (3' and 3") relative to the C=C bond of the side chain and this is indicated by the presence of a double set of proton signals in their ^{1}H NMR spectra (Table 1).

Scheme 2



1a X = H, **b** X = F; **2a-5a** X = H, R = Ph; **2b-5b** X = H, R = $C_6H_4NO_2$-3; **3c–5c** X = F, R = $C_6H_4NO_2$-3; **2c, 3d-5d** X = H, R = 4-pyridyl; **3e-5e** X = F, R = 4-pyridyl; **2d, 3f–5f** X = H, R = 3-pyridyl, **3g-5g** X = F, R = 3-pyridyl; **2e, 3h, 4h** X = H, R = Me; **2f, 3i, 4i** X = H, R = CH_2CN

TABLE 1. ^{1}H NMR Spectral Characteristics of Ethyl 3-(2-Acylhydrazino-1)-2-[tetra(penta)fluorobenzoyl]acrylates **3a-h**, δ, ppm, spin-spin coupling constants (*J*), Hz

Com-pound	Solvent	=CHNH		NHCO, br. s		=CHNH		Isomer ratio **3':3''***
		3'	**3''**	**3'**	**3''**	**3'**	**3''**	
3a	CD_3CN	11.90, br. d, $^{3}J_{HH}$ = 11.0	10.45, br. d, $^{3}J_{HH}$ = 11.0	9.70		8.31, d, $^{3}J_{HH}$ = 11.0	8.11, d, $^{3}J_{HH}$ = 11.0	3:1
3b	$CDCl_3$	12.0, br. d, $^{3}J_{HH}$ = 11.4	11.1, br. d, $^{3}J_{HH}$ = 11.4	9.99	10.4	8.71, d, J_{HH} = 11.4		5:2
3c	$CDCl_3$	12.3, br. s	11.1, br. s	10.1	10.7	8.37, s	8.64, s	5:2
3d*[2]	DMSO-d_6	12.3, br. s		11.0		8.4, s		—
3e	DMSO-d_6	11.5, br. s		11.5		8.4, s		—
3f *[3]	DMSO-d_6	12.3, br. s		11.0		8.3, s		—
3g	DMSO-d_6	11.2, br. s		11.2		8.4, s		—
3h	DMSO-d_6	13.60, br. s		10.15	11.05	8.24, s	7.83, s	4:3

TABLE 1 (continued)

Com-pound	R		6-H		COOEt			
					CH_2, q		CH_3, t	
	3'	**3''**	**3'**	**3''**	**3'**	**3''**	**3'**	**3''**
3a	7.87 (2H, m, 2'- and 6'-H), 7.56 (3H, m, 3'-,4'- and 5'-H)		7.19, m		4.04, $^3J_{HH}$ = 7.1		1.09, $^3J_{HH}$ = 7.1	
3b	8.2-8.5 (3H, m, 2'-, 4'- and 6'-H), 7.72 (1H, dd, 5'-H, $^3J_{HH}$ = 8.0)		7.02, m		4.05 $^3J_{HH}$ = 7.0	4.12 $^3J_{HH}$ = 7.0	1.07 $^3J_{HH}$ = 7.0	1.24 $^3J_{HH}$ = 7.0
3c	8.72 (1H, m, 2'-H), 8.44 (1H, m, 4'-H or 6'-H), 8.27 (1H, m, 4'-H or 6'-H), 7.72 (1H, t, 5'-H, $^3J_{HH}$ = 7.9)	8.70 (1H, m, 2'-H), 8.41 (1H, m, 4'-H or 6'-H), 8.23 (1H, m, 4'-H or 6'-H), 7.68 (1H, t, 5'-H, $^3J_{HH}$ = 7.9)	—		4.06 $^3J_{HH}$ = 7.0	4.11 $^3J_{HH}$ = 7.0	1.09 $^3J_{HH}$ = 7.0	1.01 $^3J_{HH}$ = 7.0
3d	8.9 (2H, m, 3'- and 5'-H); 7.8 (2H, m, 2'- and 6'-H)		7.5, m		4.1, $^3J_{HH}$ = 7.1		1.1, $^3J_{HH}$ = 7.1	
3e	8.8 (2H, m, 3'- and 5'-H); 7.8 (2H, m, 2'- and 6'-H)		—		4.0, $^3J_{HH}$ = 7.1		1.1, $^3J_{HH}$ = 7.1	
3f	9.1 (1H, m, 2'-H); 8.8 (1H, m, 4'-H); 7.7 (1H, m, 6'-H); 7.5 (1H, m, 5'-H)		7.5, m		4.1, $^3J_{HH}$ = 7.2		1.1, $^3J_{HH}$ = 7.2	
3g	9.1 (1H, m, 2'-H); 8.7 (1H, m, 4'-H); 8.3 (1H, m, 6'-H); 7.6 (1H, m, 5'-H)		—		4.1, $^3J_{HH}$ = 7.2		1.1, $^3J_{HH}$ = 7.2	
3h	2.12 (3H, s, CH_3CO)	1.93 (3H, s, CH_3CO)	7.41, m 6.95, m		4.14 $^3J_{HH}$ = 7.0	3.94 $^3J_{HH}$ = 7.0	1.20 $^3J_{HH}$ = 7.0	0.99 $^3J_{HH}$ = 7.0

* Measurement based on the intensity of the doubled signals

*[2] ^{19}F NMR spectrum (DMSO-d_6): 157.6 (1F, m); 156.2 (1F, m); 143.4 (1F, m); 140.1 (1F, m).

*[3] ^{19}F NMR spectrum (DMSO-d_6): 157.7 (1F, m); 156.2 (1F, m); 142.3 (1F, m); 140.2 (1F, m).

TABLE 2. ^{1}H NMR Spectral Characteristics of Ethyl 5-X-1-Acylamino-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylates **4a-e,g,h,i**, δ, ppm, spin-spin coupling constants (*J*), Hz

Compound	Solvent	NH, br. s	2-H, s	5-H	R	OCH_2, q	CH_3, t
4a	CD_3CN	10.75	8.50	7.66 m	7.97 (3H, m); 7.58 (2H, m)	4.24	1.30
4b	CD_3CN	10.9	8.54	8.01 (ddd, $^3J_{HF}$ = 10.4, $^4J_{HF}$ = 8.2, $^5J_{HF}$ = 2.2)	8.76 (1H, dd, $^4J_{HH}$ = 1.7, 2'-H,); 8.49 (1H, ddd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.4, $^4J_{HH}$ = 1.1, 4'- or 6'-H); 8.30 (1H, m, 4'- or 6'-H); 7.83 (1H, dd, $^3J_{HH}$ = 8.1, 5'-H)	4.26	1.31
4c	$CDCl_3$	12.4	8.54	—	8.98 (1H, dd, $^4J_{HH}$ = 1.8, 2'-H); 8.45 (2H, m, 4'-, 6'-H); 7.73 (1H, dd, $^3J_{HH}$ = 7.9, 5'-H)	4.09	1.19
4d	DMSO-d_6	12.9	8.81	8.04 (ddd, $^3J_{HF}$ = 10.2, $^4J_{HF}$ = 8.0, $^5J_{HF}$ = 2.1)	8.87 (2H, dd, $^4J_{HH}$ = 4.4, $^5J_{HH}$ = 1.5, 3'-, 5'-H); 7.87 (2H, dd, $^4J_{HH}$ = 4.4, ^5J = 1.5, 2'-, 6'-H)	4.26	1.30
4e	DMSO-d_6	12.85	8.72	—	8.87 (2H, dd, $^4J_{HH}$ = 4.4, $^5J_{HH}$ = 1.5, 3'-, 5'-H); 7.85 (2H, dd, $^4J_{HH}$ = 4.4, ^5J = 1.5, 2'-, 6'-H)	4.23	1.29
4g	DMSO-d_6	12.6	8.56	—	9.09 (1H, dd, $^4J_{HH}$ = 1.5, $^5J_{HH}$ = 0.9, 2'-H); 8.80 (1H, dd, $^3J_{HH}$ = 4.9, $^4J_{HH}$ = 2.1, 4'-H); 8.26 (1H, ddd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 2.1, $^4J_{HH}$ = 1.5, 6'-H); 7.58 (1H, ddd, $^3J_{HH}$ = 7.9, $^3J_{HH}$ = 4.9, $^5J_{HH}$ = 0.9, 5'-H)	4.27	1.34
4h	$CDCl_3$	11.68	8.45	7.71 (ddd, $^3J_{HF}$ = 10.5, $^4J_{HF}$ = 8.1, $^5J_{HF}$ = 2.1)	2.33 (3H, s, $COCH_3$)	4.09	1.24
4i	DMSO-d_6	12.4	8.61	8.0 m	3.99 (2H, s, CH_2CN)	4.26	1.29

Cyclization of acrylates **3** can occur by two routes. Refluxing compounds **3a-e,g,h** in benzene (toluene) for 1 h gives the 1-acylamino-substituted quinolones **4a-e,g,h** in 40-92% yields. With more prolonged heating of acrylates **3a-g** in toluene in the presence of K_2CO_3 (3-4 h), the formation of the quinolone moiety is followed by cyclization involving the oxygen atom of the amide group to give compounds **5a-g** in 56-87% yields. The acylhydrazides **3d,e,f,g** can be converted to the tricyclic compounds **5d,e,f,g** in refluxing toluene in the absence of base. Acrylate **3f** is cyclized to quinolone **5f** so readily that it is not possible to separate the compound **4f**. The bicyclic quinolones **4a-e** are converted to the tricyclic derivatives **5a-e** upon heating in toluene in the presence of K_2CO_3. Compounds **5e,g** are also obtained by refluxing the corresponding acrylates **3e,g** in acetonitrile in the presence of KF for 3 h.

Quinolones **4h,i** can also be obtained without separation of the intermediate hydrazidoacrylates **3h,i**. Hence holding a mixture of acetic acid hydrazide **2e** and 3-ethoxy-2-tetrafluorobenzoylacrylate **1a** in ethanol at room temperature for 5 h and subsequent refluxing of the residue (after removal of solvent) in toluene for 4 h gave the product **4h** in 91% yield. Heating a mixture of cyanoacetic acid hydrazide **2f** and acrylate **1a** in toluene for 1.5 h at 80°C gave quinolone **4i** in 63% yield.

The reaction of **4h,i** to **5h,i** could not be carried out either in toluene with K_2CO_3 or in dioxane with NaH. When compound **4h** was heated in acetonitrile in the presence of diazabicycloundec-7-ene the cyclization product was recorded spectroscopically using ^{1}H NMR. The ^{1}H NMR spectrum of the product showed a signal for the proton of the polyfluorobenzene fragment as a double doublet (^3J = 10.2, ^4J = 7.6 Hz) whereas in quinolone **4h** it appeared as a double doublet of doublets. Isolation of a pure product and the proof of structure for the product of this reaction were not achieved.

The structures of the synthesized ethyl 5-X-1-acylamino-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates **4a-e,g,h,i** and ethyl 2-R-8-X-9,10-difluoro-7-oxo-7-H-[1,3,4]-oxadiazino[6,5,4-*i,j*]quinoline-6-carboxylates **5a-g** were established on the basis of their ^{1}H, ^{19}F NMR, and mass spectroscopic data. Hence the ^{1}H NMR spectra of quinolones **4a-e,g,h,i** show a singlet signal for the 2-H proton, a double doublet of doublets for the 5-H proton in the case of compounds **4a,b,d,h,i**, signals for the protons of the ethyl group and the R substituent, and also a broadened singlet for the NH group proton in the region of 10.7-12.9 ppm (Table 2). The ^{19}F NMR spectra show signals for all the fluorine atoms.

The mass spectra of the compounds **4** are characterized by a low intensity molecular ion peak (3-4% in the case of quinolones **4d,h,i**) or the absence of the same, with the presence of intense peaks $[M\text{-}HF]^+$ for compounds **4a,b,e** since, under mass spectrum scanning conditions, the given quinolones readily lose HF to give the tricyclic derivatives **5**. Subsequent fragmentation is evidently associated with elimination of ethoxy and carbethoxy groups and also with the destruction of the oxadiazine ring (Table 3).

TABLE 3. Mass Spectral and ^{19}F NMR Spectral Characteristics of Ethyl 5-X-1-Acylamino-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylates **4a-e,g,h,i**

Compound	Mass spectrum, *m/z* (I_{rel}, %)	^{19}F NMR spectra (DMSO-d_6), δ_F, ppm, spin-spin coupling constants, (*J*), Hz
1	2	3
4a	$[M–HF]^+$ 370 (20), 325 (21), 298 (100), 222 (14), 195 (42)	151.31 (ddd, $^3J_{FF}$ = 23.1, $^3J_{FF}$ = 19.5, $^4J_{HF}$ = 8.3, 7-F); 148.48 (ddd, $^3J_{FF}$ = 19.5, $^4J_{FF}$ = 4.9, $^5J_{HF}$ = 2.0, 8-F); 136.45 (ddd, $^3J_{FF}$ = 23.1, $^3J_{HF}$ = 10.5, $^4J_{FF}$ = 4.9, 6-F)
4b	$[M–HF]^+$ 415 (11), 370 (13), 343 (100), 324 (15), 297 (14), 222 (9), 195 (22)	151.14 (ddd, $^3J_{FF}$ = 23.1, $^3J_{FF}$ = 19.4, $^4J_{HF}$ = 8.2, 7-F); 148.71 (ddd, $^3J_{FF}$ = 19.4, $^4J_{FF}$ = 4.9, $^5J_{HF}$ = 2.2, 8-F); 136.36 (ddd, $^3J_{FF}$ = 23.1, $^3J_{HF}$ = 10.4, $^4J_{FF}$ = 4.9, 6-F)
4c	$[M–HF]^+$ 434 (18), 388 (23), 361 (100), 342 (17), 315 (12), 240 (24), 213 (38)	160.11 (dd, $^3J_{FF}$ = 21.7, $^3J_{FF}$ = 20.2, 7-F); 154.12 (dd, $^3J_{FF}$ = 20.2, $^4J_{FF}$ = 13.9, 5-F); 147.15 (ddd, $^3J_{FF}$ = 21.7, $^3J_{FF}$ = 20.2, $^4J_{FF}$ = 9.2, 6-F); 142.82 (ddd, $^3J_{FF}$ = 20.2, $^4J_{FF}$ = 13.9, $^4J_{FF}$ = 9.2, 8-F)

TABLE 3 (continued)

1	2	3
4d	M^+ 391 (4), 371 (100), 326 (100), 300 (98), 299 (100), 222 (38)	151.13 (ddd, $^3J_{FF}$ = 23.2, $^3J_{FF}$ = 19.2, $^4J_{HF}$ = 8.0, 7-F); 148.66 (ddd, $^3J_{FF}$ = 19.2, $^4J_{FF}$ = 4.6, $^5J_{HF}$ = 2.1, 8-F); 136.32 (ddd, $^3J_{FF}$ = 23.2, $^3J_{HF}$ = 10.2, $^4J_{FF}$ = 4.6, 6-F)
4e	$[M–HF]^+$ 389 (63), 344 (48), 317 (100), 240 (24)	160.75 (dd, $^3J_{FF}$ = 22.6, $^3J_{FF}$ = 21.6, 7-F); 155.89 (dd, $^3J_{FF}$ = 21.6, $^4J_{FF}$ = 13.3, 5-F); 148.65 (ddd, $^3J_{FF}$ = 21.6, $^3J_{FF}$ = 22.6, $^4J_{FF}$ = 8.5, 6-F); 143.17 (ddd, $^3J_{FF}$ = 21.6; $^4J_{FF}$ = 13.3; $^4J_{FF}$ = 8.5, 8-F)
4g	$[M–HF]^+$ 390 (30), 34 (27), 317 (100), 240 (24), 213 (42), 185 (31)	160.81 (dd, $^3J_{FF}$ = 22.2, $^3J_{FF}$ = 21.5, 7-F); 155.91 (dd, $^3J_{FF}$ = 21.5, $^4J_{FF}$ = 13.3, 5-F); 148.68 (ddd, $^3J_{FF}$ = 21.5, $^3J_{FF}$ = 22.2, $^4J_{FF}$ = 8.5, 6-F); 143.22 (ddd, $^3J_{FF}$ = 21.5, $^4J_{FF}$ = 13.3, $^4J_{FF}$ = 8.5, 8-F)
4h	M^+ 328 (3%), 308 (27), 263 (56), 236 (100), 222 (30), 195 (46)	151.53 (ddd, $^3J_{FF}$ = 23.3, $^3J_{FF}$ = 19.4, $^4J_{HF}$ = 8.6, 7-F); 148.73 (ddd, $^3J_{FF}$ = 19.4, $^4J_{FF}$ = 4.3, $^5J_{HF}$ = 2.2, 8-F); 136.60 (ddd, $^3J_{FF}$ = 23.3, $^3J_{HF}$ = 10.8, $^4J_{FF}$ = 4.3, 6-F)
4i	M^+ 353 (3%), 333 (13), 308 (4), 288 (32), 261 (100), 223 (36), 195 (6)	151.29 (ddd, $^3J_{FF}$ = 23.2, $^3J_{FF}$ = 19.3, $^4J_{HF}$ = 7.8, 7-F); 148.29 (ddd, $^3J_{FF}$ = 19.3, $^4J_{FF}$ = 4.9, $^5J_{HF}$ = 2.0, 8-F); 136.42 (ddd, $^3J_{FF}$ = 23.2, $^3J_{HF}$ = 10.5, $^4J_{FF}$ = 4.9, 6-F)

The ^{1}H NMR spectra of the tricyclic fluoroquinolone derivatives **5** are characterized by the presence of a singlet for the 2-H proton, a double doublet for the 8-H proton (**5a,b,d,e)**, and also signals for the protons of the ethyl group and the substituent R (Table 4). The ^{19}F NMR spectra also correspond to the proposed structure **5**. In the mass spectra of quinolones **5** intense molecular ion peaks are observed. The peak with 100% intensity corresponds to fission of carbethoxy group and this underlines the high thermal stability of the tricyclic system **5** (Table 5).

TABLE 4. ^{1}H NMR Spectral Characteristics of Ethyl 2-R-8-X-9,10-Difluoro-7-oxo-7-H-[1,3,4]oxadiazino[6,5,4-*i*,*j*]quinolinecarboxylates **5a-g***, δ, ppm, spin-spin coupling constants (*J*), Hz

Com-pound	5-H, s	8-H	R	OCH_2, q	CH_3, t
5a	8.48	7.63 m	8.02 (2H, m); 7.63 (3H, m)	4.27	1.33
5b	8.72	7.59 dd ($^3J_{HF}$ = 10.5, $^4J_{HF}$ = 7.6)	7.90 (dd, 1H, $^3J_{HH}$ = 7.9, 5'-H); 8.37 (m, 1H, 4'- or 6'-H); 8.48 (m, 1H, 4'- or 6'-H); 8.54 (m, 1H, 2'-H)	4.26	1.35
5c	8.46	—	7.89 (dd, 1H, $^3J_{HH}$ = 8.1, 5'-H); 8.34 (m, 1H, 4'- or 6'-H); 8.51 (m, 1H, 4'- or 6'-H); 8.68 (m, 1H, 2'-H)	4.24	1.34
5d	8.56	7.63 dd ($^3J_{HF}$ =11.0, $^4J_{HF}$ = 7.5)	7.88 (dd, 2H, $^3J_{HH}$ = 4.5, $^4J_{HH}$ = 1.5, 2'- and 6'-H); 8.85 (dd, 2H, $^3J_{HH}$ = 4.5, $^4J_{HH}$ = 1.5, 3'- and 5'-H)	4.23	1.30
5e	8.47	—	7.85 (dd, 2H, $^3J_{HH}$ = 4.6, $^4J_{HH}$ = 1.5, 2'- and 6'-H); 8.84 (dd, 2H, $^3J_{HH}$ = 4.6, $^4J_{HH}$ = 1.5, 3'- and 5'-H)	4.22	1.28
5f	8.57	7.64 dd ($^3J_{HF}$ = 10.4, $^4J_{HF}$ = 7.6)	7.67 (ddd, 1H, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 4.9, $^5J_{HH}$ = 0.8, 5'-H); 8.32 (ddd, 1H, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 2.3, $^4J_{HH}$ = 1.5, 6'-H); 8.85 (dd, 1H, $^3J_{HH}$ = 4.9, ^4J = 2.3, 4'-H); 9.14 (dd, 1H, $^4J_{HH}$ = 1.5, $^5J_{HH}$ = 0.8, 2'-H)	4.23	1.30
5g	8.50	—	7.65 (ddd, 1H, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 4.8, $^5J_{HH}$ = 0.9, 5'-H); 8.32 (ddd, 1H, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 2.3, $^4J_{HH}$ = 1.5, 6'-H); 8.86 (dd, 1H, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 2.3, 4'-H); 9.12 (dd, 1H, $^4J_{HH}$ = 1.5, $^5J_{HH}$ = 0.9, 2'-H)	4.23	1.29

* Spectrum of compound **5a** recorded in CD_3CN, the reminder in DMSO-d_6

TABLE 5. Mass Spectral and ^{19}F NMR Spectral Characteristics of Ethyl 2-R-8-X-9,10-Difluoro-7-oxo-7-H-[1,3,4]oxadiazino[6,5,4-*i,j*]quinoline-6-carboxylates **5a-g**

Compound	Mass spectrum, *m/z* (I_{rel}, %)	^{19}F NMR spectra (DMSO-d_6), δ, ppm, spin-spin coupling constants, (*J*), Hz
5a	M^+ 370 (23), 325 (24), 298 (100), 222 (17), 195 (51)	154.65 (dd, $^3J_{FF}$ = 22.0, $^4J_{HF}$ = 7.3, 10-F); 134.91 (dd, $^3J_{FF}$ = 22.0, $^3J_{HF}$ = 10.7, 9-F)
5b	M^+ 415 (14), 370 (16), 343 (100), 324 (20), 297 (16), 222 (11), 195 (26)	154.65 (dd, $^3J_{FF}$ = 22.1, $^4J_{HF}$ = 7.8, 10-F); 134.59 (dd, $^3J_{FF}$ = 22.1, $^3J_{HF}$ = 10.5, 9-F)
5c	M^+ 433.6 (16), 389 (14), 362 (100), 42 (13), 315 (8), 240 (12), 213 (29), 185 (23)	160.58 (dd, $^3J_{FF}$ = 19.5, $^3J_{FF}$ = 20.5, 9-F); 151.45 (dd, $^3J_{FF}$ = 20.5, $^4J_{FF}$ = 5.5, 10-F); 146.25 (dd, $^3J_{FF}$ =19.5, $^4J_{FF}$ = 5.5, 8-F)
5d	M^+ 371 (50), 326 (51), 299 (100)	154.24 (dd, $^3J_{FF}$ = 22.0, $^4J_{HF}$ = 7.5, 10-F); 134.51 (dd, $^3J_{FF}$ = 22.0, $^3J_{HF}$ = 11.0, 9-F)
5e	M^+ 389 (40), 344 (45), 317 (100), 240 (36), 213 (34), 185 (34)	160.59 (dd, $^3J_{FF}$ = 20.2, $^3J_{FF}$ = 21.4, 9-F); 151.43 (dd, $^3J_{FF}$ = 21.4, $^4J_{FF}$ = 6.0, 10-F); 146.19 (dd, $^3J_{FF}$ = 20.2, $^4J_{FF}$ = 6.0, 8-F)
5f	M^+ 371 (82), 326 (73), 299 (100)	154.24 (dd, $^3J_{FF}$ = 22.0, $^4J_{HF}$ = 7.6, 10-F); 134.66 (dd, $^3J_{FF}$ = 22.0, $^3J_{HF}$ = 10.4, 9-F)
5g	M^+ 389 (34), 344 (30), 317 (100), 240 (29), 213 (33), 185 (27)	160.77 (dd, $^3J_{FF}$ = 20.2, $^3J_{FF}$ = 21.3, 9-F); 151.42 (dd, $^3J_{FF}$ = 21.3, $^4J_{FF}$ = 5.5, 10-F); 146.31 (dd, $^3J_{FF}$ = 20.2, $^4J_{FF}$ = 5.5, 8-F)

In the case of acrylates **3d,f** it was found that, when refluxed in acetonitrile in the presence of KF for 4 h, cyclization by a second route occurred involving carbonyl group and that this led to the 4,5-substituted pyrazoles **6,7**.

This reaction is accompanied by hydrolysis of the amide group (Scheme 2), while in the case of acrylate **3f** only pyrazole **7** was isolated. The structure of the products **6,7** was confirmed by ^1H and ^{19}F NMR spectroscopic data (see Experimental).

In conclusion, we should mention that the derivatives **5** are important synthetic intermediates and can be used to prepare a wide range of novel tricyclic fluoroquinolone carboxylic acid derivatives in order to study their biological activity.

TABLE 6. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
1	2	3	4	5	6	7
3a	$C_{19}H_{14}F_4N_2O_4$	55.84 / 55.62	3.35 / 3.44	7.01 / 6.83	148-150	74 (A)
3b	$C_{19}H_{13}F_4N_3O_6$	49.98 / 50.12	3.08 / 2.88	9.41 / 9.23	68-70	90 (A)
3c	$C_{19}H_{12}F_5N_3O_6$	47.74 / 48.12	2.76 / 2.56	8.96 / 8.88	79-81	79 (A)
3d	$C_{18}H_{13}F_4N_3O_4$	52.47 / 52.56	3.59 / 3.19	9.62 / 10.22	111-113	97 (B)
3e	$C_{18}H_{12}F_5N_3O_4$	50.20 / 50.36	3.00 / 2.89	10.03 / 9.79	125-127	89 (B)
3f	$C_{18}H_{13}F_4N_3O_4$	52.61 / 52.56	3.35 / 3.19	10.03 / 10.22	127-129	93 (B)
3g	$C_{18}H_{12}F_5N_3O_4$	49.97 / 50.36	3.00 / 2.82	10.40 / 9.79	117-119	97 (B)

TABLE 6 (continued)

1	2	3	4	5	6	7
3h	$C_{14}H_{12}F_4N_2O_4 \cdot H_2O$	45.92 / 45.91	3.60 / 3.85	7.81 / 7.65	133-135	71 (A)
4a	$C_{19}H_{13}F_3N_2O_4 \cdot H_2O$	56.06 / 55.89	3.77 / 3.70	6.80 / 6.86	82-84	91 (D)
4b	$C_{19}H_{12}F_3N_3O_6 \cdot H_2O$	50.43 / 50.34	3.23 / 3.11	9.15 / 9.27	124-126	82 (D)
4c	$C_{19}H_{11}F_4N_3O_6 \cdot 0.5H_2O$	49.70 / 49.38	2.85 / 2.62	9.12 / 9.05	176-178	96 (D)
4d	$C_{18}H_{12}F_3N_3O_4 \cdot C_2H_5OH$	55.10 / 54.92	4.22 / 4.15	9.58 / 9.61	140-142	40 (C)
4e	$C_{18}H_{11}F_4N_3O_4 \cdot H_2O$	51.14 / 50.60	3.09 / 3.07	9.86 / 9.83	136-138	56 (C)
4g	$C_{18}H_{11}F_4N_3O_4 \cdot H_2O$	50.81 / 50.60	3.38 / 3.07	9.78 / 9.83	112-114	78 (D)
4h	$C_{14}H_{11}F_3N_2O_4 \cdot H_2O$	49.13 / 48.56	3.48 / 3.78	8.22 / 8.09	172-174	84 D), 91 (E)
4i	$C_{15}H_{10}F_3N_3O_4$	50.96 / 51.00	3.02 / 2.85	12.77 / 11.90	213-215	63 (F)
5a	$C_{19}H_{12}F_2N_2O_4$	60.90 / 61.63	3.31 / 3.27	7.39 / 7.56	209-211	85 (I), 95 (J)
5b	$C_{19}H_{11}F_2N_3O_6 \cdot 0.5H_2O$	54.08 / 53.81	2.94 / 2.85	9.83 / 9.91	256-258	76 (I), 89 (J)
5c	$C_{19}H_{10}F_3N_3O_6 \cdot 0.5H_2O$	51.79 / 51.62	2.65 / 2.51	9.46 / 9.51	248-250	71 (I), 83 (J)
5d	$C_{18}H_{11}F_2N_3O_4$	58.10 / 58.23	2.99 / 2.99	10.86 / 11.32	244-246	69 (I), 78 (J), 61 (G)
5e	$C_{18}H_{10}F_3N_3O_4$	55.67 / 55.54	2.71 / 2.59	11.17 / 10.79	238-240	87 (I), 81 (J), 72 (H), 87 (G)
5f	$C_{18}H_{11}F_2N_3O_4$	58.42 / 58.23	2.89 / 2.99	11.11 / 11.32	216-218	67 (I), 58 (G)
5g	$C_{18}H_{10}F_3N_3O_4$	55.38 / 55.54	2.67 / 2.59	10.57 / 10.79	226-228	56 (I), 76 (H), 64 (G)
6	$C_{18}H_{11}F_4N_3O_3 \cdot H_2O$	52.53 / 52.56	3.10 / 3.19	10.07 / 10.22	143-145	47
7	$C_{12}H_8F_4N_2O_2$	50.41 / 50.09	3.15 / 2.80	9.89 / 9.72	140-142	38

EXPERIMENTAL

^{1}H NMR spectra were obtained on a Bruker WP-250 (250 MHz) instrument using DMSO-d_6, $CDCl_3$, and CD_3CN as solvents and TMS as internal standard. ^{19}F NMR spectra were recorded on a Bruker WP-80 (80 MHz) instrument using DMSO-d_6 solvent and hexafluorobenzene as internal standard. Mass spectra were taken on a Varian MAT 311A spectrometer. Scanning conditions: accelerating voltage 3 kV, cathode emission current 300 microamperes, and electron ionization energy 70 eV; direct introduction of samples into the source.

The characteristics for the compounds synthesized are given in Table 6.

Ethyl 3-[2-(R-Carbonyl)hydrazino-1]-2-[tetra(penta)fluorobenzoyl]acrylates (3a-h). A. Ethyl 2-tetra(penta)fluorobenzoyl-3-ethoxyacrylate **1a,b** (4 mmol) was added to suspension of hydrazide **2a,b,e** (3.9 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 2-3 h, the precipitated product filtered off, and recrystallized from ethanol to give the compounds **3a-c,h**.

B. Ethyl 2-tetra(penta)fluorobenzoyl-3-ethoxyacrylate **1a,b** (7 mmol) was added to suspension of pyridinylhydrazide **2c,d** (1 g, 7 mmol) in absolute toluene (15 ml). The reaction mixture was stirred at room temperature for 2-3 h and the precipitate obtained was filtered and washed with *n*-hexane to give compounds **3d-g**.

Ethyl 5-X-1-Acylamino-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates (4a-e,g,h,i). C. Solution of compound **3d** (0.8 g, 1.9 mmol) in absolute toluene (12 ml) was refluxed for 1 h and the reaction mixture was filtered hot and the product **4d** recrystallized from isopropanol. Yield 0.3 g. Acylhydrazide **3e** gave compound **4e** similarly.

D. Solution of acrylate **3b** (0.7 g, 1.5 mmol) in absolute benzene (10 ml) was held at 80°C for 2 h. After cooling, the precipitated compound **4b** was filtered off and recrystallized from ethanol. Compounds **4a,c,g,h** were obtained similarly.

E. Ethyl ester **1a** (2.2 g, 6.8 mmol) was added to suspension of acylhydrazide **2e** (0.5 g, 6.76 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 5 h and then cooled. Absolute toluene (12 ml) was added to the residue and the solution was refluxed for 4 h. The precipitated compound **4h** was filtered off and recrystallized from ethanol.

F. Ethyl 3-ethoxy-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (3.2 g, 10 mmol) was added to suspension of cyanoacetic acid hydrazide **2f** (1 g, 10 mmol) in absolute toluene (15 ml). The reaction product was held at 80°C for 1.5 h, cooled, and the precipitated compound **4i** was filtered off and recrystallized from acetonitrile.

Ethyl 2-R-8-X-9,10-difluoro-7-oxo-7-H-[1,3,4]oxadiazino[6,5,4-*i,j*]quinoline-6-carboxylates (5a-g). G. Solution of compound **3e** (0.5 g, 1.2 mmol) in absolute toluene (20 ml) was refluxed for 2 h. After cooling, the precipitated product **5e** was filtered off and recrystallized from isopropanol. Compounds **5d,f,g** were obtained similarly.

H. Solution of compound **3g** (0.5 g, 1.2 mmol) and potassium fluoride (0.14 g, 2.4 mmol) in absolute acetonitrile (10 ml) was refluxed for 2 h. After cooling, the reaction product **5g** was filtered off, washed with water, and recrystallized from ethanol. Compound **5e** was obtained similarly.

I. Potassium carbonate (0.3 g, 2.4 mmol) was added to suspension of acrylate **3g** (0.5 g, 1.2 mmol) in absolute toluene (8 ml). The reaction mixture was refluxed for 2 h and then cooled. The precipitated compound **5g** was filtered off, washed with water, and recrystallized from ethanol. Compounds **5a-f** were obtained similarly.

J. Potassium carbonate (0.1 g, 0.7 mmol) was added to solution of quinolone derivative **4b** (0.3 g, 0.7 mmol) in absolute toluene (8 ml). The reaction mixture was refluxed for 3 h and then cooled. The precipitated product **5b** was filtered off, washed with water, and recrystallized from DMF. Compounds **5a,c,d,e** were obtained similarly.

4-Carbethoxy-1-(pyridin-4-yl)carbonyl-5-(2,3,4,5-tetrafluorophenyl)pyrazole (6) and 1-H-4-carbethoxy-5-(2,3,4,5-tetrafluorophenyl)pyrazole (7). Potassium fluoride (0.14 g, 2.4 mmol) was added to solution of acrylate **3d** (0.5 g, 1.2 mmol) in absolute acetonitrile (12 ml). The reaction mixture was refluxed for 4 h and then cooled. The precipitated pyrazole **6** was filtered off, washed with water, and recrystallized from ethanol. The mother liquor was diluted with water and the precipitated compound **7** was filtered off and recrystallized from ethanol.

Compound 6. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 8.73 (2H, dd, $^4J_{HH}$ = 4.4, $^5J_{HH}$ = 1.5, 3'- and 5'-H); 8.39 (1H, s, 3-H); 7.78 (2H, dd, $^4J_{HH}$ = 4.4, $^5J_{HH}$ = 1.5, 2'- and 6'-H); 7.54 (1H, m, 6"-H); 4.20 (2H, q, CH_2); 1.10 (3H, t, CH_3). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: 117.6 (1F, m); 116.5 (1F, m); 100.9 (1F, m); 99.3 (1F, m).

Compound 7. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 13.77 (1H, br. s, NH); 8.40 (1H, s, 3-H); 7.54 (1H, m, 6"-H); 4.10 (2H, q, CH_2); 1.20 (3H, t, CH_3). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: 157.7 (1F, m); 156.7 (1F, m); 141.1 (1F, m); 139.4 (1F, m). Mass spectrum, *m/z* (%): M^+ 288 (26), 260 (17), 243 (100), 240 (65), 216 (22), 18 (21).

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